ISSN 1300-5464

Journal of Ankara Medical School

Vol 23, No 4, 2001

Journal of Ankara Medical School

Vol 23, No: 4, 2001

CONTENTS

Journal of Ankara Medical School

All the authors stated in the published paper are kindly requested to be a subscriber to the Journal. Subscription price for the teaching staff members is 20.000.000 TL; 50% reductions for research fellows, practioners, etc.; 75% reductions for students, Subscription for the foreign countries: 17$ or 40DM.

Ek bası (Reprint) ücretlidir. Reprint ücreti makalenin sayfa adedi ve reprint adedine göre yazarlara makale kabul yazısı ile bildirilir.

For Subscription :
Ankara Üniversitesi Tıp Fakültesi Vakfı - ANKARA

Editorial Office :
A.Ü. Tıp Fakültesi Yayın Komisyonu Başkanlığı Sıhhiye - ANKARA
Phone: 0 (312) 310 30 10 / 207 - 330 Fax: 0 (312) 310 63 70

ISSN 1300 - 5464

Design & Preparation: ANTIP A.Ş. 0 (312) 310 63 05 - 310 33 33 / 22 53 Cevdet Bora AKYÜZ
Constraint: BARAN Ofset 0 (312) 336 68 74

Journal of Ankara Medical School

Published Quarterly by
ANKARA UNIVERSITY MEDICAL SCHOOL

INTRUCTIONS TO AUTHORS:

Journal of Ankara Medical School publishes original articles of research on clinical and basic sciences and concise case reports.

The language of the Journal is English.

All material should be addressed to the Editor, (Ankara Ünivversitesi Tıp Fakültesi Yayın Komisyonluğu Başkanlığı, 06100-Ankara, Turkey), in three copies and a floppy disk, ideally **Microsoft Word 6.0 or 2.0**. An introductory letter identifying the authors (s), their telephone and fax numbers and their address (s) should accompany the manuscript.

Journal accepts the contributions with the understanding that neither the article nor any part of its essential results has been published or submitted for publication elsewhere prior to its appearance in this Journal. Work already presented in a congress or published as an abstract within the context of congress or scientific meetings may be accepted for publication provided that this fact is mentioned.

All materials including text, figures, tables, references and glossy prints of figures should not exceed ten pages. The upperlimit for case presentation is three pages.

Title of the Paper: Must not exceed 80 spaces. If title exceeds 80 letter space a "running title" fewer than 40 letter spaces should be prepared in order to be placed on top of odd numbered pages.

The names (s) of author(s), including first name (s) must be written below the title. The academic degree(s) of author(s) can be stated as a foot-note with an asterix placed on surname(s) of the author(s). The name and address of Correspondent author should be stated.

Summary in a foreign language: An abstract not more then 200 words must be written in English.

Key Words not more than five should be added below the summary in alphabethical order.

Form: Article submitted must be double-spaced typewritten on standard size paper (21x30 cm), margins 3 cm to the left and 2 cm to the right should be left.

Illustrations: Photographs, graphics, and all other illustrations must be numbered according to consecutive appearence order. Graphics and figures should be made on glossy paper, preferably with china ink. Photogarphs should be made on glossy paper, black and white, with sufficient contrast. A small legend must accompany each figure numbered letters.

The legends must be written on a separate sheet of paper, in the order of appearance within the article.

Figures and photographs must be presented in an envelope. Title of the article and author(s) must be written at the back of the samples with a light pencil.

The place where the illustrations are desired to appear within the text should be indicated by numbering it on left margin.

Tables: The tables must be typewritten double-spaced on a separate sheet of paper numbered with Arabic numerals. The contents of the table must be clearly expressed with a short title.

The results of the work must be stated either by table or by explanation within the text. Duplication of the above should be avoided.

The desired place for the tables should be indicated on the left margin of the written text.

References: Must be numbered in parenthesis on the same level the manuscript line. In papers representing a research work only those references which deal with the research should be mentioned. References should not exceed 25 in research and 10 in case reports. References should be arranged sequentially as they appear in the text. Example references are given below:

- **Gozal D, Tiser A, Shupak A, et al. Necrotizing fasciitis. Arch Surg 1986; 121: 233-5.**
- **Moon RE, Gorman DF. Treatment of the decompression disorders. In: Bennett BP, Eliot DH, eds. The Physiology and Medicine of Diving. 4th ed. Philadelphia: W.B. Saunders, 1993: 454-80.**

Reprints are available at prices determined by article length and quantity.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 259- 265

CEREBROSPINAL FLUID FINDINGS AND SERUM C-REACTIVE PROTEIN IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE MENINGITIS

Gönül Tanır* ❖ Necdet Kuyucu** ❖ Arzu Bakırtaş***

SUMMARY

The aim of the study is to evaluate routinely used cerebrospinal fluid (CSF) indices and initial serum C-Reactive Protein (CRP) level in the differential diagnosis of bacterial meningitis from aseptic meningitis. For this purpose records of 97 patients with acute bacterial or aseptic meningitis were analysed retrospectively. Mean CSF leukocyte count, CSF protein and glucose level and serum CRP level were found significantly different in patients with aseptic and bacterial meningitis. Polymorphonuclear leukocyte (PMNL) predominance of >50 % in CSF was found to have sensitivity and negative predictive value (NPV) 96.3 % and 96.2 % respectively for bacterial meningitis. Although specifity and positive predictive value (PPV) of cerebrospinal fluid pleocytosis, high CSF protein (> 100 mg/dl) and low CSF glucose (< 50 mg/dl) were high (> 90 %) for bacterial meningitis, their sensitivity and NPV were low (< 90 %). The most specific test was CSF glucose level below 20 mg/dl for bacterial meningitis.

As a conclusion; except PMNL predominance in CSF, routinely used CSF indices and serum CRP level could not predict bacterial meningitis alone when Gram stain is-negative.

Key Words: Aseptic, Bacterial, Meningitis, Diagnosis

ÖZET

Akut Menenjitin Ayırıcı Tanısında Beyin Omurilik Sıvısı Bulguları ve Serum C-Reaktif Protein Düzeyi

Bu çalışmanın amacı;bakteriyel menenjitin,aseptik menenjitten ayırıcı tanısında rutin olarak kullanılan Beyin Omirilik Sıvısı (BOS) bulguları ve serum C-Reaktif Protein (CRP) düzeylerinin değerini araştırmaktır.Bu amaçla 97 akut bakteriyel veya aseptik menenjitli hastanın kayıtları retrospektif olarak incelenmiştir.Bakteriyel ve aseptik menenjitli hastalarda ortalama BOS lökosit sayısı,BOS protein,glikoz düzeyleri ve serum CRP düzeyleri belirgin olarak farklı bulunmuştur.Beyin omirilik sıvısında %50'den fazla polimorfonükleer lökosit (PMNL) hakimiyetinin bakteriyel menenjit için sensitivitesi ve negatif prediktif değeri sırasıyla %96.3 ve %96.2 olarak bulunmuştur.Beyin omirilik sıvısı pleositozunun,yüksek(>100 mg/dl) protein düzeyinin,düşük (< 50mg/dl) glikoz düzeyinin bakteriyel menenjit için spesifiteleri ve pozitif prediktif değerleri yüksek (>%90) olmasına rağmen,sensitiviteleri ve negatif prediktif değerleri düşük (< %90) bulunmuştur.Bakteriyel menenjit için en spesifik test 20 mg/dl'nin altında BOS glikoz düzeyi olarak bulunmuştur.Sonuç olarak Gram boyamada bakterinin saptanamadığı durumlarda,BOS'da PMNL hakimiyeti dışında,rutin olarak kullanılan BOS bulguları ve serum CRP düzeyinin bakteriyel menenjiti belirleyemediği görüşüne varılmıştır.

Anahtar Kelimeler: Aseptik,Bakteriyel,Menenjit,Tanı

* Dr. Sami Ulus Children' s Hospital, Pediatric Infectious Diseases Department / ANKARA/ TURKEY

**Associate Professor, Dr. Sami Ulus Children' s Hospital, Pediatric Infectious Diseases Department / ANKARA/ TURKEY

***Dr. Sami Ulus Children' s Hospital, Pediatric Emergency Department/ ANKARA/ TURKEY

Received: March 02,2001 Accepted: Sept 28,2001

The management strategies and prognosis of bacterial and aseptic meningitis are quite different so early identification of the etiological agent, although difficult becomes an important issue. The differentiation between bacterial and aseptic meningitis is based on both the clinical findings and the examination of the CSF for the number and morphological characteristics of leukocytes, protein and glucose concentrations, gram staining, bacterial, viral cultures and antigen presence. The initial CSF specimen sometimes does not allow the clinician to distinguish bacterial meningitis from viral meningitis because of an overlap in some of the typical laboratory findings (1-3). Determination of serum CRP is an important tool when differentiating bacterial and viral meningitis (4 - 9).

In this retrospective study, we compared the efficacy of CSF indices and serum CRP in order to differentiate bacterial meningitis from aseptic meningitis.

PATIENTS AND METHODS:

We reviewed the charts of patients with a final diagnosis of acute aseptic or bacterial meningitis who were admitted to Dr. Sami Ulus Children' s Hospital between January and December 1999. The exclusion criteria were ; patients presenting in the first month of life, cases associated with neurosurgical procedures like CSF shunt infections, immunocompromised patients, cases of encephalitis and a history of antibiotic use within 5 days before the admission. Aseptic meningitis was defined as a CSF pleocytosis of at least 6 WBC / mm3 together with no bacterial growth on the culture nor any visible bacteria on the gram-stained smear of the CSF. The rapid recovery of patients with aseptic disease suggested us that other serious causes of meningitis such as tuberculosis or fungal infections were unlikely. Bacterial meningitis was diagnosed if the CSF culture or gram-stained smear of the CSF were positive. The information collected from each case included demographic data, the duration of symptoms and hospital stay and clinical and laboratory findings. All the patients in both groups were evaluated in the first 24 hours of their illness. Traditional methods were used to measure the CSF leukocyte counts, glucose and protein concentrations. The ratio of CSF polymorphonuclear leukocytes was calculated from the microscopical examination of Wright stained CSF smear. Serum CRP level was measured nephelometrically (Dade Behring-Behring 100). Gram staining was considered positive if any visible organisms were seen on light microscopic examination of the slide by at least two physicians. The groups of bacterial and aseptic meningitis were compared for CSF indices and serum CRP levels on admission.

In most cases the distribution of data was skewed so the Mann-Whithey U test was used for comparison of continous variables. Mean values with standart deviation (SD) are presented. The sensitivity, specifity, NPV and PPV of each variable were calculated for the bacterial meninigitis. All analyses were done with the statistical packages SPSS-PC.

RESULTS:

Sixty-nine children aged three months to 14 years (mean ± SD: 77.7 ± 46.7 months) with aseptic meningitis and 30 children aged one month to 8 years (mean ± SD: 37.4 ± 32.2 months) with bacterial meningitis were enrolled in the study. The mean age of patients with aseptic meningitis was significantly higher than that of the bacterial meningitis ($p<0.001$). Seventy percent of the aseptic meningitis cases and 57 % of the bacterial meningitis cases were boys ($p>0.05$).

Sixty-four (96.9 %) patients with aseptic meningitis and 28 (93.3 %) bacterial meningitis had history of fever on admission. The difference between the two groups considering fever was not statistically significant ($p>0.05$). Headache (70.1 %) and vomiting (82 %) were the most frequent symptoms in patients with aseptic meningitis Convulsions and decreased level of consciousness were more frequent in bacterial meningitis cases than the aseptic ones. There was one (1.5 %) patient with convulsion in aseptic meningitis group versus 9 (30 %) patients in bacterial meningitis group ($p<0.001$). Similarly there were 3 (4.5 %) patients with decreased level of consciousness in aseptic meningitis

group versus 14 (46.6 %) patients in bacterial meningitis group (p<0.001).

The pathogens isolated from the CSF of bacterial meningitis cases were Haemophilus influenzae (7), Streptococcus pneumoniae (4) and Neisseria meningitis (3). No pathogen had been isolated from16 of 30 CSF cultures. However Gram positive diplococci were detected in 11, Gram negative coccobacilli in three and Gram negative coccus in two of these culture negative CSF specimens on gram stain . We could only have done viral cultures in 6 patients in aseptic menengitis group. Echovirus 30 was isolated in one of them from feces. We think that isolation of Echovirus 30 in 42.8 % of patients with aseptic meningitis during the same period in Ankara in another reference hospital (10) could be significant epidemiologically.

Cerebrospinal fluid findings and serum CRP levels were summarized in Table 1. Although we observed significant differences between CSF protein, glucose and serum CRP levels of patients in both groups some overlapping was also present and these should have been explained. We thought that it would be suitable to show these overlapping values on another table with different cut-off levels (Table 2). The sensitivity, specificity, positive and negative predictive values of these parameters in the identification of bacterial meningitis were shown on Table 3.

The average duration of hospitalization for aseptic and bacterial meningitis group were as follows : 4.4 ± 4 days (0-17 days) and 15.1 ± 7.2 days (1-35 days). The patients defined aseptic meningitis with an apperent mild illness were followed as outpatients. There were no deaths in aseptic meningitis group but two deaths in bacterial meningitis group, one on the 1 st day and the other on the 35 th day of hospitalization. Both of these cases were pneumococcal meningitis.

Table1: CSF Findings of the Patients with Aseptic and Bacterial Meningitis

	Aseptic (n=67) Mean ± SD	Bacterial (n=30) Mean ± SD	P value
WBC (cells/mm3)	461 ± 100.7 (6-3000)	2881 ± 2329.7 (16-8000)	>0.05
Protein (mg/ dl)	32.4 ± 24.2 (10-73)	92.8 ± 87 (6-350)	<0.001
Glucose (mg/dl)	67.2 ± 11.6 (47-108)	43.2 ± 32.2 (0-102)	<0.05
CRP (mg/dl)	22.9 ± 22 (2-90)	115.3 ± 101.3 (2-387)	<0.001

Table 2: The distribution of CSF protein, glucose and serum CRP values at different cutoff levels

	Aseptic (n=67) %	Bacterial (n=30) %
CSF Protein (mg/dl)		
< 50	82.2	34.4
50-100	16.1	34.4
> 100	1.6	31
CSF Glucose (mg/dl)		
< 20	-	34.4
20-50	1.6	13.8
> 50	98.4	51.7
Serum CRP (mg/dl)		
< 20	53.7	16.6
20-40	20.9	10
> 40	25.4	73.4
CSF PMNL (%)		
< 50	46.1	3.7
50-90	45.3	44.4
> 90	8.6	51.8
CSF WBC (/mm3)		
< 1000	95.4	30.5
1000-2000	-	10
> 2000	4.5	59.5

Table 3: Sensitivity, Specifity, Positive and Negative Predictive Value for CSF Indices and Serum CRP levels for the diagnosis of bacterial meningitis

	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)
CSF Indices				
WBC (cells/mm3)				
1000-2000	70	95.5	87.5	87.7
> 2000	60	95.5	85.7	84.2
PMNL (%)				
50-90	96.3	43.1	44.1	96.2
> 90	70.4	86.2	70.4	86.2
Protein (mg/dl)				
50-100	65.5	82.3	63.3	83.6
>100	31	98.4	90	75.3
Glucose (mg/dl)				
< 20	34.5	100	100	76.8
20-50	48.3	98.4	93.3	80.5
Serum CRP (mg/dl)				
20-40	82.1	54.2	46	86.5
> 40	75	84.7	70	87.7

DISCUSSION:

Early diagnosis and treatment of acute bacterial meningitis are important to reduce mortality and morbidity. However a definite diagnosis is difficult especially in cases whom no bacteria could be seen on the Gram stain. So far there has been no single laboratory test reported that is 100 % reliable for the rapid diagnosis of acute bacterial meningitis (8).

Clinical findings such as presence of convulsions, alteration of mental status and younger age which are among classic information suggesting bacterial meningitis were also found significant in our study (11).

In this study we investigated the significance of routinely used laboratory tests for differential diagnosis of bacterial and aseptic meningitis. We

found that mean CSF leukocyte count was not statistically different in aseptic and bacterial meningitis groups and a CSF leukocyte count of more than 1000/mm3 or even more than 2000/mm^3 are not significant for the diagnosis of bacterial meningitis. In many studies it has been reported that low leukocyte counts could not rule out bacterial meningitis, moreover significantly high pleocytosis have been documented in enteroviral epidemics (3, 8, 9, 12, 13, 14, 15). We observed that PMNL predominance in CSF above 50 % is a sensitive test for the diagnosis of bacterial meningitis however an increase in PMNL predominance in CSF more than 90 % did not augment the sensitivity, in contrast reduced it from 96.3 % to 70.4 %. It has been known that a PMNL predominance in CSF is a good predictor of bacterial meningitis: However in a recent study 57 % of patients with aseptic meningitis were reported to have PMNL predominance in CSF (16). Similarly in our aseptic meningitis group PMNL predominance in CSF was present in more than half of the patients.

In our study group a CSF protein over 50 mg/dl and 100 mg/dl were found specific but not reliable in the diagnosis of bacterial meningitis, because one third of patients with bacterial meningitis had CSF protein level below 50 mg/dl. Significant decrease in CSF glucose level below 20 mg/dl was also found 100 % specific for bacterial meningitis similar to other reports (9). We had no patient in aseptic meningitis group whose CSF glucose level is below 20 mg/dl however two thirds of patients in bacterial meningitis group had CSF glucose level above 20 mg/dl. Although a low CSF glucose concentration and a high CSF protein concentration strongly suggest bacterial meningitis, normal findings could not exclude it (8, 9).

We found that mean serum CRP values were significantly different between bacterial and aseptic meningitis but in one fifth of patients with bacterial meninigitis, serum CRP levels were below 20 mg/dl and in one fourth of them it was below 40 mg/dl. So we observed that the sensitivity and NPV of high serum CRP concentrations could not reach to reliable levels, in otherwords they were below 90 %. Since 1980' s many studies reported serum CRP level is extremely reliable in distinguishing bacterial from aseptic meningitis (4, 6, 17). In contrast to our results in a recent study sensitivity, specificity and negative predictive values of serum CRP level were found as 96 %, 93 % and 99 % respectively for bacterial meningitis (8).

As a conclusion we think that PMNL predominance in CSF has a reliable sensitivity and NPV for bacterial meningitis although CSF pleocytosis even with PMNL predominance over 90 % may be present in both aseptic and bacterial meningitis. In contrast to statistically difference between aseptic and bacterial meningitis considering the mean CSF leucocyte count > 1000/mm3, CSF protein >100 mg/dl, CSF glucose < 20 mg/dl and serum CRP level > 40 mg/dl which were all highly spesific, none of these parameters had reliable sensitivity and NPV for the diagnosis of bacterial meningitis.

REFERENCES:

1. Amir J, Harel L, Frydman M, Handster R, Varsano I. Shift of cerebrospinal polymorphonuclear cell percentage in the early stage of aseptic meningitis. J Pediatr 1991; 119: 938-41.
2. Goldberg F, Weiner LB. Cerebrospinal fluid white blood cell counts and lactic acid dehydrogenase in enterovirus type 71 meningitis. Clin Pediatr 1981; 20: 327-30.
3. Singer JI, Maur PR, Riley JP, Smith PB. Management of central nervous system infections during an epidemic of enteroviral aseptic meningitis. J Pediatr 1980; 96: 559-634.
4. Clarke D, Cost K. Use of serum C- rective protein in differentiating septic from aseptic meningitis in children. J Pediatr 1983; 102: 718-20.
5. Hanson LO, Axelsson G, Linne T, Aurelius L. Serum C- reactive protein in the differential diagnosis of acute meningitis. Scand J Infect Dis 1993; 25: 625-30.
6. Peltola HO. C-reactive protein for rapid monitoring of infections of the central nervous system. Lancet 1982;1: 980-3.
7. Ponka A, Ojala K, Teppo AM, Weber THThe differential diagnosis of bacterial and aseptic meningitis using cerebrospinal fluid laboratory tests. Infection 1983; 11: 129-31 .
8. Sormunen P, Kallio MJT, Kilpi T, Peltola H. C-reactive protein is useful in distinguishing Gram stain-negative bacterial meningitis from viral meningitis in children. J Pediatr 1999; 134: 725-9.
9. Spanos A, Harrell FE, Durack DT. Differential diagnosis of acute meningitis. JAMA 1989; 262: 2700-7.
10. Uysal G, Özkaya E, Güven A. Echovirus 30 outbreak .of aseptic meningitis in Turkey. Pediatr Infect Dis J 2000; 19: 490.
11. Prober CG. Central Nervous System Infections. In: Behrman RE, Kliegman RM, Jenson HB. Eds. Nelson Textbook of Pediatrics. Philadelphiaa: WB Saunders, 2000. p. 751-7.
12. Lindberg JA. Normocellular bacterial meningitis Ugeskr Laeger. 1998;160: 7105-8 (abs).
13. Mohsenifar Z, Gillbert RP, Landsburg M. Unusual presentation of aseptic meningitis. Postgrad Med.1977; 62 : 227-9.
14. Rosenthal J, Golan A, Dagan R. Bacterial meningitis with initial normal cerebrospinal fluid findings. Isr J Med Sci Apr 1989; 25: 186-8 (abs).
15. Tang RB, Chen SJ, Wu KG, Lee BH, Hwang B. The clinical evaluation of an outbreak of aseptic meningitis in children. Chung Hua I Hsueh Tsa Chih (Taipei) 1996; 57: 134-8 (abs).
16. Negrini B, Kelleher KJ, Wald ER. Cerebrospinal fluid findings in aseptic versus bacterial meningitis. Pediatrics 2000; 105: 316-9.
17. Diculencu D, Miftode E, Turcu T, Buiuc D. The value of C- reactive protein for the differentiation of bacterial meningitis from viral meningitis. Rev Med Chir Soc Nat Iasi 1995; 99 : 144-50 (abs).

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 267-272

ORAL FEEDİNG AFTER ABDOMİNAL SURGERY : EARLY OR LATE?

Meral Barlas*** ❖ Özgür Denli**

SUMMARY

Background/Purpose: A prospective, randomized, controlled experimental study was performed to determine the effect of immediate versus delayed (72hours) postoperative oral feeding on wound healing , intestinal adhesions and weight loss after experimental abdominal surgery.

Methods: Twenty-four male New Zealand rabbits weighing 2000-3000 g were divided into two groups. Each group consist of twelve animals and underwent control, sham, splenectomy, inferior hepatic lobectomy, partial gastric and colonic resections and anastomosis respectively. An 8cm median laparotomy was performed after an anesthesia. The study consisted of the comparative values on mortality, body weight, radiologic, histopathologic examinations, bursting pressures and intraperitoneal adhesions.

Results: Abdominal wound and colonic anastomotic strength was higher ,wound healing parameters and the histopathologic results were found to be better in the early oral-fed group ($p<0,01$). However increased weight loss and decreased intraperitoneal adhesions were found in early oral fed group.There was no statistically significant difference at the laboratory examination between the groups.

Conclusions: Immediate postoperative oral feeding results, improvement in wound healing , decreased intraperitoneal adhesions and increased weight loss (light) after abdominal surgery.

Key Words: Postoperative Early Oral Feeding, Wound Healing,Intraperitoneal Adhesions,Weight Loss

ÖZET

Karın Ameliyatlarından Sonra Oral Beslenme Erken mi - Geç mi?

Amaç: Karın ameliyatlarından sonra erken veya gecikmiş (72 saat) oral beslenmenin yara iyileşmesi , karın içi yapışıklığa veağırlık kaybına etkilerini araştırmak.

Yöntem: 2000-3000 gr ağırlığında 24 adet erkek Yeni Zelanda tavşanından 2 grup yapıldı.Her grupta 12 denek olmak üzere kontrol, sham, splenektomi, karaciğer lob rezeksiyonu, parsiyel mide rezeksiyonu ve kolon rezeksiyon-anastomozu yapıldı.Cerrahi girişim anestezi uygulandıktan sonra 8 cm median laparotomiyle yapıldı. Erken ve geç beslenen 2 grupta mortalite, vücut ağırlığı, radyolojik, histopatolojik, immünsistem, patlama basınçları ve karın içi yapışıklıklar araştırıldı.

Bulgular: Erken beslenen grupta geç beslenen gruba oranla yara iyileşmesinin daha iyi , karın içi yapışıklıkların daha az ($p<0,01$)ve ağırlık kaybının hafif derecede arttığı saptandı. İki grupta da biyokimyasal tetkiklerde belirgin bir farklılık izlenmedi.

Yorum: Post-operatif erken beslenme ile, karın içi ameliyatlardan sonra ,yara iyileşmesinin olumlu etkilendiği,karın içi yapışıklıkların azaldığı ancak ağırlık kaybınının hafif derecede arttığı saptanmıştır.

Anahtar Kelimeler: Erken Oral Beslenme, Yara İyileşmesi, Karın İçi Yapışıklık, Ağırlık Kaybı

***Associate Professor, Department of Pediatric Surgery, University of Ankara, School of Medicine,Ankara,Turkey

**Resident, Department of Pediatric Surgery, University of Ankara, School of Medicine,Ankara,Turkey

*Presented at the 3. Congress of Mediterranean Association of Pediatric Surgeons(MAPS) 12-15 October 2000 Corfu,Greece

Received: Oct 17,2001 Accepted: Nov 06,2001

The beneficial effects of enteral feeding on gastrointestinal growth and function are well known. However, it is unclear whether immediate postoperative administration of nutrients improves wound healing (1,2). A prospective, randomized study of early versus delayed enteral nutrition in postsurgery patients reported a reduction in the incidence of sepsis when enteral nutrients were administered immediately after trauma (3). Wound healing is an important component for optimizing recovery after surgery and trauma. Improved wound healing should reduce wound and systemic infection and decrease hospital stay.(4,5)This study was undertaken to investigate the effect of the early or late oral postoperative feeding to the wound healing, intraperitoneal adhesions,weight loss and immune system.

MATERIALS AND METHODS

Twenty-four male New Zealand rabbits, weighing 2000-3000 g. were divided into two groups. Each group consisted of 12 rabbits and underwent control; sham, splenectomy, inferior hepatic lobectomy, partial gastric and colon resection and anastomosis. Ceftriaxone Sodium 100mg/kg intramuscular was administered preoperatively to all animals. After 40 mg/kg Ketamine HCl and Xylazine 5mg/kg intramuscular anesthesia an 8 cm median laparotomy was performed. Control group only received anesthesia, no surgical procedure was done. After the abdominal operation the wound was closed uniformly in all animals with interrupted 3/0 silk sutures in two layers. Half of the animals in all groups (the early oral-fed group) received the Rabbit food immediately after surgery. Rest of the animals received a mixture of 50 mL 5% dextrose + normal saline twice daily and they were fed with the soft formula at 72 hrs. postoperatively. Animals were weighed with an electronic scale and the data were recorded daily. On the 5th postoperative day, the skin and abdominal wall sutures were removed. A surgical glove size 7.5 was inserted into the peritoneal cavity through a small suprapubic incision. The glove was slowly inflated and the pressure was recorded till disruption of the abdominal wound occurred. After measuring the wound strength integrity of the anastomosis, existence of perianastomotic abscess or peritonitis and adhesion formations were recorded. Evaluation was performed according to Van der Ham et al (6), (Table 1). The anastomosis was carefully dissected along with 3,0 cm of healthy colon proximally and distally and cleared of stool. The proximal end was ligated using a 3/0 silk suture and a catheter was secured into the distal end via an enterostomy and attached to the bursting pressure apparatus.

Isotonic saline was infused through this catheter at a constant rate of 1 mL/min. The bursting pressure was recorded in mm-Hg as the pressure at which leakage of saline of gross rupture of the anastomosis was noted. All the measurements were performed

Table 1: Evaluation of adhesions in a 20 experimental rabbits, according to Van der Ham et al (6)

Adhesions	0	1	2	3
Early oral-fed group	7	2	1	-
Late oral-fed group	3	2	4	1

O:no adhesions,1:Minimal adhesion,mainly between anastomosis and omentum,

2:moderate adhesions(between omentum and anastomotic site ,between anastomosis and a loop of small bowel)

3:Severe and extensive adhesions including abscess formation

when the animals were anesthesized and alive. The animals were sacrified with an overdose of pentobarbital.

The abdominal wound (Table 2), anastomotic (Table 3) and partial gastric resection site was resected and fixed in 10% formalin. After being stained with hematoxylin and eosin, they were graded histologically in a blind fashion, using an Ehrlich and Hunt numerical scale as modified by Phillips et.al.(7). Evaluated parameters were inflammatory cell infiltration, white blood cell count, fibroblasts, new blood vessel development and collagen deposition. Blood samples were obtained by cardiac puncture through the chest wall and, biochemical and blood gases analyses were determined.

Mann-Whitney U test was used for statistical analysis.

Table2: The abdominal wound (20 rabbits)were graded histologically in a blind fashion, using an Ehrlich and Hunt numerical scale as modified by Phillips et.al.(7)

Histological Grading (Abdominal wound)	0	1	2	3	4
Early oral-fed group	1	1	1	3	4
Late oral-fed group	4	3	1	1	1

Evaluated parameters were inflammatory cell infiltration, white blood cell count, fibroblasts, new blood vessel development and collagen deposition.

0; No evidence 1; Occasional evidence 2; Light scattering

3; Abundant evidence 4; Confluent cells or fibers

Table-3 :Anastomotic site (4 rabbits) were graded histologically in a blind fashion, using an Ehrlich and Hunt numerical scale as modified by Phillips et.al.(7)

Histological Grading (Anastomotic site)	0	1	2	3	4
Early oral-fed group	-	-	1	-	1
Late oral-fed group	-	2	-	-	-

.Evaluated parameters were inflammatory cell infiltration; white blood cell count, fibroblasts, new blood vessel development and collagen deposition.

RESULTS

The daily weight of the animals in the early oral-fed group was 2569.083 ± 435.41 gram whereas the animals in the late oral-fed group a value of 2683.167 ± 509.15 gram (p> 0.05) The measured abdominal wound strength was 86,7 ± 1,6128 mm-Hg in the early oral-fed group. This value for late oral-fed group was a mean of 79,5 ± 1,0686 mm-Hg (p<0,01)The bursting pressure of colonic anastomosis were 400 mm-Hg and 360 mm-Hg in early and late oral-fed group respectively. Only one animal from partial gastric resection group which was late oral-fed was died due to dehiscence of gastric sutures.

Seven of animals in the early oral-fed group showed no intestinal adhesions, when 2 had an adhesion scare of 1 which exhibits minimal adhesions, and 1 had moderate adhesions between

omentum and anastomotic site. On the late oral-fed group the severity and number adhesions were higher when compared to the early oral-fed group. Three of the animals had no adhesion, 2 of the animals had minimal adhesion whereas 4 had moderate adhesions between omentum and a loop of small bowel and 1 had severe and extensive adhesions including abscess formation (Table1). The CBC, blood gases and biochemical examination revealed no significant difference ($p>0.05$) . The radiologic examination with upper gastrointestinal system with barium showed no sign of obstruction. In the 5th postoperative day and no difference among groups. Histological examination of abdominal wound (Table 2),Anastomoses (Table 3) showed a more profound inflammatory reaction (erosions microabscesses, necroses) in late oral-fed group compared to the early oral-fed group. Healing of the anastomoses was better in early oral-fed group compared to the others.

DISCUSSION

The appropriate interval of time between surgical intervention or injury and initiation of postoperative nutritional support must be defined to determine when adverse effects occur from failure to administer needed nutrients. Immediate postoperative enteral feeding results in decreased weight loss and improved wound healing after abdominal surgery in rats. (1,8-10) Their experimental model consists of only inserting of gastroduodenal feeding tubes. However in this study includes a wide range of abdominal operation like partial gastric resection, splenectomy, hepatic lobectomy and colonic resection and anastomosis.

Initiation of nutritional support early after injury has also been shown by others (11-14).

In this study abdominal wound strength was found to be significantly higher in the early oral-fed group than the late oral-fed group. Also the colonic anastomotic bursting pressure were higher. The histopathologic findings supported a better wound healing process in the early oral-fed group. These data confor with the literature demonstrating a better wound healing in early institution of enteral feeding after surgery (15,16)

The severity and number of intestinal adhesion in the early oral-fed group also reveal a better wound healing process (table 1). We chose to study the effects of wound healing at 5 days after surgery which represents a frequent time for mobilization of patients after abdominal surgery. Severe malnutrition adversely affects wound healing. Short-term dietary restriction is associated with impaired colonic healing in experimental studies and decreased wound healing in surgical animals and patients. Impaired wound healing results from reduced fibroblast proliferation, collagen synthesis and angiogenesis (2,10). Studies of wound healing and methods of improving wound healing are relevant to clinical practice. It is hoped that faster healing will decrease the risk of infection, result in faster mobilization of the patient and decrease hospital stay . In this regard, early oral feeding decreases infections and hospital stay in patients after abdominal surgery(16-18).

We found that immediate postoperative oral feeding results in improvement in wound healing, decreased inrtaperitoneal adhesions, and increased weight loss after abdominal surgery.

REFERENCES

1- Zaloga GP,Bortenschlager L,Black KW,Prielipp R;Immediate post-op enteral feeding decreases weight loss and improves wound healing after abdominal surgery in rats. Crit Care Med 1992; 20:115-118.

2- Irwin TT :Effects of malnutrition and hyperalimentation on wound healing. Surg Gynecol Obstet 1948;86:107-113

3- Moore EE,Jones TN: Benefits of immediate jejunostomy feeding after major trauma. J Trauma 1986; 26: 874-880

4- Silk DBA: Towards the optimization of enteral nutrition . Clin Nutr 1987; 6: 61-74.

5- Senkal M,Mumme A,Eickhoff U,Geier B,Spath G,Wulfert D,Joosten U,Frei A,Kemen; M.Early post-op enteral immunonutrition:clinical outcome and cost comparison analysis in surgical patients.Crit Care Med 1997;25:1489-1496

6- Van der Hamm A C,Kort WJ, Wetima MI, Van der Inhg HF, Jeekel J: Effect of fibrin sealand on the healing colonic anastomosis in the rat. Br J Surg 1991: 78:49-53.

7- Phillips JD,Kim CS,Fonkalsrud EW ,Zeng H,Dindar H:Effects of chronic corticosteroids and vitamin A on the healing of intestinal anastomoses. Am J Surg 1992;163;71-77

8-Bickel A,Shtamler B,Mizrahi S;Early oral feeding following removal of nasogastric tube in gastrointestinal operations.Arch Surg.1992;127 :287-289.

9-Cornelia SC,Eddie LKD,Paul B,Mervyn S;Randomised trial of safety and efficacy of immediate post -op enteral feeding in patients undergoing gastrointestinal resection.Br Med J 1996;312. 869-871.

10-Demetriades H,Botsios D,Kazantzidou D,Sakkas L,Tsalis K,Manos K,Dadoikus I;Effect of early post-op enteral feeding oh the feeling of colonic anastomoses in rats.Comparison of three different enteral diets.Eur Surg Res 1999;3:57-63.

11- Jenkins M,Gottschlich M,Baumer T:Enteral feeding during operative procedures. Asbstr.JPEN 1991;15:22S

12- Meltvedt R,Khecht B,Gibbons G,Stahler C,Stojowski A,Johansen K;Is nasogastric suction necessary after elective colon resection?Am J Surg 1985;149:620-622.

13- Michowitz M,Chen J,Waizbard E,Bawnik JB;Abdominal operations without nasogastric tube decompression of the gastrointestinal tract.Am Surg 1988;54:672-675

14- Reasbeck PG,Rice ML,Herbison GP;Nasogastric intubation after intestinal resection. Surg Gynecol Obstet 1984;158:354-358

15- Robert WI,Charles FF;A comparison of levin and sump nasogastric tubes for post-op gastrointestinal decompression.Am Surg 1987;53 :50-53

16- Sander RB,Stephen MC,Steven DW,Juan JN; Must early post-op oral intake be limited to laparascopy? Dis Colon Rectum 1994;37:584-589.

17- Argov S,Goldstein Y,Barzilai A;Is routine use of the nasogastric tube justified in upper abdominal surgery? Am J Surg.1980;139:849-850.

18-Bauer JJ,Gelernt IM,Salky BA,Kreel I;Is routine post-op nasogastric decompression really necessary? Ann Surg.1985;201:233-236.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 273-278

TISSUE ENGINEERING;CHICK EMBRYONIC CELL CULTURES AND PATCHING INTESTINAL DEFECT

M.Emin Boleken** ❖ Meral Barlas***

SUMMARY:

This study was carried out using the tissue engineered intestine of chick embryonic cell as a patch of necrotic intestinal segment.

Thirteen Ross chickens intestinal cells which was harvested from 19 days old embryos and one month old of 20 Syngeneic Ross chickens served as donors and recipients respectively.

Synthetic polyurethanes have been used as matrices for chick cell attachment,growt and implantation.Cell culture were prepared as described by Evans et al.

After ketamin sulfate anesthesia at laparatomy,1,5 cm ileal defect were patched with four days embryonic cell culturing patch with tissue engineering techniques in vitro. These patched intestine were investigated as second look operations on the first postoperative day and 10^{th} ,20^{th},60^{th} day corresponding to 5,5,5,5 chickens respectively and two centimeter proximal and distal of patched intestinal segments were resected. X-Ray of Gastrointestinal passage was made 60^{th} day postoperatively with barium sulphate meal.

Animal survival rate was %100.There was no evidence of intestinal obstruction or dilatation with barium meal .Microscopically,the neomucosa consisted of a thin layer of columnar epithelial cells at 10 and 20 days and covering the whole patch area by 60 days.

The tissue engineered intestine was lined with well developed neomucosa,and could be available for not to jeopardize the ischemic bowel.

Key Words: Tissue Engineering, Chicken Cell Culture ,Intestinal Patching

ÖZET

Doku Mühendisliği; Civciv Embriyo Hücre Kültürü ve Barsak Yamanması

Çalışma,doku mühendisliği yöntemiyle üzerinde civciv embriyo hücreleri üretilmiş poliüretan membranın piliç barsağı defektine yamanarak yeni mukoza meydana gelip gelmiyeceğini araştırmak amacıyla yapılmıştır. Kısabarsak sendromuna alternatif bir tedavi olarak " doku mühendisliği barsağı" yönteminin kullanılıp kullanılamıyacağını saptamakdır.

Bu amaçla 19 günlük Ross civciv embriyosu ve bir aylık Ross piliçler denek olarak kullanılmıştır. 20 cm uzunluğunda, 2 mm çapındaki civciv embriyosu ince barsakları alınarak Evans yöntemiyle kültüre hazırlandı. İskelet olarak poliüretan membran kullanıldı. Petri kutularının içine 2,4 cm çaplı poliüretan membran yerleştirilip üzerinde dört gün primer hücre kültürü yapıldı. 4 gün sonra üzerinde kültür hücreleri içeren poliüretan membran alınıp Ross piliç ince barsağında oluşturulan 1,5 cm çapındaki defekte yamandı.

Civciv embriyosu barsak hücre kültürleri içeren poliüretan membranların piliç barsağına yamanmasından 1, 10, 20, ve 60 gün sonra yamalı segmentler çıkarılıp HE, Musikarmen ile boyandığında ameliyat sonrası 1. günde poliüretan yamanın intakt olduğu ve barsak içi materyal ile kaplandığı, 10. ve 20 günlerde poliüretan mebran üzerinin tek sıralı yeni mukoza hücreleri ve 60. günde yamanın makroskobik olarak farkedilemediği defektin tamamen çok katlı mukoza ile örtülü olduğu görülmüştür.

Bu çalışmada barsakta lokalize nekroze alanların üzerinde civciv embriyo kültür hücreleri bulunan poliüretan membranla yamanmasının olanaklı olduğu saptanmıştır.

Anahtar Kelimeler: Doku Mühendisliği,Civciv Hücre Kültürü,Barsak Yaması

* Presented as a poster at the 8.Biomedical Science andTechnology Symposium 5-8 September 2001.METU,Ankara ,Türkiye

** Resident Ankara University Faculty of Medicine , Department of Pediatric Surgery

***Assocate Professor; Ankara University Faculty of Medicine , Department of Pediatric Surgery

Received: Oct 24,2001 Accepted: Oct 30,2001

Short bowel syndrome(SBS) is a clinical condition characterized by malabsorption and malnutrition after massive small bowel resection.Total parenteral nutrition has improved survival for patients;however,prolonged hyperalimentation often leads to a variety of complications such as catheter sepsis and loss of vascular access,progressive hepatic and renal insufficiency,and bone demineralization (1). Multiple innovative surgical techniques for bowel lengthening or slowing of intestinal transit to increase the absorptive times have been developed with limited clinical success.Small bowel transplantation is the most promising therapy for patients with short bowel syndrome;however ,it has been a limited method of therapy because of complications related to rejection,immunosuppression,and infection. Furthermore, the severe shortage of donor organs especially in the pediatric population has been a major problem for organ transplatation (2-4). The tissue engineered intestinal patch using polyurethane membrane scaffolds as a new approach to the therapy of short bowel syndrome has been proposed as an experimental alternative .

MATERIALS AND METHODS

Thirteen Ross chickens which was 19 day- old embryos served as donors for isolation of intestinal epithelial organoid unit isolation.Twenty syngeneic Ross chickens weighing 1500g housed individually,alloved access to food,water ad.libitum and used as recipients.All eggs and animals were purchased from Nar Chicken (Ayaş,Ankara) .Sythetic polyurethanes have been used as matrices for chicken cell attachment and implantation(5).Intestinal epithelial organoid units were isolated as described by Evans et al(6).

Anesthesia was achieved with intramuscular ketamine(50mg/kg).Through an abdominal midline incision,intestinal patching was performed by indentifying the distal ileum and making a 1,5 cm longitudinal incision on the antimesenteric border.The defects were closed with 1,8x1cm patches of 4 day culturing of organoid units using polyurethane membrane scaffolds with continuous 6/0 atraumatic silk(fig:1,2)The patched intestine was placed into the abdominal cavity and

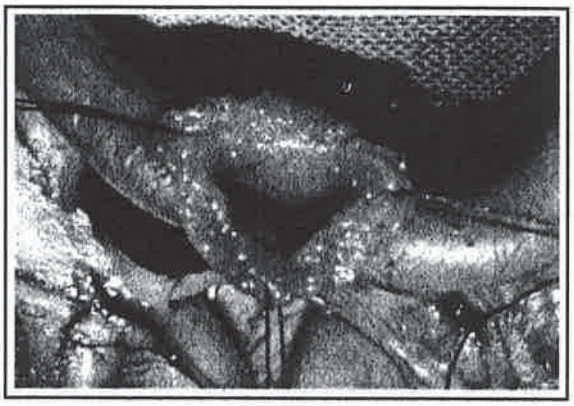

Fig1:The defect caused by 1,5 cm incision at the antimesenteric border of small intestine

Fig 2:The antimesenteric border of small intestinal defect was patched with 1,8x1cm synthetic polyurethane membrane including cell culture of 19 days old chicken embryo with 6/0 silk

the abdomen was closed.The chickens were fed normally.

Second–look operations were performed at intervals from 1 day and 10,20,and 60 days corresponding 5,5,5,5 chickens respectively.The ileum with a segment 2cm.proximal

and distal to the patch was removed and specimens were immersed in %10 buffered formalin solution .Observation for the folloving were made;mortality,radiological examination of the intestinal system using barium sulphate and light microscopic evalation of the neomucosa with hematoxylin-eosin(H&E), and musicocarmen staining (3,4).

RESULTS

All chicken survived .Only one animal died

immediately after the implantation of the engineered intestine from an anesthetic accident.

Radiologic examination of the gastrointestinal system in chickens was made 60 days postoperatively with intramuscular(10 mg/kg) ketamine administration.Barium sulfate was given to 5 chickens by feeding tube without fasting .Six hours later peranal barium passage was detected.Gastrointestinal seriogram shoved no intestinalobstruction or dilatation.Barium passage to the cloaca is readily seen (Fig 3) .

Gross examination of the chickens at the second look operation at the first postoperative day shoved fiber material of ingested food with intact engineered intestinal patch .

Second look operation of 10,20 and 60th day there was minimal adhesions of the engineered intestinal patch to the surrounding structures.There are not any abscess or granulation tissue in the abdominal cavity.Examination of the chickens at 10th days single layer of neomucosa and mucine incluiding epithelial cells was seen with musicocarmen staining (Fig4)At the 20th days showed moderate layer mucosa on the inner site of the engineered intestinal patch .Histological analysis of the enginereed tissue of the 60th day shoved a multilayered mucosa but it was difficult to notice the patching site as macroscopically in 5 chicken (Fig5).

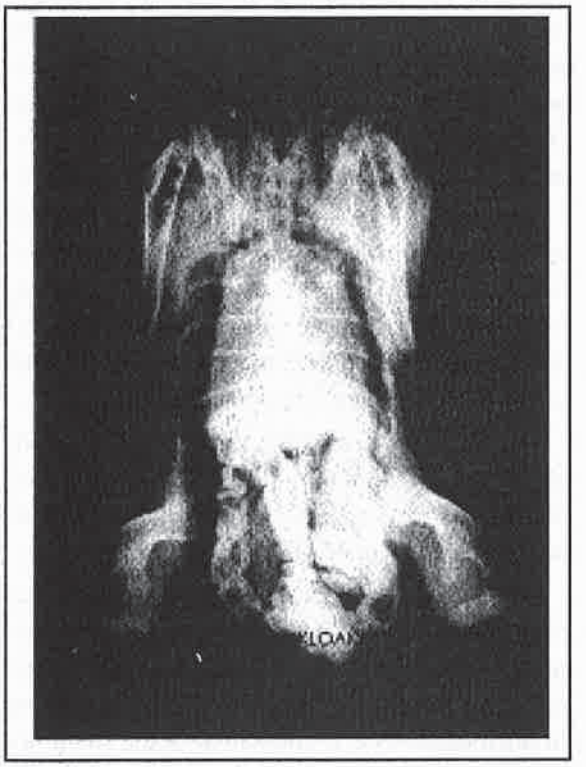

Fig 3:Radiological examination of the gastrointestinal system in chickens , 60 days postoperatively.Barium sulfate was given by a feeding tube without fasting.Barium passage till the cloaca is readily seen. No pathological appearance of the gastrointestinal system was detected in 5 chickens

Fig 4:Histopatological examination of patched intestinal specimen 10 days postoperatively.Single layer of neomucosa and musine including epithelial cells (Musicarmen x 10)

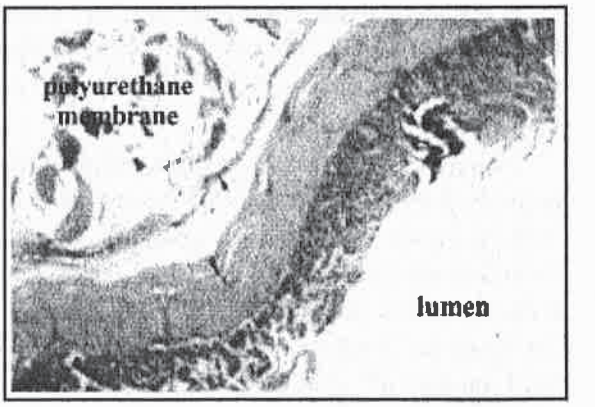

Fig 5:Histopathological examination of tissue engineered intestinal patch 60 days after implantation;Multiple layer of neomucosa was well developed and without any interruption to native intestine (arrow),(Hematoxylen-Eosin x40)

DISSCUTION

Short bowel Syndrome is a clinical condition that afflicts adult and children characterized by malabsorption,malnutrition, electrolyte imbalance, vitamin deficiency diarrhea, and progressive weight loss when less than one third of normal jejunal-ileal length remains.Prolonged intravenous hyperalimentation is associated with significant morbidity and martality.Small intestinal trans plantation,although a promising method of treatment,currently remains an experimental therapy reserved for patients with severe complications of total parenteral nutrition (TPN).

The severe scarcity of donor organs,especially in the pediatric population,has became a major limitation in the field of organ transplantation and has stimulated investigation into intestinal organoid units transplanted on polyurethane polimer scaffolds for tissue engineering of small intestine(1-3).

The loss or failure of an organ or tissue is one of the most frequent,devastating ,and costly problems in human healt care.A new field, tissue engineering, applies the principles of biology and engineering to the development of functional substitutes for damaged tissue(7-9).Investigators have attempted to engineer every mammalian tissue and discuss replacement of ectodermal,endodermal,and mesodermal tissue(10-16).

In this study tissue engineered patch of intestine was patent in all 20 chickens by second look operation at the first,10,20,60th days respectivelly.

Hematoxylin and Eosin stained speciment demonsrated the development of a neomucosa lining the lumen of the patched intestine and characterized by a columnar epithelium containing both goblet and paneth cells.There was a single and moderate layer mucosa on the inner site of patch on the 10th and 20th day respectively in all 10 animals(fig 3).

Histological analysis of the enginereed tissue of the 60th day shoved a multilayered mucosa but it was difficult to notice the patching site as macroscopically in 5 chicken. (Fig.5)

Epithelial cells of the intestine have potent proliferation,migration,and regeneration potential.Studies have reported that intestinal defects patched with colon serosa,abdominal wall pedicle flap,human amniotic membrane,and prosthetic materials became covered with the regenerative mucosa(4,17-20).The growth of regenerative mucosa was associated with increased epithelial cell proliferation in the mucosa surrounding the defect.In this study, neomucosa of the patched intestine was present booth of the inner and outer site of the intestinal lumen. In some of the chickens the wall was occupied with scar tissue and island of the neomucosa was found in deeper part of the intestine.These findings suggested that epithelial cells of native intestine did not migrate onto the polyurethane surface and that the neomucosa of tissue – engineered intestine originated from the implanted epithelial organoid units.

In conclusion,we have demonsrated that intestinal epithelial organoid units transplanted onto synthetic polyurethan scaffolds can be successfully patched to the native small bowel.The patched tissue enginereed intestinal lumen is lined with a well-developed neomucosal layer.

Future directions of this study include investigation into the function of the tissue-enginereed intestine such as absorptive capability,wall motility, and neural innervation.

Continued investigation into intestinal regeneration using isolated intestinal epithelial organoid units on biodegradable polymer scaffolds may yield many insights into the mechanisms involved in organogenesis and adaptation of the small bowel as well as lead to novel approaches to the treatment of the SBS.

REFERENCES

1-Dudrick SJ, Latifi R, Fosnocht DE et al. Management of the short bowel syndrome. Surg Clin North Am 1991;71:525-643

2-Thompson JS. Recent advances in the surgical treatment of the short-bowel syndrome. Surgery Annual 1990;22:107-127

3-Thompson JS. Surgical aspect of short bowel syndrome. Am J surg 1995;170:532-536

4-Barlas M, Gökçora H, Erekul S et al. Human amniotic membrane as a intestinal patch for neomucosal growth in the rabit model. J Pediatr Surg 1992;27(5):597-601

5-Hasırcı N. Polyurethanes as biomedical materials.In:Surface properties of biomaterials. Edited by West R and G. Batts. Butterworth-Heinemann Ldt. 1994; p: 81-90

6-Evans GS, Elint N, Somers B et al. The devolopment of method for the preparation of rat intestinal epithelial cell primary cultures. J Cell Sci 1992; 101:219-231

7-Grery MO, Vacanti JP. Tissue engineering neointestine. In:Principles of tissue engineering. 1 st ed. R.G. Landers Company and Acedemic Press, inc. 1997; Chapter 29: 441-460

8-Choi RS, Riegler M, Pothoulakis C et al. Studies of brush border enzymes, basement membrane components and electrophysiology of tissue engineered neointestine.J Pediatr Surg 1998;33:1

9-Choi RS, Vacanti JP. Preleminary studies of tisse engineered intestine using isolated epithelial organoid units on tubuler synthetic biodegradable scaffolds. Transplant Proc 1997;28:848-852

10-Gilbert JC, Takeda T, Stein JE et al. Cell transplantation of genetically altered cells on biodegradable polymer scaffolds in syngenetic rats. Transplantation 1993;56(2):423-427

11-Kaihara S, Kim S S, Kim B S et al. Long-term follow-up of tissue-engineered intestine after anostomosis to native small bowel. Transplantation 2000 ; 69(9): 1927-1932

12-Kaihara S, Kim SS, Benvenuto S et al. Succesfull anostomosis between tissue-engineered intestine and native small bowel. Transplantation 1999; 67(2) : 241-245

13-Kim S S, Kaihara S, Benvenuto S et al. Regenerative signals for intestinal epithelial organoid units transplanted on biodegradable polymer scrafolds for tissue engineering of small intestine. Trasplantation 1999 ; 67(2) : 227-233

14-Organ GM, Mooney DJ, Hansen LK et al. Enterocyte transplantation using cell- polymer devices to create intestinal epithelial-lined tubes. Transplant Proc 1993 ;25 :998-1002

15-Vacanti JP, Morse MA, Saltzman WM et al. Selective cell transplantation using bioabsorbable artificial polymers as matrices. J Pediatr Surg 1988 ; 23 (1) : 3-9

16-Vacanti JP, Vacanti CA. The Challenge of tissue Engineering. In:Principles of tissue engineering. 1 st ed. R.G. Landers Company and Acedemic Press, Inc. 1997; Chapter 1:1-5

17-Watson LL, Feiedman HI, Griffin Dg et al. Growth of intestinal neomucosa on prosthetic materials. J Surg Res 1880; 28:280-284

18-BinningtonHB,Siegel BA,Kissane JM,Ternberg JL.A technique to increase jejunal mucosa surface area.J Ped Surg 1973;8:765

19-Thompson JS,Vanderhoof JA,Antonson DL,Newland JR,Hodgson PE.Comparison of technique for growing small bowel neomucosa .J Pediatr Surg 1984;36:401

20-Lillemoe KD,Berry WR Harmon JW,et al.Use of vascularized abdominal wall pedicle flap to grow small bowel neomucosa.Surgery 1982;91:293

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 279-284

OVERDISTENSION OF THE BLADDER AND THE EFFECTS OF PIROXICAM: AN EXPERIMENTAL STUDY IN RABBITS

A.Ebru Sakallıoğlu* ❖ Meral Barlas**

SUMMARY

The effects of piroxicam on the duration and severity of damage to the mucosal barrier of the urinary bladder after overdistension was investigated.

Overdistension of the bladder was induced for 3h in 16 New Zealand male rabbits by giving Ringer's lactate infusion (40mL/Kg/hr) and furosemide (1mg/Kg) to the peritoneal cavity. Insertion and insuflation of 8 Fr Foley catheter balloons was used for obstruction of the bladder neck. In both control(C) and piroxicam (P) groups of 8 rabbits 20 mL of 2% solution of Trypan blue in 0.9% NaCl solution was instilled into the bladder for 1hr at 0,24, 48h and 7days after overdistension. In group (P) daily intramuscular injection of 5mg/Kg piroxicam was administered for 7days. Full-thickness samples were taken from the bladder dome and body above the ureteral orifice at 0,24, 48h and 7days after overdistension.. Histopathologic investigation was made for the permeability and inflammatory reaction of the bladder wall. The control group received isotonic saline instead of piroxicam

The bladder wall was deep blue throughout in both groups at 0, 24, and 48 hrs. These changes were nearly normalized in 7days. The severity and duration of inflammatory reaction was lower in piroxicam group than the control. Piroxicam group was nearly normalized on the 7th post procedure day, but in the C group submucosal capillary congestion and proliferation continued.

The bladder wall damage occurred after overdistension and leads urothelium leakage, inflammatory reaction respectively.Inflammatory reaction can be prevented by administration of anti-inflammatory drugs such as piroxicam but the prevention of increased permeability is unclear.

Key Words: Overdistension, Bladder,Inflammation, Permeabilityt, Piroxicam

ÖZET

Mesane Distansiyonuna Piroksikamın Etkileri

Mesane aşırı distansiyonu ile oluşan geçirgenlik artışı, ve inflamasyonun non-steroid anti-inflamatuar piroksikam ile azaltıp azaltılamayacağını saptamaktır.

Bu amaçla onaltı adet erkek Yeni Zelanda tavşan kullanıldı. Herbirinde 8'er adet tavşan bulunan 2 grup oluşturuldu.Tavşanların tümünde 3 saatlik mesane aşırı distansiyonu için mesane boynu tıkandıktan sonra intraperitoneal Ringer laktat (20mL/Kg) ve 0.5mg/Kg furosemid uygulandı. Distansiyon sonrası %2 lik "trypan blue" mesane içine enjekte edildi.Bir saat süreyle mesane içinde bıraklıdı ve boşaltıldı.Sekiz tavşana günde bir kez piroksikam (5mg/Kg) im uygulandı, 8 tavşan ise kontrol grubu olarak ayrıldı. Heriki grupta da 0., 24. ve 48. Saatlerde ve 7.günde mesane kubbesi ve üreter ağızlarından tam tabaka biyopsiler alındı. Bu örneklerde geçirgenlik ve inflamasyon histopatolojik olarak değerlendirildi..

Her iki grupta 0, 24, 48.saatlerde alınan örneklerde mesanenin tüm katmanları boyanmış iken 7. günde boyanmanın kaybolduğu saptandı.Piroksikam grubunda inflamasyonun süresi ve şiddetinin daha az 7.günde ise normale döndüğü kontrol grubunda ise submukozal kapiller konjesyon ve proliferasyonun devam etmekde olduğu izlendi Aşırı distansiyon sonrası oluşan mukozal hasarın nedeni ürotelial kaçak ve ağır inflamatuar reaksiyondur. Oluşan inflamatuar yanıt piroksikamla önlenebilirken mukozal geçirgenlikteki artışın engellenemediği kanısına varılmıştır.

Anahtar Kelimeler: Mesane Aşırı Distansiyonu,Proksikam, İnflamasyon ,Permeabilite

*Ressident Department of Pediatric Surgery, University of Ankara School of Medicine,Ankara

**Associate Professor Department of Pediatric Surgery, University of Ankara School of Medicine,Ankara

Received: Oct 24,2001 Accepted: Nov 12,2001

Bladder is anatomically and chemically protected against urine and bacterial adherence. Three to seven layers of umbrella cells with unique tight junctions reduce the permeability of urothelium and the highly anionic glycosaminoglycan layer on the surface of the mucosa prevents the bacterial adhesion and penetration of substances from the urine across the mucosal epithelium into the bladder wall [1-5]

Overdistension is defined as being above 120% of bladder capacity [6-8]. It occurs after acute or chronic outlet obstruction. Interstitial cystitis, recurrent bacterial cystitis, unstable bladder and acute obstructive disorders such as urethral obstruction are associated with overdistension. It causes urinary incontinence, urgency and severe pain [9-11]. Pathologies associated with acute overdistension cause functional disorders and severe tissue damage resulting from inflammatory reactions and increased permeability.But, as noted, above it also causes severe tissue damage due to inflammatory reaction and increase in permeability and this technique is not able to the uncontrolled contractions of the detrusor muscle in unstable bladder [6,8].

Piroxicam, is a non-steroid anti-inflammatory drug of novel structure. It has along half-life, permitting once-daily dosing, which should favor compliance. It is excreted as the glucuronide conjugate and a small extend unchanged [12].

The aim of this study is to investigate the effects of non-steroid anti-inflammatory drug piroxicam on the duration and severity of damage to the mucosal barrier of the urinary bladder after overdistension using Trypan blue as a marker for defects in integrity of the mucosal epithelium of the bladder [3,7,13].

MATERIALS AND METHODS:

Sixteen male white New Zealand rabbits (2500-3000gm) were anesthetized with ketamine-xylazine mixture (29.2 mg/mL ketamine, 8.3 mg/mL xylazine). The bladders were catheterized by Foley catheters of 8 Fr with 2mL of saline instillation into their balloons.Ringer's lactate infusion (40mL/Kg/hrs) and furosemide (1mg/Kg) was administered intraperitoneally to produce forced diuresis. Overdistension was defined as an intravesical pressure above 20 cmH2O by a Statham pressure transducer attached to 8 Fr catheter for each rabbit. This is equal to 120% of bladder capacity which was measured as 40mL, for rabbits. 0,24, 48h and 7days after overdistension of 3 hours, the bladders were emptied and 20 mL of 2% solution of trypan blue prepared in 0.9% NaCl solution was instilled into the bladders for 1hr, the bladders were emptied and washed for cleaning the unpenetrating dye with 20mL of isotonic saline for 5 times. The 8 rabbits of piroxicam group were given daily intramuscular injection of 5mg/Kg piroxicam for 7days. To investigate changes in permeability, a semi quantitative scoring system was used for Trypan blue staining of the bladder [1] by independent two surgeons who were unaware of the groups:

0=negative, 1=weak, 2=1ntermediate, 3=strong.

After scarifying rabbits by over dosage of pentobarbital full-thickness samples were taken from the bladder dome and body above the ureteral orifice at 0, 24, 48h and 7days after overdistension in both groups.

Histopathological investigations included the observation of inflammatory reaction cells, the structure of bladder mucosa and the healing of the bladder from the biopsy materials from the Hematoxylen-Eosin stained bladder dome and body above the ureteral orifice.

Investigation was made in 16 male rabbits:

1- The capacity of bladder was measured (40mL).

2-The intravesical pressures , after over distension of the bladder

3-The full-thickness samples were taken from the bladder dome and body above the ureteral orifice at 0, 24, 48h and 7days after overdistension. The permeability was investigated macroscopically.

4-The existence and amount of inflammatory cells in the biopsy materials

5-The effects of piroxicam to the increased permeability and inflammatory reaction of the bladder after overdistension.

RESULTS:

All animals survived the experiment.

In the investigation of permeability at 0, 24 hrs the control group's materials were strongly stained [3] by trypan blue, and at 48 hrs the staining was weak [1]. The bladder was stained strongly at 0 hr [2], intermediate at 24 hrs, and weak at 48 hrs in the piroxicam group. These changes were nearly normalized in 7days in both groups. No significant differences between the groups were detected at the investigation of permeability changes.

The most severe inflammatory reaction was observed at 24 hr in both groups but the piroxicam group's inflammatory changes were limited to the serosa, while control group's biopsies showed a full thickness inflammation with ulcers on histopathological examination. Though healing was initiated in both groups at 48 hours, the piroxicam group seemed to be more quickly normalized. Piroxicam group was nearly normalized with minimal congestion while the control group demonstrated a continuing congestion in all layers of the wall with a submucosal capillary proliferation on the 7^{th} post procedure day (Table 1).

DISCUSSION:

Prolonged overdistension technique developed by Helmstein in 1972 has been a suggested treatment of bladder instability and refractory interstitial cystitis. Though overdistension is suggested to decrease the severe symptoms such as severe pain, incontinence and urgency of these pathologies by increasing the bladder capacity [8,11], it also causes severe tissue damage due to inflammatory reaction and increase in permeability This technique is not able to the uncontrolled contractions of the detrusor muscle in unstable bladder [6,8].

Previous studies have shown that mucosal surface of the bladder is damaged by overdistension [3,5]. The urothelial damage in overdistension is caused partially by mechanical overstretching, and the interruption of capillary perfusion. The response of the bladder to the acute severe outlet obstruction is the increase in mass of the organ. The change in mass has been attributed to the connective tissue deposition, edema, smooth muscle hypertrophy and/or hyperplasia [14,15]. The damage including increased permeability and severe inflammation continues for several days and makes the bladder unprotected against the bacteria and urine solutes [3].

In previous studies local administration of anionic polyelectrolytes such as heparin and pentosanpoysulphates were investigated but a little decrease in permeability with no effects on the inflammation were detected [8,16].

The results demonstrated that piroxicam causes a significant decrease on the severity and duration of the inflammation with no effect on the permeability. In a recent study in rats Leppilahti et al.(3) has found that in the healthy bladders the most severe phase of inflammation is on the second day. The peak inflammatory reaction was observed on the 2^{nd} post procedure day in the present study. The inflammatory reaction is

Table 1: The results of histopathological examination of bladder walls in both groups

	0 hours	24 hours	48 hours	7 days
Control	Minimal inflammation in all layers	ulcer and serositis	healing	congestion, capillary proliferation
Piroxicam	Minimal serosal inflammation	serositis	healing	minimal congestion

nearly finished on the 7th day.This is parallel to Leppilahti's results(3).

But it must be kept on minds that the inflammation results with some sequels such as decrease in bladder capacity, urinary incontinence, and urinary urgency. For therapeutic overdistension, while Ramsden et al(11) has preferred to fill the bladder with saline through a Foley catheter with a special balloon until the intravesical pressure is equal to blood pressure, and waiting for 2hrs[11-14], Pengelly et al(8) preferred to limit the overdistension periods with 30minutes repeated 4 times with 15 minutes intervals of rest [8]. The authors suggest piroxicam to be a preferable choice to decrease the duration and severity of inflammation resulted from overdistension even in therapeutic administration. So it may be useful in preventing complications (bladder rupture, severe abdominal pain, pyelonephritis) of overdistension therapy, as seen by Pengelly [8].The severe proliferative reaction and connective tissue sequestration are blamed for to initiate the relapses of complaints [3,8]. Although bladder distension has been used as a method for treating unstable bladder and interstitial cystitis via a mechanical increase in bladder capacity and temporary damage to the innervation of the bladder, there is a potential irritative substance penetration and adversely resulting inflammatory reaction at a later time [1,3,9]. So the failure of overdistension therapy with continuity or relapses of complaints, in a significant number of patients may be the result of the severe inflammation and increase in permeability detected in Leppihlati's and our studies [3].

In conclusion, piroxicam administration to rabbits during and after overdistension decreases the duration and severity of inflammation with no effect on the permeability of the bladder wall. This may protect the bladder from urine solutes and bacteria and the severe sequels of mechanical overstretching. But further studies, especially consisting of collagen sequestration are needed to investigate the volume-damage relationship of urinary bladder to prevent the damage caused by overdistension either therapeutic or pathologic.

REFERENCES:

1. Dunn M, Smith JC, Ardran G.M: Prolonged bladder distension as a treatment of urgency and urge incontinence of urine: Br J Urol 1974; 46: 645-649
2. Hurst RE, Rhodes SW, Adamson PB, Parsons CL, Roy JB: Functional and structural characteristics of the glycosaminoglycans of the bladder luminal surface: J Urol,1987; 138:433 -437
3. Leppilahti M, Kallioinen M, Tammela TL: Duration of increased mucosal permeability of the urinary bladder after acute overdistension: An experimental study in rats: Urol Res 1999; 27:272-276
4. Parsons CL, Lilly JD, Stein P: Epithelial dysfunction in non-bacterial cystitis (interstitial cystitis). J Urol1991;145:732-735
5. ParsonCL, Greebspan C, et al. Role of surface mucin in primary antibacterial defence of the bladder: Urology 1977 ; 9:48-52
6. Kato K, Wein AJ, Kitada S, Haugaard N, Levin RM: The functional effect of mild outlet obstruction on the rabbit urinary bladder J Urol 1988140: 880-884
7. Monson FC, Wein AJ, McKenna BA, Whitmore K, Levin RM: Indigo carmine as a quantitative indicator of urothelial integrity: J of Urol 1991 145:842 -845
8. Pengelly AW, Stephenson TP, Milroy EJ, Whiteside CG, Turner-Warwick R: Results of prolonged bladder distension as treatment for detrusor instability. Br J Urol 1978;50:243-245
9. Dunn M, Ramsden J: Interstitial cystitis, treated by prolonged bladder distension: Br J Urol 1977; 49:641-645
10. Koff SA: Non-neuropathic vesicourethral dysfunction in children. Reed Educational and Professional Publishing Ltd., Oxford 1997
11. Ramsden PD, Smith JC, Dunn M, Ardran GM: Distension therapy for the unstable bladder: Later results including an assessment of distension: Br J Urol1976; 48: 623-629
12. Payan D, Katzung BG. Non-steroidal anti-inflammatory drugs; nonopioid analgesics; drugs used in gout. Appleton & Lange, Van Zang Streets Norwalk, Connecticut 1995
13. Lasanen L. Combined Trypan blue and glyoxylic acid-induced catecholamine fluorescence in the female rat urinary bladder after distension: Scand J Urol Nephrol 1993; 27: 175-178
14. Tammel TLJ, Levin RM: The influence of acute overdistension on rat bladder function and DNA synthesis. J Urol 1993;150:1533-1538
15. Tong YC, Monson FC, Erika B, Levin RM: Effects of acute invitro overdistension of the rabbit urinary bladder on DNA synthesis: J Urol 1992; 148:1347-1350
16. Michael R, Ruggieri PM: Heparin inhibition of increased bacterial adherence following overdistension, ischemia and partial outlet obstruction of the rabbit urinary bladder: J Urol 1986; 136:132-138

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 285-294

MEDIASTINAL MASSES: A RETROSPECTIVE STUDY

Erkan Yıldırım* ❖ Koray Dural* ❖ Serdar Han* ❖ Neslihan G. Ulaşan*
Rasih Yazkan* ❖ Ünal Sakıncı*

SUMMARY

Purpose We achieved a retrospective analysis of the 65 patients who have hospitalized and have treated for their mediastinal lesions at our chest surgery department from March 1992 to December 2000 in the view of the literature.

Material and Method We collected all the patient datas from the patient files in the archive, operation and pathological reports and from the endocrinology clinical records.

Results The median age was 40.7 years (range: 14 to 72) and female / male ratio was 19 / 46. Twenty-eight patients were asymptomatic (43 %) and 37 patients were symptomatic (57 %). Chest pain and fallen eyelids were the most frequent symptoms (20.0 %). All the diagnosis were done according to PA- Lateral chest radiographies, computerized tomographies, electromyographies (EMGs), fine needle aspiration biopsies and the clinical findings. The mediastinal masses were detected mostly in the anterior compartment (72.3 %). The frequent pathological diagnosis were the ones of thymic origin (35.4 %). The median sternotomy was the most used incision for excision of the masses (52.8 %). The median hospital stay was 18.4 days.

Conclusion Preoperatively the transthoracic biopsy had a worth in determining the diagnosis. We do emphasize spending effort to get a preoperative diagnosis. And this will help the physician to decide the operation procedure to perform. We determined the lymphomas as the second most frequent tumor (different than the literature) probably due to the our patients being in the middle age group. We have found out that the CT was valuable at showing the nature and the localization of the mediastinal masses. Median sternotomy can be safely used for the anterior mediastinal tumors. The surgery has less morbidity and mortality rates at the mediastinal lesions. Meanwhile, we did not have any major morbidity or mortality due to the surgery.

Key Words Mediastinum, Mass, Surgery

ÖZET

Mediastinal Kitleler :Retrospektif Çalışma

Giriş Kliniğimizde Mart 1992 ve Aralık 2000 tarihleri arasında yatırılıp tanı ve tedavisi sağlanan mediastinal kitle lezyonu olan 65 hastanın retrospektif analizi literatür ışığında yapıldı.

Gereç ve Yöntem Hastalar hakkındaki tüm bilgiler arşivden bulunan hasta dosya kayıtlarından, ameliyat notlarından, patoloji raporlarından, ve endokrinoloji kliniği kayıtlarından sağlandı.

Sonuçlar Yaş ortalaması 40.7 (14 ile 72 yaş arası), kadın / erkek oranı 19 / 46 idi. Yirmi sekiz hasta asemptomatik (% 43) iken 37 hasta semptomatik (% 57) idi. Semptomlar içerisinde en sık görüleni göğüs ağrısı (% 20.0) ve göz kapağında düşme (% 20.0) idi. Hastalarda tanı PA – Lateral akciğer grafisi, kompüterize tomografi, ince iğne aspirasyon biopsisi ve klinik bulgularla konuldu. Kitle lokalizasyonu en sık ön mediastende (% 72.3) idi. Tüm mediastinal kitleler içerisinde patolojik olarak en sık tespit edilen timik kökenli lezyonlar (% 35.4) idi. Yapılan cerrahi müdahale en sık median sternotomi insizyonu (% 60.3) ile olan kitle eksizyonu idi. Ortalama hastanede kalış süresi 18.4 gün idi.

Yorum Preoperatif tanı konulmasında transtorasik iğne biopsisinin değeri büyüktür. Preoperatif tanının olması ameliyat prosedürünü tespit etmede yön göstericidir ve tüm hastalarda preoperatif tanıyı koymak için ciddi çaba harcanması gereğini vurguluyoruz. Lenfomaları literatürden farklı olarak 2. sıklıkta (muhtemelen hasta yaş grubunun orta yaş olmasından dolayı) tespit ettik. CT' nin kitle görünümünü ve lokalizasyonunu tespit etmede oldukça değerli olduğunu gördük. Ön mediastinal kitle eksizyonunda median sternotomi güvenle kullanılabilir. Cerrahi, mediastinal lezyonlarda oldukça düşük morbidite ve mortalite oranlarına sahiptir. Kendi olgularımızda, cerrahiye ait herhangi major morbidite veya mortalite ile karşılaşılmadı.

Anahtar Kelimeler Mediasten, Kitle, Cerrahi

*Ankara Numune Education and Research Hospital, *Department of Chest Surgery* / Ankara

Received: Aug 14,2001 Accepted: Oct 30,2001

There have been reports of increasing frequency about the mediastinal masses. (1 - 8). More than 2400 cases with mediastinal masses have been reported in large series. In the large series published from Duke University, it has been taken attention to the change of the histological and the anatomical distribution of the mediastinal tumors (9).

Amram J. Cohen et al. (1991), had informed increase in the frequency of the malign diseases and the tumors at the anterior compartment especially the lyphomas in an analysis of 230 patients during a 45 year period (9).

Since 1979, after starting the frequent usage of the computerized tomography (CT), the other diagnostic methods has been used in a decreasing manner (9).

Primary anterior mediastinal tumors composes the 50 % of all the mediastinal masses. The most frequent tumor type is thymoma at this compartment (10, 11).

We have analysed the patients with the mediastinal masses hospitalized during the last 8 years for the clinical findings, diagnostic methods, therapeutic approaches in the light of the literature.

Materials and Methods

All the datas of the patients have been obtained from the patient files in the archive department, operation and the pathological reports and the documents of the endocrinology clinic.

We got hemograms, electrocardiograms, pulmonary function tests for all the patients routinely in the preoperative period.

These datas were analysed for the demographical informations, clinical appearances, and at the same time thoracic incision types and the operation procedures.

At the same time, the localizations and the histological diagnosis were recorded. The causes of the early postoperative morbidity amd the mortality were examined, either.

The cases of direct invasions from the lung tumors to the mediastinum, esophageal tumors and the herniations through the mediastinum were all excluded at this study.

We have divided the mediastinum into three compartments named as anterior, medial and posterior compartments (10). We have recorded the mass localizations according to this cassification.

Results

From March 1992 to December 2000, 65 patients with mediastinal masses were analysed in the view of the literature.

The number of the female patients were 19 (28 %) and the male were 46 (72 %). Median age was 40.7 (range: 14 to 72); two patients were younger than 18 years old.

There were 28 asymptomatic patients (43 %) and 37 symptomatic (57 %).

Twenty - one symptomatic patients (57.1 %) had malign disease. The most frequent symptoms were chest pain (20.0 %) and the fallen eyelids (20.0 %) (Table 1).

Table 1 *Symptoms*

SYMPTOMS	NUMBER	%
Asymptomatic	28	43.1
Chest pain	13	20.0
Fallen eyelid	13	20.0
Weakness / Fatigue	10	15.4
Respiratuary symptoms*	9	13.8
Diplopia	2	3.1
Headache or sore throat	2	3.1
Dysphagia	2	3.1
Miscellaneous	10	15.4

**Respiratuary symptoms*: dyspnea, cough

The MG patients were classified according to the Osserman classification (Group 1: Ocular, Group 2A: Mild generalized disease, Group 2B: Moderately severe generalized disease, Group 3: Acute fulminating disease, Group 4: Late severe disease); 1 patient in group I, 6 group II, 2 group III and 2 group IV. We preoperatively got all MG patients taken EMGs (pathognomonic repetitive stimulations were determined).

As adjunctive diagnostic methods, PA and la-

teral chest x-rays were obtained at all patients and CT (computerized tomography) at only 35 patients; the delay due to the technical and financial problems for getting CT done, made us to decide not to wait for the tomographic imaging.

Preoperative diagnosis were done using thymic biopsy at 2 patients (1 normal thymus; clinically Myasthenia Gravis and 1 malign thymoma), axillary lymph node biopsy at 1 patient (reactive lymph node hyperplasia), transthoracic mass biopsy at 15 patients

(10 lymphoma) and 11 MG were detected according to the clinical findings and the EMGs. At the rest of the patients diagnoses were taken postoperatively by the pathological examinations.

Preoperatively, anticholinesterase medication was given to the 4 patients, anticholinesterase + immunesuppresive therapy + plasmapheresis to the 3 patients and anticholinesterase + plasmapheresis to the 2 patients. Postoperatively, plasmapheresis was done for three periods to the 5 patients, again. The patients whom we could not perform plasmapheresis were due to the neurology clinical technical insufficiency for plasmapheresis.

Postoperatively, only 2 patients had respiratory insufficiency and followed with intubation . One of them had respiratory insufficiency preoperatively, either. This patient could not be able to be extubated for 2 weeks postoperatively and died due to the respiratory failure.

The anatomic localizations of the mass at the 47 patients were anterior mediastinum of which 18 (38.3 %) were malign and 29 (61.7 %) benign in pathology.

The most of the lesions at this compartment were in thymic origin (23 patient; 50 %) and the lyphomas (12 patient; 25.5 %) (Table 2).

The most frequent surgical procedure was mass excision performed after median sternotomy (28 patients; 52.8 %).

The other procedures were standard 12 left and 8 right posterolateral thoracotomy incisions following by mass excisions and 5 mediastinotomy incisions together with incisional mass biopsies.

Complete mass excision was only able to be achieved at the 35 cases of whom pathologic reports were benign at 28 and malign at 7 cases. Two patients determined to be inoperable due to the major vascular invasions and the 10 pre-diagnosed lyphoma patients were all transferred to an Oncology Department in order to get an adjuvant therapy.

The frequency of the solid lesions were 97 % and the cystic ones were 3 %. The ratio of the malign lesions to the benign was 27 / 38 (malign 41.5 %, benign 58.5 %). Pathological diaognosis has been presented at Table 3.

Table 2 *Anatomic Localizations*

Localization	Benign		Malign		Total	
	No.	%	No.	%	No.	%
Anterior Mediastinum	29	44.6	18	27.7	47	72.3
Middle Mediastinum	-	-	8	12.3	8	12.3
Posterior Mediastinum	9	13.8	1	1.53	10	15.4
Total	**38**	**58.5**	**27**	**41.5**	**65**	**100**

Table 3 *Pathological Diagnosis*

PATHOLOGICAL DIAGNOSIS	PATIENT NO.	FREQUENCY (%)
Lymphoma	20	30.8
Thymoma	19	29.2
Neurogenic tumors	10	15.4
Germ Cell Tumors	7	10.8
Malign Tymoma	4	6.2
Aberrant Thyroid	4	6.2
Thymic cyst	1	1.5

Here presented some radiographic figures for the mediastinal masses: (Fig 1 - 3)

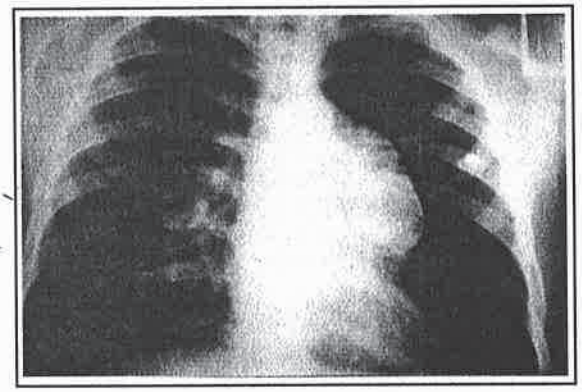

Figure 1: PA X-Ray Image of a case with "Hodgkin Lymphoma"

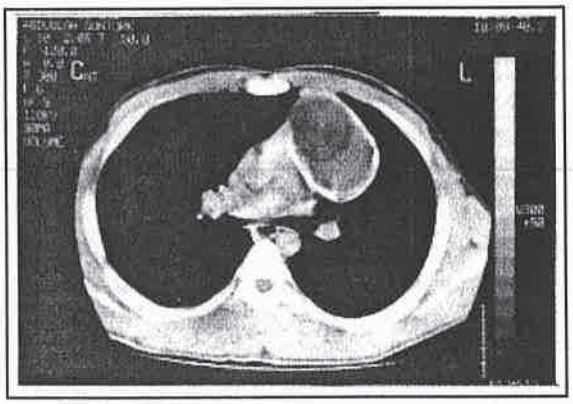

Figure 2: CT Image of "Mature Cystic Teratoma"

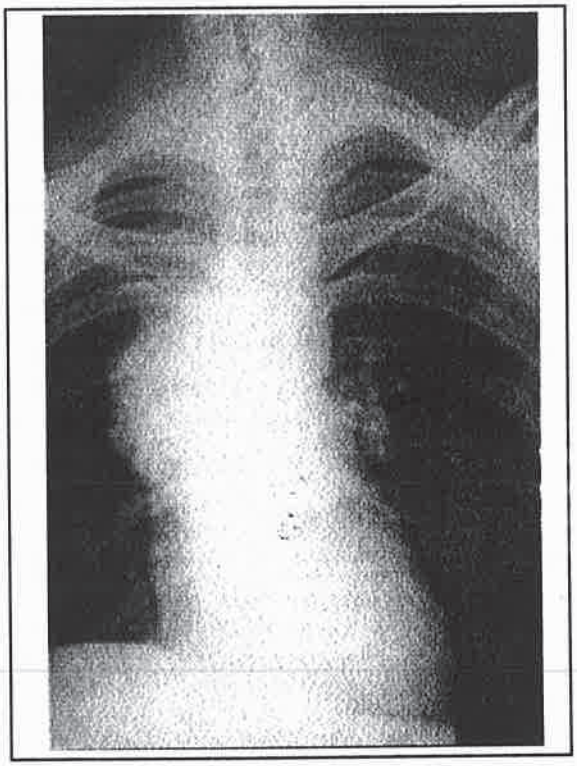

Figure 3: PA X-Ray Image of "Malign Seminoma"

Only 1 patient died of respiratory insufficiency at the 14th postoperative day; was performed thymectomy for the thymic hyperplasia. This patient had respiratory problem preoperatively and was accepted to be at the 4th group (Osserman classification). The other major complications were 2 dehiscences at the wound (Table 4).

Table 4 *Complications*

MAJOR COMPLICATIONS	NO	%
Exitus	1	1.5
Wound Dehiscence	2	3.1
MINOR COMPLICATIONS		
Pneumonia	3	4.6
Atelectasis	5	7.7
Elevated Diaphragm	3	4.6
Wound Infection	3	4.6

Discussion

The primary mediastinal cyts and tumors have been reported in an increasing trend(1 - 8).

In the literature, the 916 cases reported in 1971 by Wyculis et al. and 354 cases reported in 1987 by Davis et al. were the largest studies according to the case numbers (6).

Amram J. Cohen et al. presented a series of 230 cases during a 45 – year period which was the third largest study reported for the mediastinal tumors and cysts (9). In the light of these reported series, we could detailly get information for either localizations, histological diagnosis, clinical findings, diagnostic methods, therapeutic approaches and additionally morbidity and mortality causes.

The median age at a series of primary nonseminomateous mediastinal germ cell tumor was found to be 30.5 (18 – 48) (1). The patients with Kleinefelter syndrome having germ cell tumor are at youngest age group (median age: 17 years old)(12). Angiolipomas are benign tumors that are seen at young adults (13). The median age was found to be 28.8 ± 17.9 at the patients with mediastinal primary cysts and the tumors (newborn – 69 years old) (9). The cases with mediastinal masses are mainly male and the median age is

37 (15 – 72) (8). Thymomas are frequently seen at the adults over 40 years old (male and female are affected equally); thymic carcinomas are mainly seen at middle aged males; thymic carcinoids typically affects the males at the 3rd and 4th decades; thymolipomas are seen at the young adults (no difference of sex); mediastinal seminomas are frequently determined at the male in the 3rd and 4th decades and lymphangiomas are typically seen at very youngest children (50 % at birth and 90 % before 2 years old) (11).

The median age of the patient population that we analysed was 40.7 (range: 14 to 72). The number of the female patients was 19 (29.2 %) and the male 46 (70.8 %). Two patients were under 18 years old.

Two - thirds of the mediastinal tumors are symptomatic at the children whereas one-third at the adults (9). Clinical appearances of the massive thymic hyperplasia (MTH) can be in either three forms; 1) asymptomatic, an anterior mediastinal mass determined at the chest radiography by chance (38 %), 2) the clinical effects of the mediastinal compression, eg. respiratuary distress (29 %), dysphagia or airway obstruction, 3) acute or reccurent pulmonary infection (35 %) (14). Some authors found the symptomatic patient ratio higher at their series and as the frequent symptoms ache, cough and dyspnea were reported (7). The 57 % of the population we analysed was symptomatic. Fallen eyelids and the chest pain were the frequent symptoms (20.0 %). In harmonious with the literature, the 59.5 % of the symptomatic patients had benign (22 patients) and 40.5 % malign lesions (15 patients). The less frequent symptoms were perspiration, back pain and the lack of appetite.

The patients with the mature teratomas are frequently asymptomatic, but chest pain, dyspnea, cough, and the other symptoms of the compression may be seen at the bigger masses. Trichophytosis (hair expectoration) is seen very rarely, but pathognomonic for ruptured mediastinal

teratoma (11). We determined the germ cell tumors at 7 patients (10.8 %) of whom clinical findings were not pathognomonic.

The plain chest radiography is the cheapest and the easiest method in doubting for diagnosis of the mediastinal masses. But, after having been started to use CT since 1979, the diagnosis, the nature, boundaries and the compression effects at the adjacent organs of the mediastinal masses have been shown more efficiently (9). PA and the lateral chest radiographies were obtained for all the patients in our series. But, CT could have been taken for only 35 patients (53.8 %) due to the technical and financial problems.

Fine needle aspiration biopsy method can be used for the diagnosis of the lipothymomas, but it is not advised for the risk of malign tumor implantation (11). While having got 67 specific specimens at a study of 84 fine-needle aspiration biopsies, 13 pneumothoraces, 3 drainages and 2 hemoptzias were determined as complication (7). For the aim of getting preoperative diagnosis, we used 2 thymic biopsies, 1 axillary lymph node biopsy and 15 transthoracic fine needle biopsies (10 absolute diagnosis could be got; 1 pneumothorax was determined). The transthoracic biopsy can give out positive results for especially the anterior mediastinal masses preoperatively.

VATS (video – assisted thoracoscopic surgery) is a reliable diagnostic and therapeutic method for benign lesions of the middle and posterior mediastinum (4). Median sternotomy has been started to use much for anterior mediastinum. At the same time, cervical mediastinal exploration and anterior mediastinotomy have recently been performed as the only surgical approach for the anterior mediastinal tumors (9). We got out diagnosis of the 5 patients by performing mediastinotomy and incisional biopsies. We determined the efficacy of the mediastinotomy higher at the diagnosis of the anterior mediastinal masses. We used median sternotomy for 28 patients (52.8 %). The other surgical incisions were the standard left and right posterolateral thoracotomy incisions.

The majority of the mediastinal tumors (57 %) are located at the anterior compartment; thymoma, germ cell tumor and lymphomas. The enterogenic cysts are found at the middle mediastinum, whereas neurogenic tumors are at the posterior compartment (6, 9). Although the intrathoracic neurogenic tumors are the most frequent mediastinal tumors, they are generally located posteriorly and originated from an intercostal nerve or sympathetic chain (16). Thymomas and the thymic cysts are the antero – superior mediastinal masses. Teratomas, seminomas, non – seminomatous germ cell carcinomas, mediastinal lymphangiomas, mediastinal goitre and parathyroid adenomas are all located at the anterior mediastinum (11). At our series, the anatomical localizations were well – adjusted with the literature. Seventy-two percent of the masses were located at the anterior mediastinum; 18 malign and 29 benign lesions. On the other hand, 8 masses all of which were malign, were determined at the middle compartment and 10 masses; 1 malign and 9 benign, at the posterior mediastinum.

The neurogenic tumors were at the third row (15.4 %); 9 benign and 1 malign. At the general evaluation of the other series, the neurogenic tumors were determined at the first, the thymomas 2nd, lymphomas 3rd line. At the series of Amram J. Cohen et al., the thymic cysts were the most frequent masses (24.3 %); the neurogenic tumors 16.9 %; lymphomas 15.7 % (Hodgkin 96. % and non – Hodgkin lymphoma 4.0 %) (9).

Some authors have reported the rate of the neurogenic tumors the more (7). Some other authors have determined the thymic lesions as the most frequent anterior compartment masses (6). Thymic originated lesions were the most frequent tumor of our study (35.4 %); 19 benign and 4 malign lesions. But, the lymphomas were the second most seen tumors different than the literature (30.8 %; probably due to the patient population being at the middle – age group).

The pathologic reports of all the patients whom performed anterior mediastinotomy + incisional biopsy were all matching the lyphoma. These patients were all consulted and transferred to the Oncology Department for getting chemo therapy.

Two patients were accepted as being inoperative due to the major vascular invasions.

We performed 35 complete excisions. Seven of 35 patients were malign and the 28 benign lesions. At the rest 13 patients, we could not perform total excision due to the attachments or invasions to the adjacent tissues.

The median sternotomy incision or cervical mediastinal exploration together with anterior mediastinotomy have been using as the only surgical approach in an increasing manner(9). The posterolateral thoracotomy incision is advised instead of the median sternotomy due to the better vascular control and permitting to excision of the bigger masses (14). The standard posterolateral thoracotomy incision is superior for exploration and intervening to the lesions of the posterior compartment and the bulging masses to the hemithorax cavities and must be preferred.

In spite of some series supporting that thymectomy gives good results at group I and II MG patients (Osserman's classification) (17), on the other hand some authors advise thymectomy for the groups I – III patients, either (18, 19). We got 73 % improvement rates at group I and II patients at our series.

Hemangiopericytoma is a frequently hypervascular tumor and that's why the intractable intraoperative bleeding rate is higher. In order to decrease the intraoperative bleeding rate, the embolization before the thoracotomy is being advised (20). The posterior microneurosurgery and thoracoscopic intervention are being advised for the benign mediastinal dumbbell tumors (neurogenic or nonneurogenic) (13). VATS is a safer surgical method for especially the middle or posterior mediastinal benign masses (4). We need time to get experience to perform VATS for the mediastinal masses.

The perioperative death is the prevailing major complication and the most frequent minor complications are markedly pulmonary (pneumothorax, pneumonia and atelectasis necessitating bronchoscopy). The other major complications are paraplegia, chylothorax, pulmonary emboli and the wound dehiscence (9). Due to the anatomic closeness and furthermore the spinal cord supplying its blood at the level of T7 – L1 from the aorta (Adamkiewcz artery), it may be a surgical problem of resecting a bigger mass radically from the posterior mediastinum. That's why, the spinal cord arteriography must be performed preoperatively (21). We rarely determined per- and early post – operative complications; 1 patient died due to the respiratory failure at the 14th postoperative day. The other major complication was the dehiscence of the skin incision. The seldom minor complications were pneumonia, atelectasia, diaphragm elevation and wound infection.

Conclusion

The age group was almost between the 3rd and the 5th decades. Male gender preponderance was determined (46 / 19).

Forty-three percent of the patients were asymptomatic, but on the other hand the chest pain and the fallen eyelids were the most frequent symptoms at the symptomatic group (20 %).

We determined that the CT was a valuable imaging technique at clearing up the nature of the mass, localizations and the adjacent anatomical relations when compared with the intraoperative findings. So, preoperative CT must be taken for all the patients.

Most of the mediastinal masses were localized at the anterior mediastinal compartment (72.3 %) and the leader masses were of the lymphomas (30.8 %), thymomas (29.2 %) and neurogenic tumors (15.4 %).

The transthoracic needle biopsy has a great value at getting preoperative tissue diagnosis (10 of 15 patients). Having got the preoperative diagnosis has a valuable role in deciding for the operation procedure and we do emphasize that all efforts must be spent for getting the preoperative diagnosis.

The median sternotomy and the mass excision were the most performed surgical method (52.8 %) in harmony with the literature. There appeared no major complications belonging to the surgical methods. The postoperative mortality and the morbidity rates were determined very low.

The duration between the diagnosis and the surgical intervention at MG patients is the most prognostic factor. As soon as the MG diagnosis

done, the operation must be performed. After thymectomy, complete remission was determined at 2 patients, clinical improvement at 5, moderate improvement at 3 and worse at 1. Postoperative follow – up duration was averagely 25 months (range: 5 to 61 months).

When appreciated according to the preoperative medical therapy durations, 1 patient for 24 months (who died at the 2nd postoperative day), 1 for 16 months and all the rest less than 10 months. General improvement rate was 73 % (8 of 11 patients) at these MG patients who had thymectomized. Meanwhile, we could not report any survey ratio of the our series due to the poor follow-ups.

We do believe in that the surgery has a very valuable role at the therapeutic approach of the mediastinal masses, but on the other hand, we also claim that the aggressive combined chemo – radiotherapy together with the surgery has an important role on the long – term survey.

REFERENCES

1, Garret LW, MD, Grant DT, BS, Jonathan CN, MD, and Robert JA, MD. Intensive chemotherapy and radical resections for primary nonseminomatous mediastinal germ cell tumors. Ann Thorac Surg 2000; 69: 337 – 44.

2. Ichiro F, MD, Akira M, MD, PhD, Yoshitaka F, MD, PhD, Yosuke Y, MD, Tomoki Y, MD, Takayuki M, MD, and Tadaaki E, MD, PhD. Thymic neuroendocrine tumor (Thymic carcinoid): A clinicopathologic study. Ann Thorac Surg 1999; 67: 208 – 11.

3. Miguel FH, MD, Jon AVH, MB, Francisco JP, MD, Michael JH, MD, and J. Aidan C, MD. Mediastinal paraganglioma: A surgical experience. Ann Thorac Surg 1993; 56: 1096 – 100.

4. Todd LD, MD, Mark JK, MD, Frank CD, MD, Gary GK, MD, Leslie JK, MD, Malcolm MD, Jr, MD, and John CW, MD. Multicenter VATS experience with mediastinal tumors. Ann Thorac Surg 1998; 66: 187-92.

5. Manjit SB, MD, Robert JG, MD, William GJ II, MD, Patricia MMcC, MD, Valerie WR, MD, Michael EB, MD, PhD, and Nael M, MD. The clamshell incision: An improved approach to bilateral pulmonary and mediastinal tumor. Ann Thorac Surg 1994; 58: 30 – 3.

6. Shields TW. Overview of primary mediastinal tumors and cyts. In: Shields TW, 5th ed. General Thoracic Surgery. Lippincott Williams & Wilkins, 2000: 2105 – 109.

7. Layerly HK, Sabiston DC, Jr. Primary neoplasms and cyts of the mediastinum. In: Fishman AP, 2nd ed. Pulmonary diseases and disorders . McGraw Hill, 1988: 2087 -93.

8. Sayar A, Güleç H, Ölçmen A, Akın H, Bekar Y, Metin M, Kaya E, Ölçmen M. Ön mediasten kitlelerinin tanı ve tedavisinde cerrahi. Solunum Hastalıkları Eylül 1999; 10 (3): 215 – 18.

9. Cohen AJ, MD, Thompson LN, MD, Edwards FH, MD, and Bellamy RF, MD. Primary cysts and tumors of the mediastinum. Ann Thorac Surg 1991; 51: 378 – 86.

10. Shields TW. The mediastinum, its compartments, and the mediastinal lymph nodes. In: Shields TW, 5th ed. General Thoracic Surgery. Lippincott Williams & Wilkins, 2000; 1983 – 86.

11. Strollo DC, MD, FCCP; Christenson CMLR, MC, USAF; and Jett JR, MD, FCCP. Primary mediastinal tumors. Part 1*, Chest 1997; 112: 511 – 22.

12. Bebb GG, MD, Grannis FW, Jr, MD, Paz IB, MD, Slovak ML, PhD, and Chilcote R, MD. Mediastinal germ cell tumor in a child with precocious puberty and Kleinefelter syndrome. Ann Thorac Surg 1998; 66: 547 – 8.

13. Negri G, MD, Regolo P, MD, Gerevini S, MD, Arrigoni G, MD, and Zannini P, MD. Mediastinal dumbbell angiolipoma. Ann Thorac Surg 2000; 70: 957 – 8.

14. Linegar AG, MB, ChB, Odell JA, FRCS(Edin), Fennell WMP, FRCS(Eng), Close PM, Path MRC, Groot De MK, FRCS(C), Casserly DR, ChD, and Perold JI, Mmed(Path). Massive thymic hyperplasia. Ann Thorac Surg 1993; 55: 1197 – 201.

15. McManus KG, MD, Allen MS, MD, Trastek VF, MD, Deschamps C, MD, Crotty TB, MD, and Pairolero PC, MD. Lipothymoma with red cell aplasia, hypogammaglobulinemia, and lichen planus. Ann Thorac Surg 1994; 58: 1534 – 6.

16. Singer RL, MD. Thoracoscopic excision of a malignant schwannoma of the intrathoracic vagus nerve. Ann Thorac Surg 1995; 59: 1586 – 7.

17. Osserman KE , Genkis G . Studies in myasthenia gravis : review of a twenty-year experience in over 1200 patients . Mt Sinai J Med 1971 ; 38: 497 –537.

18. Nussbaum M , Rosenthal G , Samaha F , Grinvalsky H , Qinlan J , Schmerler M . Management of myasthenia gravis by extended dissection. Surgery 1992 ; 112 : 681 – 8.

19. Papatestas AE , Genkis G , Kornfeld P , Eisenkraft JB. Effects of thymectomy in myasthenia gravis. Ann Thorac Surg 1987; 206: 79 – 88.

20. Morandi U, MD, Stefani A, MD, Santis De M, MD, Paci M, MD, and Lodi R, MD. Preoperative embolization in surgical treatment of mediastinal hemangiopericytoma. Ann Thorac Surg 2000; 69: 937 – 9.

21. Fadel E, MD, Court B, MD, Chapelier AR, MD, PhD, Droz JP, MD, and Dartevelle P, MD. One - stage approach for retroperitoneal and mediastinal metastatic testicular tumor resection. Ann Thorac Surg 2000; 69: 1717 – 21.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 295-300

RELATIONSHIP OF p53 ANTIBODIES AND p53 PROTEIN OVEREXPRESSION IN SUPERFICIAL AND INVASIVE BLADDER CANCER

Alper Çiçek* ❖ Öztuğ Adsan* ❖ Binhan Kağan Aktaş*
Esma Yolcu ❖ Mehmet Öztürk** ❖ Ali Memiş***

SUMMARY

p53 gene alteration or p53 accumulation are usually associated with poor prognosis for cancer patients. Serum p53 antibodies are an indirect result of a p53 gene point mutation. We examined both sera and tumor samples of 57 patients with bladder cancer to evaluate association between serum p53 antibodies and p53 overexpression in the tisssue. p53 antibodies were detected in 7 patients and only 3 of them were positive for western immunoblotting for p53 antibody. p53 overexpression in the tissue was found in 16 patients of 54 and majority of the positive cases (14/16) were muscle-invasive bladder cancer. But correlation between serum p53 antibodies and tissue p53 overexpression was found low. Only 3 sera positive for p53 antibodies of the 16 cases with p53 overexpression. There was close correlation between overexpression of p53 and the tumor stage.

The low percentage of the positivity of p53 antibody in bladder cancer decreases the probability of using p53 antibody as a tumor marker in the bladder cancer.

Key Words: *Transitional Cell Carcinoma, p53 Protein, p53 Antibodies.*

ÖZET

Yüzeyel ve İnvazif Mesane Kanserinde p53 Antikoru İle p53 Protein Overekspresyonu Arasındaki İlişki

p53 gen değişiklikleri veya p53 birikimi kanser hastaları için genellikle kötü prognozla beraberdir. Serumda tespit edilen p53 antikorları, p53 gen nokta mutasyonunun indirekt sonucudur. Serumda p53 antikoru ile dokudaki p53 overekspresyonu arasındaki ilişkiyi bulmak amacıyla 57 mesane kanserli hastanın doku ve serum örnekleri çalışıldı. p53 antikoru 7 hastada tespit edilirken bunlardan sadece 3 tanesi western immünoblotting p53 antikoruna pozitif reaksiyon verdi. p53 overekspresyonu ise 54 hastanın 16'sında saptanırken bunların 14'ü invazif mesane kanseriydi. Fakat serum p53 antikoru ile doku p53 overekspresyonu arasındaki bağlantı zayıf bulundu. 16 hastanın sadece 3'ünde serum p53 antikoru pozitif bulundu. Buna karşılık tümör evresi ile doku p53 overekspresyonu arasında yakın bir ilişki vardı.

Mesane kanserinde p53 antikor pozitifliğinin düşük bulunması, mesane kanserinde p53 antikorunun tümör belirleyicisi olarak kullanımını düşürmektedir.

Anahtar Kelimeler: *Değişici Epitel Karsinomu, p53 Protein, p53 Antikoru.*

Mutations of the p53 tumor suppressor gene are demonstrated in many cancers (1,2). The level of nuclear accumulation of p53 protein which can be detected by immunohistochemical staining shows the mutant p53 protein has a longer half-life than the wild-type p53 protein. The inac-

* Department of Urology, Numune Education and Research Hospital, Ankara.

** Department of Molecular Biology and Genetics, Bilkent University, Ankara.

Received: Sep 27,2001 Accepted: Oct 17,2001

tive p53 mutants lose ability and therefore allow uncontrolled cell proliferation with uninhibited replication of defective DNA. The p53 gene alterations or p53 protein accumulation are usually associated with poor prognosis for cancer patients (3). Serological analysis detects p53 antibodies in sera of patients attesting an abnormal quantity of p53 protein inside cancer cells (4). Therefore serum p53 antibodies are an indirect result of a p53 point gene mutation.

In the present study, we examined the association between serum p53 antibodies status and p53 overexpression in the tissue and evaluated the clinical significance of serum p53 antibodies in patients with bladder cancer.

MATERIAL AND METHODS:

Patient samples: Both sera and tumor samples were collected prospectively from 54 patients with bladder carcinoma. They were 47 men and 7 women aged 20-84 years. All male, but not female patients were smokers. There was no evidence of occupational exposure to aromatic amines. Serum samples were stored at -20°C, tumor samples were embedded in paraffin blocks and stored at room temperature before analysis.

Enzyme Linked Immunosorbent Assay (ELISA) tests: Newly developed ELISA assays for p53 was used. Briefly, 96-well ELISA plates (polysorb, Nunc) were coated with 100 ng/well recombinant human p53, which have been produced as histidin-tagged polypeptides in E.Coli and purified by affinity chromatography. After blocking of unoccupied protein-binding sites with a blocking buffer (5% non-fatty milk powder in phosphate-buffered saline; pH 7.4, containing 0.5% Tween-20), 200 µl sera(1:200 dilution in blocking buffer) were incubated for 1hr, followed by incubation with alkaline phosphatase-conjugated anti-human Ig (Dako, diluted at 1:2000 in blocking buffer). Wells were extensively washed with phosphate-buffered saline after each incubation. Finally the enzyme substrate (supplied as Fast PNPP tablets from Sigma) was added into each well and the reaction product was measured at 405 nm using an ELISA reader (Beckman, Biomek Plate Reader) after 2 hours incubation. Each sample was tested in duplicate and the average OD were calculated (variation between duplicates was less than 15%).

Western immunoblotting: Affinity purified histidine-tagged p53 (100 ng each) were migrated on SDS-PAGE and transferred onto PVDF membranes using a dry-blot apparatus (Biorad). The membranes were incubated with blocking buffer (as described above), followed by incubation with diluted human sera. (1:400 in blocking buffer) for 1 hour. Membranes were then washed 3 times with washing buffer (PBS+0.2% Tween-20) and incubated in 1 hour with HRP-conjugated rabbit anti-human Ig antibodies (Dako, 1/1500 diluted in blocking buffer). The membranes were then washed as described and treated with a chemiluminescent substrate following the instructions of the supplier (Biorad) and exposed to X-ray films.

Immunoperoxidase staining for p53: Paraffin-embedded tumor samples were cut using a rotary microtome into 5 micron slices. Each slide was then incubated with an p53 mouse monoclonal antibody (DO-7 from DAKO). Bound antibodies were detected with biotin streptavidin-peroxidase system. Slides were then stained with DAB (3,3'-diaminobenzidine from DAKO) chromohen, followed by a counter-staining with hematoxylene.

RESULTS:

Analysis of p53 autoantibodies: Sera collected from 54 patients with bladder cancer as well as 60 control sera obtained from patients with benign urogenital diseases were tested for the presence of p53 autoantibodies using newly developed ELISA assays and western immunoblotting tests. ELISA-positive sera were tested for the presence of p53 autoantibodies by western immunoblotting. Recombinant p53 proteins were separated by SDS-PAGE, followed by transfer onto PVDF membranes. These membranes were then used for testing patient sera. Only 3/7 tested sera contained antibodies recognising p53. Thus, the presence of p53 autoantibodies was confirmed with only 3 sera. The remaining 4 sera were negative. This could be due to either low titer of p53 antibodies or false positivity of the ELISA test.

Analysis of p53 protein in tumors: In parallel to autoantibody studies, tumor samples from the same patients were tested independently for the p53 protein expression. Nuclear p53 immunoreactivity was noted in more than 25% of cells in 16/54 (30%) tumors (Table 1). None of the tumors displayed positive cytoplasmic immunostaining. There was a close correlation between the nuclear staining for p53 and tumor stage. Of the 54 tumors, 25 were superficial (tumor stage: T1N0M0) and only 2(8%) displayed positive p53 staining. The remaining 29 tumors were muscle-invasive (tumor stages were greater than T2) and 14 of them (48%) were positive for nuclear p53 staining (Table 2).

Correlation between p53 autoantibodies, nuclear p53 immunostaining and tumor stage: As shown in table 2, p53 autoantibodies were not detected in patients with superficial tumors (0/25). In contrast, 10% of patients with muscle-invasive tumor (3/29) developed p53 autoantibodies. As expected, p53 autoantibodies were detected in the tumor p53 protein-positive subgroup of patients with muscle-invasive tumors, but the frequency of p53 autoantibody development was low and seen only in 21 % of the subgroup (3/14).

Table 1: Distribution of p53 overexpression of the patients according to tumor stage.

STAGE	p53 OVEREXPRESSION				TOTAL	
	NEGATIVE		POSITIVE			
	n	%	n	%	n	%
SUPERFICIAL	23	42.60	2	3.70	25	46.30
INVASIVE	15	27.80	14	25.90	29	53.70
TOTAL	38	70.40	16	29.60	54	100.00

Table 2: Correlation between the results of p53 antibody and p53 overexpression.

PATIENTS	P53 OVEREXPRESSION	p53 ANTIBODY
SUPERFICIAL (n=25)	2 (%8)	0 (%0)
INVASIVE (n=29)	14 (%48)	3 (%10)
TOTAL (n=54)	16 (%30)	3 (%5.5)
CONTROL (n=60)	NA*	0 (%0)

* NA: Not Available.

DISCUSSION:

Mutated p53 gene product is the most common studied genetic alteration in various cancer (1,2,5). This protein is detected easier than the wild one because of long life. Detection of p53 protein by using immunohistochemical method demonstrated prognostic value in urothelial carcinoma (5,6). Expression of p53 is accepted late term genetic alteration in urethelial carcinoma (5).

We found 30 % of the 54 patients with bladder carcinoma demonstrated an overexpression of p53 protein in tumor cell nuclei. While we found 8% positivity in superficial group, the positivity of p53 protein was 48% in muscle-invasive group. There was close correlation between overexpression of p53 and the tumor stage. Immunohistochemical studies showed that overexpression of tumor p53 protein was found in up to 78% of bladder cancer (5,7).

Antibodies against cellular protein p53 in sera was first demonstrated in patients with breast cancer (8). Determination of p53 antibodies in sera of patients with various cancer was accepted

poor prognostic factor by many authors. On the other hand p53 antibodies can be detected in severe inflammatory diseases such as pancreatitis (9). A strong correlation has been reported between the presence of p53 autoantibody and accumulation of p53 protein in patients with various cancer types like head and neck cancer and breast cancer (8,10). But in urological cancers, the correlation was not found by authors (5,11,12,13).

In our study we aimed to demonstrate the correlation of p53 autoantibodies with p53 overexpression. We found 5.5% (3/54) of the patients with bladder cancer developed p53 autoantibodies, as 30% (16/54) of the patients showed p53 overexpression. All patients who showed positivity for p53 autoantibodies were muscle-invasive bladder cancers. In immunostaining evaluation only two patients with superficial bladder cancer displayed positive p53 staining, the others were muscle-invasive cases. All sera-positive patients had p53 protein-positive tumor tissue. Our results are similar with Lang et al., Wunderlich et al. and Morita et al. (11,12,13).

In spite of the prognostic value of p53 antibody in some tumors except urological malignancies, p53 autoantibody status seems not to be useful for evaluating the patients with bladder cancer. The low percentage of the positive p53 antibody of the patients with bladder cancer decreases the probability of using p53 autoantibody as a tumor marker in bladder cancer.

REFERENCES:

1. Hollstein M, Sidransky D, Vogelstein B, Harris CC: p53 mutations in human cancers. Science 1991; 253: 49-53.
2. Soussi T, Legros Y, Lubin R, Ory K, Schlichtholz B: Multifactorial analysis of p53 alteration in human cancer a rewiev. Int J Cancer 1994; 57: 19.
3. Lane DP: Cancer, p53 guardian of the genome. Nature 1992; 358: 15-16.
4. Angelopoulou K, Diamandis EP, Sutherland DJA, Kellen JA, Bunting PS: Prevalence of serum antibodies againist the p53 tumor suppressor gene protein in various cancers. Int J Cancer 1994; 58: 480-487.
5. Burkhard FC, Markwalder R, Thalmann GN, Studer UE: Immunohistochemical determination of p53 overexpression. An easy and readily avaible method to indentify progression in superficial bladder cancer? Urol Res 1997; 25: 31-35.
6. Sarkis AS, Dalbagni G, Cordon-Cardo C, Melamed J, Zhang Z: Association of p53 nuclear overexpression and tumor progression in carcinoma in situ of the bladder. J Urol 1994; 152: 388-392.
7. Lipponen PK: Over-expression of p53 nuclear oncoprotein in transitional-cell bladder and its prognostic value. Int J Cancer 1993; 53: 365-370.
8. Willsher PC, Pinder SE, Robertson L, Nicholson RI, Ellis IO, Bell JA, Blamey RW, Green JA, Robertson JF: The significance of p53 autoantibodies in the serum of patients with breast cancer. Anticancer Res 1996; 16 (2): 927-930.
9. Readle J, Oremek G, Welker M, Roth WK, Caspary WF, Zeuzem S: p53-autoantibodies in patients with pancreatitis and pancreatic carcinoma. Pancreas 1996; 13 (3): 241-246.
10. Shin DM, Kim J, Ro JY, Hittelman J, Roth JA, Hong WK: Activation of p53 gene expression in premalignant lesions during head and neck tumorigenesis. Cancer Res 1994; 54: 321-326.
11. Wunderlich H, Hindermann W, Hüller M, Reichelt O, Werner W, Schubert J, Kosmehl H: The correlation of p53 protein overexpression and p53 antibodies in serum of patients with transitional cell carcinoma of the urinary bladder. Urol Int 2000; 64: 13-17.
12. Lang C, Unteregger G, Kartarius S, Gunther J, Bonkhoff H, Montenarh M, Zwergel T: p53 autoantibodies in patients with urological tumors. Br J Urol 1998; 82 (5): 721-726.
13. Morita T, Tachikawa N, Kumamaru T, Nukui A, Ikeda H, Suzuki K, Tokue A: Serum anti-p53 antibodies and p53 protein status in the sera and tumors from bladder cancer patients. European Urology 2000; 37 (1): 79-84.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 301-312

LAPLACE OPERATIONS FOR ISCHEMIC CARDIOMYOPATHY

A. Rüçhan Akar ❖ Neyyir Tuncay Eren ❖ Tümer Çorapçıoğlu ❖ Hakkı Akalın

SUMMARY

Despite marked improvement in the pharmacologic treatment of ischemic end-stage heart failure, the prognosis continues to be grave. The annual mortality rate for congestive heart failure with class III or IV symptoms is nearly 40%. Heart transplantation is available only for limited number of patients. New approaches to resolve this problem include medical therapies (digoxin, diuretics including spironolactone, ACE inhibitors, beta- blockers and phosphodiesterase inhibitors) to stabilize patients, followed by chamber remodeling. Advances in cardiac surgical techniques have changed the number and types of operations performed on this group of patients and thus the indications for these operations have begun to cover a wider and more complex range of patients. In patients with severe coronary artery disease and poor left ventricular function, coronary artery bypass grafting has a positive impact on long- term survival. In patients with heart failure and no angina, new surgical strategies are recomended. Mitral valve repair techniques, reducing left ventricular diameter, reconstruction of left ventricular elliptical shape (Laplace's law) may improve ventricular function and survival by reducing left ventricular wall stress.

Key Words: Law Of Laplace, Left Ventricular Volume Reduction Surgery, Mitral Valve Repair, Ischemic Cardiomyopathy, Myocardial Viability

ÖZET

İskemik Kardiyomiyopatilerde "Laplace Operasyonları"

Terminal dönem iskemik kardiyomiyopatilerin medikal tedavisinde önemli gelişmeler sağlanmasına karşın, hastalığın prognozu halen oldukça kötüdür. NewYork Kalp Birliği sınıflamasına göre semptomları III ve IV düzeyindeki konjestif kalp yetmezliği olan hastalarda yıllık mortalite oranları yüzde 40'a yaklaşmaktadır. Bu hastaların tedavisi için öngörülen kalp nakli ise yalnızca küçük bir gruba uygulanabilmektedir. Bu problemin çözümü için uygulanan tedaviler arasında medikal tedavi yöntemleri (digoksin, spironolaktonu da içeren diuretic grubu, ACE inhibitörleri, beta blokörler ve fosfodiesteraz inhibitörleri) hastaları stabilize ederken, kalp boşluklarının yeniden şekillendirilmesi bunu izlemektedir. Kalp cerrahisi tekniklerindeki gelişmeler bu hasta grubuna uygulanan operasyonların hem sayısını hemde şeklini değiştirmiş olup, ameliyat endikasyonları komleks hasta grubunu içermeye başlamıştır. Üç damar hastası ve sol ventikül fonksiyon bozukluğu olan hastalarda koroner by-pass ameliyatının uzun dönem yaşam oranlarını pozitif yönde etkilediği bilinmektedir. Ancak, kalp yetmezliği gelişmiş fakat anjinası olmayan hasta grubuna, yeni cerrahi uygulamalar önerilmektedir. Mitral kapak onarım teknikleri, sol ventrikül çapının azaltılması, sol ventrikül eliptik şeklinin tekrar sağlanması Laplace kanununa göre ventrikül duvar stresini azaltarak fonksiyonunu iyileştirebileceği beklenmektedir.

Anahtar Kelimeler: Laplace Kanunu, Sol Ventrikül Hacim Azaltıcı Operasyonlar, Mitral Kapak Onarımı, İskemik Kardiyomiyopati, Miyokard Viabilitesi

Department of Cardiovascular Surgery, Ankara University Medical Faculty, Turkey
Department of Cardiothoracic Surgery and Cardiology, University Hospitals of Leicester, UK

Received: Oct 09,2001 Accepted: Nov 14,2001

Historical Perspective

Left ventriculoplasty

The term dyskinesia refers to a post-ischemic fibrous area of ventricle that moves in a paradoxical manner during ventricular systole and diastole, ie, an aneurysm. Akinesia indicates that such an area of scarred ventricle exhibits no movement during either systole or diastole (1). The term 'ischemic cardiomyopathy' was introduced by Burch in 1972 to express a poorly functioning left ventricle due to diffuse patchy fibrosis caused by chronic myocardial ischemia (2). Patients with an end-systolic volume index >100 mL/m^2 do not benefit from revascularization alone and require an operation that reduces ventricular volume (3). The endoventricular circular patch plasty (EVCPP) technique was first used by Dor et al. in 1984 to re-establish a more normal morphology of the left ventricular cavity distorted by post-infarction ventricular aneurysm (4). This technique had been applied to treat end-stage ischaemic cardiomyopathy defined as non-aneurysmal akinetic diffuse left ventricle by the same group since 1997 (1) (Figure-1). Batista et al. published a case of a 34-year-old male with dilated cardiomyopathy in whom they performed a new surgical procedure; i.e., ventricular volume reduction to improve function in 1996 (5). Batista pointed out the importance of preserving original left ventricular diameter (Law of Laplace) in all types of cardiomyopathies (5). Since that report reduction ventriculoplasty has been used worldwide as an alternative to heart transplantation in a multitude of patients with dilatative cardiomyopathy (Figure-2). Recently Qin et al. reported the results of infarct exclusion (IE) surgery, a technique of left ventricular (LV) reconstruction for dyskinetic or akinetic LV segments in patients with ischemic cardiomyopathy by using epicardial real-time 3-dimensional echocardiographic evaluation (6). They confirmed significant decreases in LV end-diastolic (EDVI) and end-systolic (ESVI) volume indices, and significant increases in LV ejection fraction after IE surgery and at follow-up. These changes imply a reduction in LV wall stress after IE surgery and are predictive of symptomatic improvement. Green et al. reported an experimental study which examined the effects of partial left ventriculectomy on three- dimensional (3-D) LV geometry, wall stress and passive LV mechanics in excised porcine hearts. They confirmed that after partial left ventriculectomy the left ventricle be-

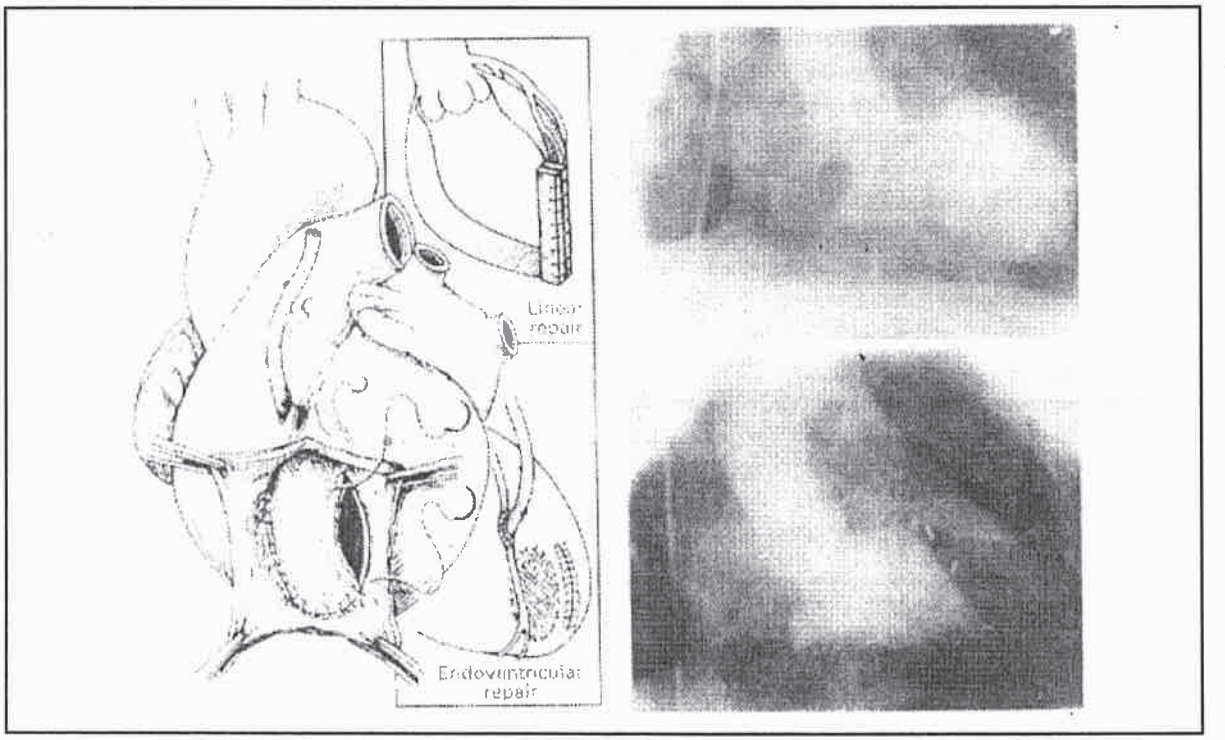

Figure 1. Left ventricular restoration by endoventricular patch repair "the Dor Procedure"

came more elliptical and chamber size decreased, which resulted in lower regional LV wall stress and myocardial stiffness causing lower myocardial oxygen consumption and improve LV pump efficiency (7). The consequences of LV wall stress reduction are summerised in Table-1.

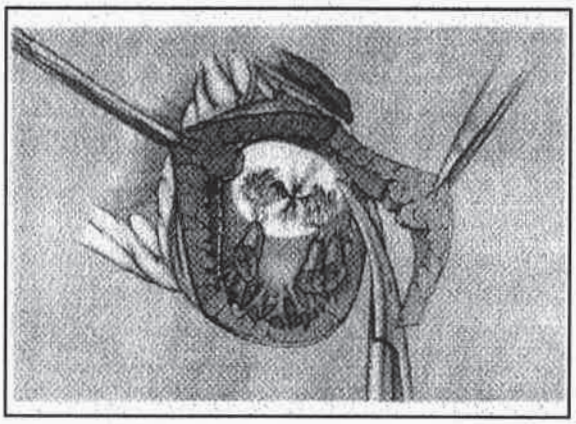

Figure 2. The Batista operation

ined into the value of the mitral valve apparatus, the causes of LV dysfunction in mitral regurgitation, and into the objective markers of LV function that permit the clinician to recommend surgery before muscle dysfunction has become severe and irreversible (10). The SAVE (Survival and Ventricular Enlargement) study data demonstrated, 19.4% incidence of ischemic mitral regurgitation (IMR) following myocardial infarction (11). Ischemic mitral regurgitation (IMR) occurs in approximately 3% of the patients undergoing coronary angiography (12), and in 4-5% of patients undergoing coronary artery bypass surgery (13). IMR is the third most common cause for mitral valve surgery (11). While mitral valve repair techniques are evolving, ischaemic mitral regurgitation continues to be a surgical challenge while increasing demand for surgical correction of IMR.

Mitral valve surgery for IMR has been associ-

Table 1. WHY REDUCTION OF WALL STRESS HELPS?

• Myocardial oxygen consumption
• Myocardial efficiency (less energy for the same work)
• Neurohormone feedback
• Myocyte fiber orientation
• Reprogram to fetal phenotype (LVAD)
• Myocyte and mitochondrial recovery (LVAD)

New ventricular remodeling approaches have been applied in experimental models. Liel-Cohen et al. reported a sheep model where LV was remodeled by plication of the infarct region to reduce myocardial bulging, without muscle excision (8). Different surgical techniques for ischemic cardiomyopathy are summerised in Table-2.

Ischemic mitral regurgitation (IMR)

IMR patients can be under extreme levels of myocardial wall stress which may lead to irreversible left ventricular dysfunction (9). More recently, however, substantial insight has been gated with an increased operative risk, as compared to both isolated myocardial revascularisation or isolated mitral valve procedures for other etiologies of mitral insufficiency. Lillehei et al. first described the importance of conservation of the subvalvular apparatus in the preservation of systolic function for mitral valve surgery (14). Carpentier et al. (1968) first reconstruct the mitral valve by using a prosthetic ring. Subsequent studies confirmed that IMR is actually due to dysfunction of the ischemic left ventricular wall or papillary muscles. By definition in IMR, the mitral valve leaflets and chordae has normal

function. Papillary muscle discoordination with annular dilatation distorts leaflet coaptation sufficiently to produce mitral regurgitation (15). More recently, this knowledge has been applied with good results in the management of patients with ischaemic mitral regurgitation. Reported significant determinants of survival were severity of mitral regurgitation, depressed left ventricular ejection fraction, acute papillary muscle rupture, cardiogenic shock, cardiomegaly, left heart failure, and acute and multiple myocardial infarctions,

Table 2. Surgery for Ischaemic Heart Disease

1. Coronary artery bypass grafting
2. "LA PLACE" operations
   - Mitral Valve Repair
   - Aneurysmectomy
   - Dor procedure
   - Batista procedure
   - LVAD to recovery
3. Heart transplantation

pulmonary hypertension, advanced age (16).

Ischemic mitral regurgitation may result from rupture of the papillary muscles, distortion of papillary muscle geometry, aneurysm formation, or ventricular and annular dilatation and is nearly always associated with regional or global left ventricular dysfunction. The one exception is a ruptured papillary muscle, which is an acute catastrophic entity that not infrequently occurs in the setting of a small infarct in patients with single blood supply to the papillary muscle. In patients with IMR, the leaflets and subvalvular apparatus usually are completely normal, annular dilatation may be present, yet leaflet motion typically is either normal (Carpentier type I) or restricted during systole (Carpentier type IIIb). The most common cause of MR is incomplete closure of the mitral valve due to apical displacement of the papillary muscle (17). Recent experimental studies have revealed that acute posterolateral LV ischemia in sheep is associated with annular dilatation and incomplete mitral leaflet coaptation due to early systolic "loitering" (or delayed closure) of both leaflets, which can cause ischemic MR (18). Mitral annular area reduction and fixation with an annuloplasty ring eliminated delayed leaflet coaptation and prevented mitral regurgitation during acute left ventricular ischemia after ring implantation (19).

Surgical outcome of valvular heart disease has steadily improved over the past two decades. However ischemic mitral regurgitation is well known to have a grave prognosis. Surgical treatment options for IMR are controversial; 1) coronary artery bypass grafting alone, 2) mitral valve repair with annuloplasty ring, 3) other mitral valve repair techniques, 4) mitral valve replacement with preservation of part or all of the mitral apparatus 5) mitral valve replacement with removal of the mitral apparatus. In IMR the mitral valve leaflets and chordae are structurally normal and does not need replacing. Coronary artery bypass surgery alone may improve left ventricular function and reduce the degree of MR. In coronary artery surgery, moderate IMR raises the operative mortality to 6-11% (13). In case mitral regurgitation is not corrected, hospital mortality as well as late survival is profoundly worsened. A retrospective long-term study of more than 2000 patients who underwent CABG alone, showed that uncorrected mitral regurgitation nearly doubled the risk of late death. Patients with severe mitral regurgitation, symptoms of heart failure, and significant left-ventricular dysfunction (ejection fraction<35%) are more likely to benefit from valve repair at the time of CABG. Mitral valve repair and myocardial revascularisation for IMR have an operative mortality that ranges from 3 to 30% and a rate of re-operation of up to 15%. In 1986, Kay et al. reported operative treatment of 141 patients with ischemic mitral insufficiency. Valve repair was done in two thirds of the patients, using primarily the suture annuloplasty technique. Operative risk was increased in patients with recent

myocardial infarction or low ejection fraction, and by the use of valve replacement instead of repair. In a series of 638 patients with mitral insufficiency undergoing Carpentier-type mitral valve reconstruction with ring annuloplasty at NYU since 1979, 115 (18%) had insufficiency secondary to coronary artery disease. The overall operative risk for combined coronary bypass and valve reconstruction was 15.7%. Factors that predicted increased operative risk were ischemic etiology, previous cardiac surgery, NYHA functional class and age. In addition, concomitant procedures, ischaemic etiology, and pulmonary hypertension were associated with increased risk of late cardiac death. Of importance, the freedom from reoperation was equally good in ischemic patients as in their non-ischemic counterparts. Thus, valve repair was quite durable in the ischemic population.

Another controversial condition in IMR is management of moderate (2+) MR. The decision to operate is normally easy in extreme cases but not when the degree of insufficiency is moderate (2+). SAVE (Survival And Ventricular Enlargement) study data proved that even mild IMR is an independent predictor of post-MI mortality. The same trial has also showed that IMR patients had larger end- systolic and end-diastolic volumes and more spherical ventricles than patients without MR. Grigioni et al (20) recently graded the degree of MR with quantitative echocardiographic measurements in 303 patients with previous Q-wave MI. They confirmed that the mortality risk was directly related to the degree of IMR as defined by effective regurgitant orifice and regurgitant volume. Excess mortality was reported when regurgitant volume > 30mL and effective regurgitant orifice > $20mm^2$. They conclude that quantification of MR in the post-MI chronic phase is essential for risk stratification and recommend prompt medical and surgical therapeutic options. On the basis of these studies operative decision of this group can be extended to Grade 2+ MR. However, recently Ryden et al. reported a case-control study focusing on functional status and mortality in patients with grade (2+) ischemic MR (21). This study concluded that CABG on patients with grade 2 ischemic MR reduces angina pectoris and improves functional status to the same extent as in CABG patients without MR. Their results do not exclude that there might be individual patients that would benefit from a valvular or annular procedure in combination with CABG.

Current techniques of mitral valve repair ischemic MR rely on decreasing valve area to increase leaflet apposition, but fail to address subvalvular dysfunction. The "edge-to-edge" technique, introduced by Alfieri initially applied for degenerative mitral valve disease (22) (Figure-3). While increasing number of patients with ischemic cardiomyopathy receiving Alfieri technique, the "bow-tie" repair technique was recently introduced by Umana JP et al. with partial left ventriculectomy, which apposes the anterior leaflet to a corresponding point on the posterior leaflet creating a double- orifice valve (23). Results of different surgical strategies for ischemic cardiomyopathy summerised in Table-3.

Assesment of Stunned and Hibernating Myocardium

Myocardial stunning is a form of ischemic injury which occurs with transient ischemia followed by re-establishment of flow. It is associated with reversible myocardial systolic and diastolic dysfunction lasting hours to days without evidence of myocardial necrosis. The first demonstration of stunning was obtained two decades ago in experimental models in which the absolute regional flow to the myocardium was reduced by occlusion of a coronary artery (24). A typical feature of stunning is the ability of myocardial function to improve upon inotropic stimulation which confirms that cells are viable and capable of contracting. It has been documented in patients with angina (chronic stable and/or unstable), acute myocardial infarction, heart failure and/or severe left ventricular dysfunction.

Randomized clinical trials have demonstrated that coronary artery bypass grafting (CABG) confers a survival benefit versus medical therapy in patients with multivessel coronary artery disease, particularly in the setting of decreased left ventricular function (25). Among patients with ische-

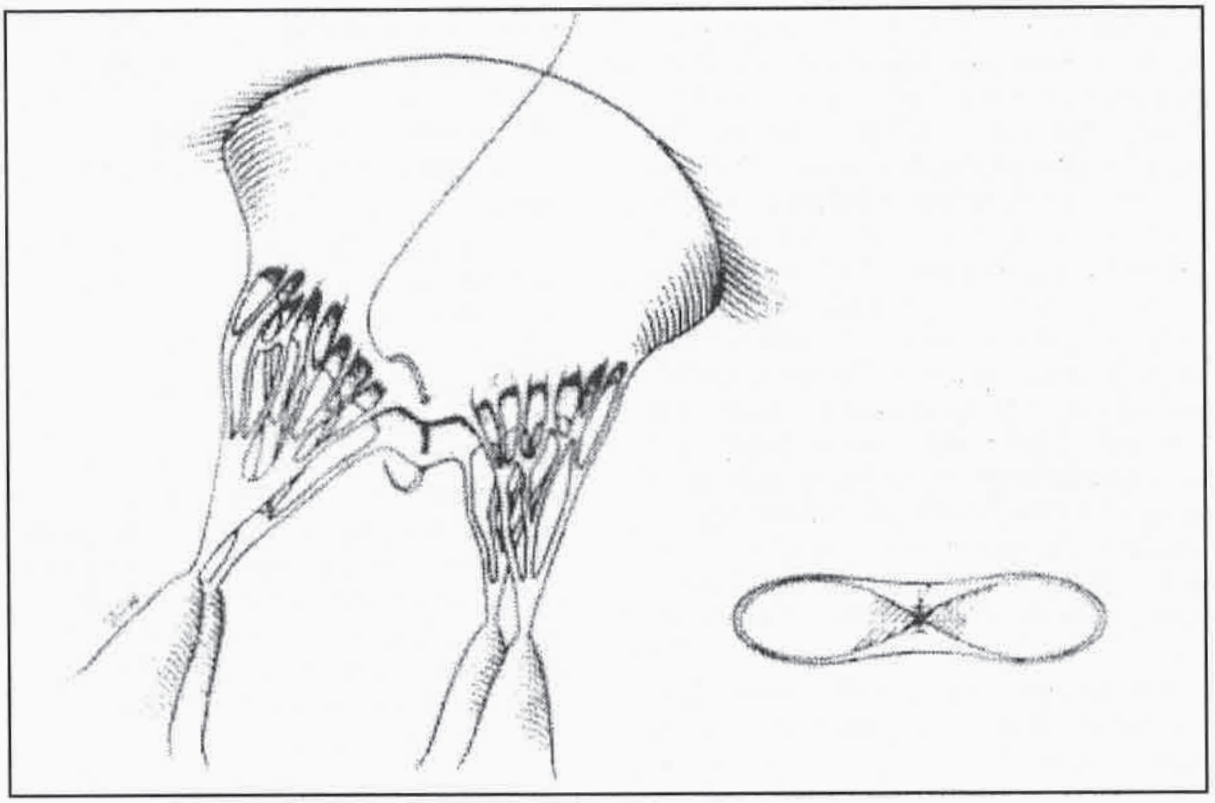

Figure 3. "The Alfieri suture or edge-to-edge repair" for mitral regurgitation

mic cardiomyopathy, there is clear evidence that those with identifiable hibernating myocardium are more likely to demonstrate improvement in LV ejection fraction following CABG than those patients without hibernating myocardium (26). Stategy of selecting patients for surgical revascularization using viability imaging modalities in addition to clinical and angiographic data has been shown to result in fewer complications and lower mortality rates (27). Tests commonly used for documenting that there is viable myocardium in the area of dysfunction are dobutamine echocardiography, 201Thalium isotope studies, and quantitative positron emission tomography (PET) and single photon emission computed tomography (SPECT). Recently, it has been shown that diastolic wall thickness <5 mm on low-dose dobutamine echocardiography was the best simple and single predictor of non- recovery of left ventricular dysfunction (28). With the application of magnetic resonance imaging (MRI) in clinical cardiology an important and exciting diagnostic tool has been added for the prospective identification of viable myocardium for purposes of guiding therapeutic interventions in individual patients (29). In terms of diagnostic accuracy, sensitivity and specificity of dobutamine TEE and dobutamine MRI yielded similar results for the detection of myocardial viability as defined by 18F-fluorodeoxyglucose (FDG) uptake (30) . While cardiac surgeons extend their role in the treatment of ischemic cardiomyopathy, viability testing for hibernating myocardium should lead to improved patient outcome. This information can also be used during performing left ventricular volume reduction surgery or mitral valve reconstruction procedures. We believe that the success of Batista operation in ischaemic cardiomyopathy depends on resecting non-viable myocardial segments.

Left Ventricle Assist to Recovery

Implantable left ventricular assist devices (LVAD) are common as a bridge to transplantation. There are few reports published using left ventricular assist devices as a bridge to recovery

Table-3. Surgical treatment of ischemic mitral regurgitation and cardiomyopathy. Literature review

Author	Operation	Number of patients	Year	Hospital Mortality	Follow-up Survival
Dor V (43)	EVCPP	700	1984-1999	12%	80%
Suma H (44)	EVCPP	54	1997-2000	12.9%	89%
Kay (45)	CABG and Mitral valve replacement	28	1971-1983	15%	55% at 5-years 43% at 10 years
Hendren	CABG and Mitral valve repair	65	1991	9.2%	48% at 5-years (annular dilatation) 96% at 3-years (leaflet prolapse)
Galloway (41	CABG and Mitral valve repair	115	1985-1995	15.7%	57% at 10-years
Cohn (46)	CABG and Mitral valve repair or replacement	150	1984-1994	9.3%	

(31-33). One of the main purposes in using LVAD to assist recovery in patients with heart failure, is to reduce the external work of the left ventricle. In addition (LVAD) support induces changes in myocardial structure. Li et al. demonstrated downregulation matrix metalloproteinases and collagen content after LVAD support (34). Fully portable systems have been in the market that allows selected patients with end-stage cardiomyopathy to undergo outpatient treatment while waiting for heart transplantation (35).

Rhythm Maintanance

Management of ischemic cardiomyopathy has two important targets; 1) Maintanance of better *contraction* with lower myocardial wall stress, 2) *Maintanance of conduction.*

Intraventricular conduction delay and left bundle branch block (LBBB) cause dyssynchronous right ventricular and LV contraction and worsen LV dysfunction in cardiomyopathies. Pacing for patients with severe heart failure without bradyarrhythmia has been proposed as an additi-

on to medical therapy over the past decade (36). *Cardiac resynchronisation* is a therapeutic option in patients with advanced CHF and LBBB. Currently available LV leads can be placed epicardially by thoracotomy or transvenously via the coronary sinus into a cardiac vein. Recent clinical studies in limited numbers of patients suggest remarkable benefit of cardiac resynchronisation in patients with severe CHF symptoms. It has been estimated that approximately 10% of patients with heart failure would benefit from biventricular pacing (37). The high incidence of sudden death among these patients has encouraged ongoing clinical trials to evaluate the benefit of a system that combines biventricular pacing and cardioversion-defibrillation into a single implantable device.

Monitoring Left Ventricular Wall Stress

Left ventricular remodelling in the early and late stages after myocardial infarction are under intense study. Worsening of heart failure is associated with a progressive enlargement of the left ventricle, with increases in end-systolic left ventricular wall stress, alteration of left ventricular geometry from a more ellipsoid to a more spherical shape (38). In ischemic cardiomyopathy, regional variations in myocardial wall stress may be responsible for initiation of physiologic and cellular changes that result in LV remodelling. However regional variations could be a disadvantage for accurate measurements myocardial wall stress.

Currently there are various techniques available for evaluating left ventricular diameters, regional and global wall stress measurements but formulae for global stress cannot be applied to ischemic ventricles (39). LV models can be constructed from rotated orthogonal apical images using echocardiographic imaging (40).Three- dimensional cine magnetic resonance imaging (MRI) is an excellent tool monitoring LV wall stress (41). The end systolic wall stress can be calculated by three methods: Grossman's formula (CR) using the wall thickness and radius of curvature, Janz's formula (CS) using the surfaces, and a three-dimensional approach (C3D) providing a precise calculation of the radius of curvature (42).

Conclusion

Heart failure is an increasing problem because of successful therapies in younger age groups and an overall incidence of ischemic heart disease in the general population. Ischemic cardiomyopathy secondary to myocardial infarction is the most prevalent entity among the several causes for cardiac failure. Among the surgical options for these patients, neither transplantation nor current ventricular assist devices are able to treat a sufficient number of patients. Effective surgical alternative strategies for patients with ischemic cardiomyopathy who are considered to be candidates for cardiac transplantation continue to evolve including mitral valve reconstruction techniques, left ventricle volume reduction operations or combined procedures. Better understanding of physiopathological mechanisms will allow surgeons to produce further treatment options for this increasing problem among the population. Future studies involving viability tests, experimental models of ischaemic cardiomyopathy will contribute to elucidate the complex relationship between LV geometry, remodelling, and myocardial wall stress and to develop therapeutic tools applicable in the clinical setting. Molecular mechanisms of angiogenesis, namely of vascular endothelial growth factor (VEGF) and angiopoietin may have a role in the management strategies in the near future.

REFERENCES

1. Dor V. Reconstructive left ventricular surgery for post-ischemic akinetic dilatation. Semin Thorac Cardiovasc Surg 1997; 9(2):139-145.
2. Burch GE. Ischemic cardiomyopathy. Am Heart J 1973; 86(2):276.
3. Garcia-Rinaldi R, Soltero ER, Carballido J, Mojica J, Gonzalez-Cruz J, Cosme O et al. Left ventricular volume reduction and reconstruction in ischemic cardiomyopathy. J Card Surg 1999; 14(3):199-210.
4. Dor V. Left ventricular restoration by endoventricular circular patch plasty (EVCPP). Z Kardiol 2000; 89 Suppl 7:70-75.
5. Batista RJ, Santos JL, Takeshita N, Bocchino L, Lima PN, Cunha MA. Partial left ventriculectomy to improve left ventricular function in end-stage heart disease. J Card Surg 1996; 11(2):96-97.
6. Qin JX, Shiota T, McCarthy PM, Firstenberg MS, Greenberg NL, Tsujino H et al. Real-time three-dimensional echocardiographic study of left ventricular function after infarct exclusion surgery for ischemic cardiomyopathy. Circulation 2000; 102(19 Suppl 3):III101-III106.
7. Green GR, Moon MR, Deanda A, Jr., Daughters GT, Glasson JR, Miller DC. Effects of partial left ventriculectomy on left ventricular geometry and wall stress in excised porcine hearts. J Heart Valve Dis 1998; 7(5):474-483.
8. Liel-Cohen N, Guerrero JL, Otsuji Y, Handschumacher MD, Rudski LG, Hunziker PR et al. Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: insights from 3-dimensional echocardiography. Circulation 2000; 101(23):2756-2763.
9. Carabello BA. Sudden death in mitral regurgitation: why was I so surprised? J Am Coll Cardiol 1999; 34(7):2086-2087.
10. Carabello BA. The pathophysiology of mitral regurgitation. J Heart Valve Dis 2000; 9(5):600-608.
11. Galloway AC, Grossi EA, Spencer FC, Colvin SB. Operative therapy for mitral insufficiency from coronary artery disease. Semin Thorac Cardiovasc Surg 1995; 7(4):227-232.
12. Hickey MS, Smith LR, Muhlbaier LH, Harrell FE, Jr., Reves JG, Hinohara T et al. Current prognosis of ischemic mitral regurgitation. Implications for future management. Circulation 1988; 78(3 Pt 2):I51-I59.
13. Dion R, Benetis R, Elias B, Guennaoui T, Raphael D, Van Dyck M et al. Mitral valve procedures in ischemic regurgitation. J Heart Valve Dis 1995; 4 Suppl 2:S124-S129.
14. Fasol R, Lakew F, Pfannmuller B, Slepian MJ, Joubert-Hubner E. Papillary muscle repair surgery in ischemic mitral valve patients. Ann Thorac Surg 2000; 70(3):771-776.
15. Gorman JH, III, Gorman RC, Jackson BM, Hiramatsu Y, Gikakis N, Kelley ST et al. Distortions of the mitral valve in acute ischemic mitral regurgitation. Ann Thorac Surg 1997; 64(4):1026-1031.
16. Pinson CW, Cobanoğlu A, Metzdorff MT, Grunkemeier GL, Kay PH, Starr A. Late surgical results for ischemic mitral regurgitation. Role of wall motion score and severity of regurgitation. J Thorac Cardiovasc Surg 1984; 88(5 Pt 1):663-672.
17. David TE. Techniques and results of mitral valve repair for ischemic mitral regurgitation. J Card Surg 1994; 9(2 Suppl):274-277.
18. Glasson JR, Komeda M, Daughters GT, Bolger AF, Karlsson MO, Foppiano LE et al. Early systolic mitral leaflet "loitering" during acute ischemic mitral regurgitation. J Thorac Cardiovasc Surg 1998; 116(2):193-205.
19. Timek T, Glasson JR, Dagum P, Green GR, Nistal JF, Komeda M et al. Ring annuloplasty prevents delayed leaflet coaptation and mitral regurgitation during acute left ventricular ischemia. J Thorac Cardiovasc Surg 2000; 119(4 Pt 1):774-783.

20. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001; 103(13):1759-1764.

21. Ryden T, Bech-Hanssen O, Brandrup-Wognsen G, Nilsson F, Svensson S, Jeppsson A. The importance of grade 2 ischemic mitral regurgitation in coronary artery bypass grafting. Eur J Cardiothorac Surg 2001; 20(2):276-281.

22. Alfieri O, Maisano F. An effective technique to correct anterior mitral leaflet prolapse. J Card Surg 1999; 14(6):468-470.

23. Umana JP, Salehizadeh B, DeRose JJ, Jr., Nahar T, Lotvin A, Homma S et al. "Bow-tie" mitral valve repair: an adjuvant technique for ischemic mitral regurgitation. Ann Thorac Surg 1998; 66(5):1640-1646.

24. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982; 66(6):1146-1149.

25. Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. Circulation 1985; 72(6 Pt 2):V123-V135.

26. Baer FM, Voth E, Deutsch HJ, Schneider CA, Horst M, de Vivie ER et al. Predictive value of low dose dobutamine transesophageal echocardiography and fluorine-18 fluorodeoxyglucose positron emission tomography for recovery of regional left ventricular function after successful revascularization. J Am Coll Cardiol 1996; 28(1):60-69.

27. Haas F, Haehnel CJ, Picker W, Nekolla S, Martinoff S, Meisner H et al. Preoperative positron emission tomographic viability assessment and perioperative and postoperative risk in patients with advanced ischemic heart disease. J Am Coll Cardiol 1997; 30(7):1693-1700.

28. La Canna G, Rahimtoola SH, Visioli O, Giubbini R, Alfieri O, Zognio M et al. Sensitivity, specificity, and predictive accuracies of noninvasive tests, singly and in combination, for diagnosis of hibernating myocardium. Eur Heart J 2000; 21(16):1358-1367.

29. Baer FM, Theissen P, Schneider CA, Kettering K, Voth E, Sechtem U et al. MRI assessment of myocardial viability: comparison with other imaging techniques. Rays 1999; 24(1):96-108.

30. Baer FM, Voth E, LaRosee K, Schneider CA, Theissen P, Deutsch HJ et al. Comparison of dobutamine transesophageal echocardiography and dobutamine magnetic resonance imaging for detection of residual myocardial viability. Am J Cardiol 1996; 78(4):415-419.

31. McCarthy PM, Smedira NO, Vargo RL, Goormastic M, Hobbs RE, Starling RC et al. One hundred patients with the HeartMate left ventricular assist device: evolving concepts and technology. J Thorac Cardiovasc Surg 1998; 115(4):904-912.

32. Pietsch L, Laube H, Baumann G, Konertz W. Recovery from end-stage ischemic cardiomyopathy during long-term LVAD support. Ann Thorac Surg 1998; 66(2):555-557.

33. McCarthy PM, Young JB, Smedira NG, Hobbs RE, Vargo RL, Starling RC. Permanent mechanical circulatory support with an implantable left ventricular assist device. Ann Thorac Surg 1997; 63(5):1458-1461.

34. Li YY, Feng Y, McTiernan CF, Pei W, Moravec CS, Wang P et al. Downregulation of matrix metalloproteinases and reduction in collagen damage in the failing human heart after support with left ventricular assist devices. Circulation 2001; 104(10):1147-1152.

35. Myers TJ, Dasse KA, Macris MP, Poirier VL, Cloy MJ, Frazier OH. Use of a left ventricular assist device in an outpatient setting. ASAIO J 1994; 40(3):M471-M475.

36. Varma C, Camm AJ. Pacing for heart failure. Lancet 2001; 357(9264):1277-1283.

37. Farwell D, Patel NR, Hall A, Ralph S, Sulke AN. How many people with heart failure are appropriate for biventricular resynchronization? Eur Heart J 2000; 21(15):1246-1250.

38. Florea VG, Mareyev VY, Samko AN, Orlova IA, Coats AJ, Belenkov YN. Left ventricular remodelling: common process in patients with different primary myocardial disorders. Int J Cardiol 1999; 68(3):281-287.

39. Ginzton LE, Rodrigues D, Shapiro SM, Laks MM, Conant R, Lobodzinski SM. Estimation of regional end-systolic wall stress during exercise in coronary artery disease. Am Heart J 1996; 132(4):733-746.

40. Solomon SD, Aikawa Y, Martini MS, Rosario L, Makker G, Gerson D et al. Assessment of regional left ventricular wall stress after myocardial infarction by echocardiography-based structural analysis. J Am Soc Echocardiogr 1998; 11(10):938-947.

41. Balzer P, Furber A, Delepine S, Rouleau F, Lethimonnier F, Morel O et al. Regional assessment of wall curvature and wall stress in left ventricle with magnetic resonance imaging. Am J Physiol 1999; 277(3 Pt 2):H901-H910.

42. Delepine S, Furber A, Balzer P, Rouleau F, Lethimonnier F, Le Jeune JJ et al. [MRI quantification of regional variations of left ventricular parietal stress in normal subjects]. Arch Mal Coeur Vaiss 1999; 92(9):1189-1196.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 3, 2001 313-318

ENDOMETRIOSIS AND ADHESION MOLECULES

Cem S. Atabekoğlu* ❖ Yaprak Engin** ❖ Yusuf Üstün** ❖ Ruşen Aytaç***

SUMMARY

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity. Endometriosis is one of the most commonly encountered diseases in reproductive-age female. The precise etiology of the disease remains poorly understood. The mechanism of adherence of endometrial cells to the peritoneal lining is still unknown. Cell adhesion molecules are found to be expressed in endometriotic lesions and in cells and tissues that are potentially involved in the development of endometriosis. This paper reviews the role and importance of cellular adhesion molecules.

Key Words: Endometriosis, Adhesion Molecules.

ÖZET

Endometriozis ve Adhezyon Molekülleri

Endometriozis, endometrial bezlerin ve stromanın uterus dışında ektopik olarak yerleşmesidir. Endometriozis üreme çağındaki kadınlarda en sık karşılaşılan jinekolojik problemlerden biridir. Etiolojisi hala tam olarak bilinmemektedir. Endometrial hücrelerin peritona tutunma mekanizması hala açığa kavuşturulamamıştır. Ancak hücre adhezyon moleküllerinin, endometriotik odaklarda ve endometriozis gelişiminde rol alan dokularda arttığı tespit edilmiştir. Bu makale hücre adhezyon moleküllerinin endometriozis etiolojisindeki rollerini ve önemini anlatmaktadır.

Anahtar Kelimeler: Endometriozis, Adhezyon Molekülleri.

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity and the precise etiology and pathophysiology of the disease remain poorly understood. The most widely accepted theory is retrograde menstruation, introduced by Sampson in 1927. According to Sampson's theory, fragments of endometrium are refluxed through the fallopian tubes into the peritoneal cavity, then attach and grow on peritoneal surfaces. It has been observed that shedded menstrual endometrium is viable and that blood and viable endometrial cells are present in peritoneal fluid. These findings, together with the clinical observation of a high prevalence of endometriosis in adolescent girls with congenital menstrual outflow obstruction[1], support Sampson's implantation theory.

The mechanism of adherence of endometrial cells to the peritoneal lining is still unknown. It is not clear whether endometrial stroma or epithelium can attach to the peritoneum[1] or the mesothelial lining acts as a defensive barrier which

* Ankara University Faculty of Medicine, Gynecology and Obstetrics Department, Doctor.

** Ankara University Faculty of Medicine, Gynecology and Obstetrics Department, Research Resident

*** Ankara University Faculty of Medicine, Gynecology and Obstetrics Department, Associate Professor

Received: June 28,2001 Accepted: Nov 05,2001

prevents the adhesion of ectopic tissues.[2,3] Koks et al support the contention that ectopic cells adhere preferentially to subepithelial structures suggesting that exposition of peritoneal subepithelial structures due to damaging challenges would increase the risk of developing endometriosis in all women with patent Fallopian tubes, rather than the mere presence of retrogradely shed endometrial cells. [4] In Witz's study, explants of human peritoneum from the anterior abdominal wall and the posterior surface of the uterus were cultured with whole fragments of mechanically dispersed endometrium. Adhesion of endometrial fragments to the surface of peritoneum was evaluated. Immunohistochemical staining of mesothelium with antibodies to cytokeratin was used to ensure an intact layer of mesothelium beneath the endometrial implants. Approximately 10% of the endometrial implants had intact mesothelium at the site of attachment. Endometrial stromal cells, and not epithelium, attached to the mesothelium.[2] Nissole et al revealed that cultured endometrial implants could adhere to intact peritoneum without peritoneal damage. According to Nissole et al, primary role in this adhesion process was own to stromal cells and damaged mesothelium was unneccessary.[5]

Cell adhesion molecules, such as cadherins and integrins, could be involved functionally in the shedding of endometrium during menses and in the adhesion of endometrial cells to the peritoneum. Cell adhesion molecules are expressed in endometriotic lesions and in cells and tissues that are potentially involved in the development of endometriosis. [6] Cellular adhesion molecules (CAM) found on cell membranes, are protein molecules that provide cell-cell and cell-extracellular matrix interactions. They act via their receptors. Cadherins belong to a group of calcium dependent transmembrane glycoproteins that mediate adhesion between cells that express the same cadherin.[7] Cadherins are responsible for cytoskeletal organization. Three types of cadherins have been described: E-(epithelial), N-(neural), P-(placental). E-cadherin is expressed in all proliferating epithelial cells derived from the ectoderm and the endoderm. E-cadherin has an important role in forming adhesions between epithelial cells.[8] Two cells carrying E-cadherin on cell surfaces adhere to each other.[9] E- and P-cadherin expression has been demonstrated in the cell-to-cell boundaries of the endometrium during the early follicular phase of the cycle in human endometrium samples.[10]

Integrins are a class of adhesion molecules that participate in cell-to-cell and cell-to-substratum interactions and are present on essentially all human cells. In recent years, the mechanisms surrounding the interactions of cells with the components of extracellular matrix proteins became clearer with the isolation and characterization of cell surface receptors for extracellular matrix components.[11,12] Integrins are integral membrane glycoproteins that anchor extracellular adhesion proteins to cytoskeletal components.[3,12] Integrins are heterodimers composed of different β subunits and a common β subunit and include cell surface receptors for fibronectin, collagen, and laminin (Table).[3,4,12] In general, integrins in the β1 and β3 subfamilies have been found to mediate cell adhesion to extracellular matrix components including fibronectin, collagen, and laminin, whereas members of the β2 subfamily are mostly involved in cell-to-cell adhesion.[3,11]

Table : Functions of integrins

Integrin	Function
α1, α2, α3	Collagen-laminin receptor
α6	Laminin receptor
α4, α5, β3	Fibronectin-fibrinogen receptor
β4	Cell adhesion to laminin
β1	Fibronectin receptor

A wide component of integrin expression has been demonstrated on normal endometria throughout the menstrual cycle, and this varied distribution emphasizes their varied roles in the mechanisms of cell-cell and cell-substrate interactions. The integrins that serve as collagen-laminin receptors are widely distributed within the endometrium whilst α6, the laminin receptors, and β4, the cell adhesion to laminin molecule, have a

more localized distribution on the basal aspects of surface epithelium and endometrial glands in keeping with its localization to hemidesmosomes.[13] The distribution of expression of the integrins that mediate fibrinogen-fibronectin binding was more limited. Only vascular mesenchymal tissue was found to express α4, and staining for β3 and α5 was not demonstrated on any endometrial glands and was sparse in the other endometrial tissue components. Although the integrin α5β1 has been described as the classical fibronectin receptor, this lack of expression has been reported in other normal tissues.[14] Bridges et al described the expression of a number of integrins in synchronously sampled endometria and endometriosis and have shown no major differences between the two. The similarity further strengthens the hypothesis that the endometrium is the progenitor of endometriosis.[15] Laminin and fibronectin are known to play a key role in normal and tumoral cell adhesion. They promote interaction between the epithelial cells and the extracellular matrix and provide preferred substrates for adhesion and migration. Immunohistochemical study demonstrates the presence of laminin in the basement membrane of endometrium and endometriotic lesions and fibronectin in the stromal cells of these tissues. Like Bridges et al, Beliard et al found no qualitative difference in the expression of the adhesive glycoproteins, laminin and fibronectin and the collagen-laminin receptors of the integrin family between endometrium and endometriosis.[14] The study of Hii et al showed a significant increase in the percentage of vessels expressing αvβ3 in the endometrium of women with endometriosis compared with controls. This difference was more pronounced in the secretory phase than the proliferative phase. The results of this study provide evidence for increased endometrial angiogenesis in women with endometriosis compared with controls, and suggest that glandular expression of αvβ3 is not related to uterine receptivity per se.[16]

At the initial step of endometriosis, adhesion of endometrial cells to the extracellular matrix is an important process. Monocyte chemotactic protein-I (MCP-I), a potent chemotactic factor produced in many cell types, is elevated in the peritoneal fluid of women with endometriosis. Garcia-Velasco et al stated cell adhesion to extracellular matrix was an important event that led to stimulation of MCP-I expression, and this process was told to be mediated by integrins.[17] Findings of Lessey et al confirm the patterns of endometrial integrins and they suggest important roles for integrins in the process of implantation and decidualization. Aberrant integrin expression in the native endometrium is associated with the finding of endometriosis and may identify some women with decreased cycle fecundity due to defects in uterine receptivity.[18]

Although the precise function of endometrial tenascin is unknown, like other components of extracellular matrix, its function is mediated through integrin receptor. Harrington et al revealed elevation of tenascin expression in the stroma of the functional region of the endometrium during the proliferative stage of the menstrual cycle and in endometriosis. They also found tenascin expression in endometriosis not to be modulated according to the stage of the menstrual cycle. It was concluded that expression of tenascin was strictly regulated in endometrium and might be important in endometrial regeneration and in the pathogenesis of endometriosis.[19]

Cultured human endometrial stromal cells express and shed intercellular adhesion molecule-I (ICAM-I) from their surface suggesting that they can be a source of ICAM-I in vivo.[20] Intercellular adhesion molecules (ICAM-1, ICAM-2, ICAM-3 (CD50), are membrane bound molecules belonging to the immunoglobulin supergene family that are involved in immunological reactions. Placido et al stated that serum ICAM-I concentrations were higher in patients with endometriosis stage I-II, or with nonpigmented peritoneal lesions and accepted their serum concentrations as additional markers for the early detection of recurrence of the disease during the monitoring of treatment outcome.[21] Fukaya et al found that the levels of ICAM-I in patients with endometriosis were significantly higher than those in patients without endometriosis and stated that the increased levels of ICAM-I might impair natural killer

activity and accelerate the progression of the disease.[22]

Although several mechanisms have been proposed to explain the pathogenesis of endometriosis, a definitive theory on the overall process has yet to be established. But this review reveals adhesion molecules may play important roles in the initiation and regulation of endometriotic lesions and may contribute to the pathogenesis of endometriosis.

REFERENCES:

1- Bartosik D, Jacops S, Kelly L. Endometrial tissue in peritoneal fluid. Fertil Streril 1986; 46:796-800.

2- Witz CA, Monotoya-Rodriguez IA, Schenken RS. Whole explants of peritoneum and endometrium: a novel model of the early endometriosis lesion. Fertil Steril 1999;71:56-60.

3- Groothuis PG, Koks CA, de Goeij AF, Dunselman GA, Arend SJW, Evers JL. Adhesion of human endometrium to the epithelial lining and extracellular matrix of amnion in vitro; an electron microscopic study. Human Reprod 1998; 13:2275-81.

4- Koks CA, Groothuis PG, Dunselman GA, de Goeij AF, Evers JL. Adhesion of shed menstrual tissue in an in vitro model using amnion and peritoneum: light electronic microscopic study. Human Reprod 1999;14:816-22.

5- Nissolle M, Casanas-roux F, Marbaix E, Jadoul P, Donnez J. Transplantation of cultured explants of human endometrium into nude mice. Human Reprod 2000;15:101-6.

6- Van der Linden PJ, de Goeij AF, Dunselman GA, van der Linden EP, Ramaekers FC, Evers JL, Expression of integrins and E-cadherin in cells from menstrual effluent, endometrium, peritoneal fluid, peritoneum, and endometriosis. Fertil Steril 1994;61:85-90.

7- Takeichi M. Cadherin cell adhesion receptors as a morphogenetic regulator. Science 1991;251:1451-5.

8- Shiozaki H, Oka H, Inoue M, Tamura S, Monden M. E-cadherin mediated adhesion system in cancer cells. Cancer 1996;77:1605-13.

9- Shapiro L, Fannon AM, Kwong PD, Thompson A, Lehmamn MS, Grubel G. Structural basis of cell-cell adhesion by cadherins. Nature 1995; 374:327-37.

10- Wijnhoven BPL, Dinjens WN, Pignatelli M. E-cadherin-catenin cell-cell adhesion complex and human cancer. British J Surgery. 2000;87:992-1005.

11- Ruoslahti E, Pierschbacher MD. New perspective in cell adhesion: RGD and integrins. Science 1987;238:491-7.

12- Hemler ME. VLA proteins in the integrin family: structures, functions, and their role on leukocytes. Annu Rev Immunol 1990;8:365-400.

13- Faber M, Wewer UM, Berthelsen JG, Liotta LA, Albrechtsen R. Laminin production by human endometrial stromal cells to the cyclic and pathologic state of the endometrium. Am J Pathol 1986:124:384-98.

14- Beliard A, Donnez J, Nisolle M, Foidart JM. Localization of laminin, fibronectin, E-cadherin, and integrins in endometrium and endometriosis. Fertil Steril 1997;67:266-72.

15- Bridges JE, Roche W, Englefield P, Thomas EJ. Expression of integrin adhesion molecules in endometrium and endometriosis. Br J Obstet Gynecol 1994; 101: 696-700.

16- Hii LLP, Rogers PAW. Endometrial vascular and glandular expression of integrin avb3 in woman with and without endometriosis. Human Reprod 1998;13:1030-5.

17- Garcia-Velasco JA, Seli E, Arici A. Regulation of monocyte chemotactic protein-1 expression in human endometrial stromal Cells by integrin-dependent cell adhesion. Biology of Reproduction 1999;61:548-52.

18- Lessey BA, Castelbaum AJ, Buck CA, Lei Y, Yowel CW, Sun J. Further characterization of endometrial integrins during the menstrual cycle and in pregnancy. Fertil Steril 1994;62:497-506.

19- Harrington DJ, Lessey BA, Rai V, Bergovist A, Kennedy S, Manek S, Barlow DH, Maron HJ. Tenascin is differentially expressed in endometrium and endometriosis. J Pathol 1999;187:242-248.

20- Somigliana E, Vigano P, Gaffuri B. Human endometrial stromal cells as a source of soluble intercellular adhesion molecule (ICAM)-1 molecules. Human Reprod 1996;11;1190-4.

21- Placido GD, Alviggi C, Palma GD, Carravetta C, Matarese G, Landino G, and Racioppi L. Serum concentrations of soluble human leukocyte class I antigens and of the soluble intercellular adhesion molecule-1 in endometriosis: relationship with stage and non-pigmented peritoneal lesions. Human Reprod 1998;13:3206-210.

22- Fukaya T, Sugawara J, Yoshida H, Murakami T, Yajima A. Intercellular adhesion molecule-1 and hepatocyte growth factor in human endometriosis: original investigation and a review of literature. Gynecol Obstet Invest 1999;47:11-6.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 3, 2001 319-324

CUTANEOUS SINUS TRACT OF DENTAL ORIGIN: A CASE REPORT

A. Tülin Güleç* ❖ Deniz Seçkin* ❖ Şule Bulut** ❖ Evren Sarıfakıoğlu*

SUMMARY

Although the most common cause of chronic draining sinus tracts of the face and neck area is an odontogenic infection, these lesions continue to be diagnostic dilemma. They are frequently misdiagnosed by physicians and dentists, causing improper or insufficient therapeutic interventions. A detailed dental examination including roentgenographic surveys of the teeth is the first step that leads to the correct diagnosis. Non-surgical endodontic therapy is recommended as the treatment of choice. We report a case of cutaneous odontogenic sinus tract to the chin and review the current literature.

Key Words: Cutaneous, Sinus Tract, Odontogenic

ÖZET

Dental Kökenli Kütanöz Sinüs Oluşumu: Olgu Sunumu

Yüz ve ense bölgesinde kronik drenaja yol açan sinüslerin en sık görülme nedeni odontojenik enfeksiyonlar olmasına rağmen, bu lezyonlar halen tanı güçlüğüne yol açabilmektedir.Tıp ve diş doktorları tarafından yanlış tanı konması uygunsuz ya da yetersiz tedavi girişimlerine neden olmaktadır. Doğru tanıya ulaşabilmek dişlerin radyografik incelemesini de içerecek detaylı bir diş muayenesi ile mümkündür. Cerrahi olmayan endodontik yaklaşım tedavi için en sık önerilen yöntemdir. Burada, çenede ortaya çıkan bir kutanöz sinus olgusu sunulmakta ve bu konudaki literatür bilgileri gözden geçirilmektedir.

Anahtar Kelimeler: Deri, Sinus Traktusu, Odontojenik

Cutaneous odontogenic sinuses are erythematous, nontender, intermittently draining nodular lesions located on the face and neck. They are the most common cause of chronic sinus tracts of this area. Nevertheless, they are frequently misdiagnosed as the possibility of an odontogenic infection is not recognized or neglected. Ultimately, improper therapy results in recurrence, persistence or progression of the lesion causing a significant morbidity. Conservative nonsurgical root canal therapy sometimes complimented by surgery, or extraction of the offending teeth are the choices for the treatment.

CASE REPORT

A 47-year-old woman presented with a nodular lesion on her face that had been discharging pus intermittently for 7 months. She could not recall any previous trauma to the site. Dermatologic examination revealed a non-tender, erythematous, nodular, draining lesion on the patient's chin (Fig. 1). Dental examination showed poor oral hygiene and severe chronic periodontitis, but no acute infection. Radiography demonstrated diffuse periapical radiolucency associated with the right central mandibular incisor (Fig. 2). The

Başkent University Faculty of Medicine, Departments of Dermatology* and Periodontology** Ankara, Turkey

Received: Feb 19,2001 Accepted: March 12,2001

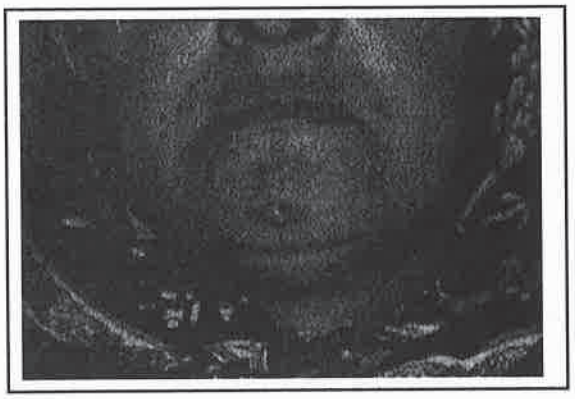

Figure 1. A cutaneous draining sinus of dental origin presented as an erythematous nodule on the patient's chin.

patient was diagnosed with chronic apical periodontitis. Since it was too late for her oral condition to be corrected with endodontic treatment, the tooth was extracted and the scar on her chin was revised later.

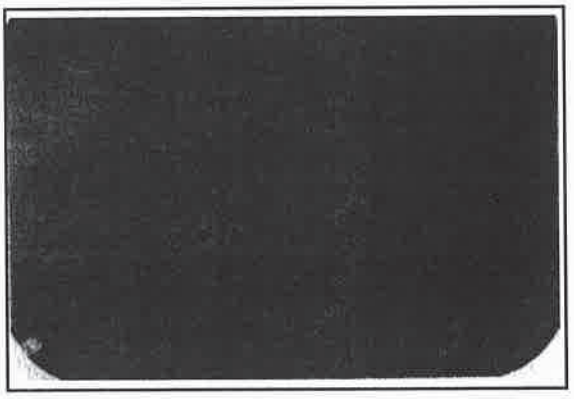

Figure 2. A periapical radiograph demonstrating periapical radiolucency surrounding the lower right central incisor (tooth No. 25).

DISCUSSION

Our patient was promptly and correctly diagnosed with cutaneous sinus tract of dental origin when she presented for the first time after suffering from the disease for 7 months. Many patients with this condition are not as fortunate. Approximately half of them undergo multiple surgical interventions and/or biopsies,[1-5] are given repeated courses of antibiotics,[1-3,5,6] and are even subjected to radiation therapy[6] or electrodesiccation[4] before the correct diagnosis is made and appropriate therapy is prescribed.

Periapical dental abscess due to a carious tooth is the main cause of odontogenic sinus tract formation.[1,3,7-10] Pulpal degeneration due to trauma or periodontal infection are the other etiologic factors.[1] Chronic dental infection penetrates the alveolar bone and spreads along the path of least resistance. Eventually, the infection moves into the surrounding soft tissue and forms a path for drainage.[1,3,7-10] The site of extraoral drainage depends on which tooth is diseased. Most cutaneous sinus tracts are associated with the anterior mandibular teeth, and these tracts arise in the chin or submental area.[7,8,10,11] The typical extraoral cutaneous drainage areas associated with the involved teeth are listed in Table 1.

Diagnosing cutaneous odontogenic sinuses can be challenging. Patients are often unaware that they have any dental problems,[8] and the associated cutaneous lesion may appear early, or up to 30 years after a primary dental problem occurs. Also, the cutaneous lesion is often distant from the site of primary infection.[9] Chronic purulent drainage through the sinus tract prevents pressure buildup, and the swelling and pain typically associated with this;[7] thus, most patients are asymptomatic. In addition, unsuspecting physicians often tend to overlook the possibility that a dental infection may produce a draining sinus tract. Illustrating the difficulty that can be encountered, a literature review revealed one case of cutaneous odontogenic sinus tract in which the correct diagnosis was made 32 years after the discharging lesion was first observed.[12]

Recognition of the cutaneous lesion as a sinus tract is the first important diagnostic step. Palpation of the involved area for a cord-like tract, and "milking" this tract for purulent material can be helpful.[10] After a detailed dental examination has been completed, including vitality tests, the patient should undergo panoramic and periapical radiographic examination. If needed, sinograms may provide further radiologic evidence.[1,8,9]

The differential diagnosis for this condition includes infectious disease, congenital fistulae, and various neoplastic diseases (Table 2).[1-13] Appropriate therapy for the dental pathology le-

ads to resolution of the skin lesion. Non-surgical endodontic treatment or surgical root canal therapy are the best options if the tooth can be restored. If this is not possible, extraction of the offending tooth is indicated.[1,5-11] Systemic antibiotic therapy is neither necessary nor recommended, as this will halt the drainage only temporarily. Local excision of the lesion will not stop the drainage either, and may cause tissue breakdown that results in further facial deformity; therefore, this should also be avoided.[2,7] When appropriate dental therapy is applied, the drainage will cease and the sinus tract will spontaneously close down within a few weeks. A residual fibrous tract and mild dimpling or umbilication of the skin usually remains. Surgical revision for esthetic reasons may be performed if the patient desires.

Table 1 Typical sites of extraoral drainage resulting from dental infection

Site of dental origin		Site of cutaneous drainage
1. Maxillary		
A. Molars and premolars	→	Cheek
B. Incisors and canines	→	Nasolabial fold
		Nose
		Upper lip
		Infraorbital region
2. Mandibular		
A. Molars and premolars	→	Submandibular region
		Neck
B. Incisors and cuspids	→	Chin
		Submental region

Table 2 The list of differential diagnoses for cutaneous odontogenic sinuses

Infectious Diseases	**Neoplasia**
Actinomycosis	Basal cell carcinoma
Atypical mycobacteria	Squamous cell carcinoma
Dacryocystitis	Metastatic tumor
Deep mycoses	
Furuncle	**Others**
Infected cyst (epidermal, pilar, dermoid)	Foreign-body implantation
Mycobacterium infection	Osteoradionecrosis
Leishmaniasis	Pyogenic granuloma
Osteomyelitis	Trauma
Suppurative lymphadenitis	
Syphilis (gumma, osteitis)	
Congenital Fistulae	
Branchial cleft cyst	
Parotid gland fistulae	
Preauricular sinus	
Salivary gland and duct fistulae	
Thyroglossal duct cyst	

REFERENCES

1. Kaban L. Draining skin lesions of dental origin: the path of spread of chronic odontogenic infection. *Plast Recons Surg* 1980; 66: 711-717.
2. Lewin-Epstein J, Taicher S, Azaz B. Cutaneous sinus tracts of dental origin. *Arch Dermatol* 1978; 114: 1158-1161.
3. Karp MP, Bernat JE, Cooney DR, Jeweet TC Jr. Dental disease masquerading as suppurative lesions of the neck. *J Pediatr Surg* 1982; 17: 532-536.
4. Bart RS, Kopf AN. A dental sinus appearing as atypical epithelial hyperplasia that suggested a squamous-cell carcinoma. *J Dermatol Surg Oncol* 1981; 7: 208-209.
5. Çalışkan MK, Şen BH, Özinel MA. Treatment of extraoral sinus tracts from traumatized teeth with apical periodontitis. *Endod Dent Traumatol* 1995; 11: 115-120.
6. Gorsky M, Kaffe I, Tamse A. A draining sinus tract of the chin. *Oral Surg* 1978; 46: 583-587.
7. McWalter GM, Alexander JB, del Rio CE, Knott JW. Cutaneous sinus tracts of dental etiology. *Oral Surg Oral Med Oral Pathol* 1988; 66: 608-614.
8. Cioffi GA, Terezhalmy GT, Parlette HL. Cutaneous draining sinus tract. *J Am Acad Dermatol* 1986; 14: 94-100.
9. Held JL, Yunakov MJ, Barber RJ, Grossman ME. Cutaneous sinus of dental origin: A diagnosis requiring clinical and radiologic correlation. *Cutis* 1989; 43: 22-24.
10. Cohen PR, Eliezri YD. Cutaneous odontogenic sinus simulating a basal cell carcinoma: case report and literature review. *Plast Recons Surg* 1990; 86: 123-127.
11. Tidwell E, Jenkins JD, Ellis CD, *et al.* Cutaneous odontogenic sinus tract to the chin: a case report. *Int Endo J* 1997; 30: 352-355.
12. Bernick SM, Jensen JR. Chronic draining extraoral fistula of 32 years' duration. *Oral Surg* 1969; 27: 790.
13. Perry TL. Dental sinus of dermal origin. *Arch Derm* 1972; 106: 420-421.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 325-328

FRESH THROMBUS OF THE EXTRACRANIAL INTERNAL CAROTID ARTERY

Ağahan Ünlü* ❖ Hasan Çağlar Uğur** ❖ Mehmet Arslan** ❖ Nihat Egemen***

SUMMARY

A 40 year-old patient with a history of fluctuating hemiparesis of acute onset a month before she was admitted to our clinic. A diagnosis of fresh thrombus of the extracranial internal carotid artery was confirmed through digital subtraction angiography. No other clinical manifestations were observed in general examinations. Since fresh thrombus of extracranial internal carotid artery is not frequent, we decided to present this case and briefly reviewed the literature on this subject.

Key Words: Carotid Artery, Thrombosis, Surgery

ÖZET

Ekstrakraniyal Karotis Arterin Taze Trombusu

40 yaşındaki hasta kliniğimize 1 ay once başlayan hemiparezi atağı nedeniyle başvurdu. Yapılan serebral anjiografi ile internal karotisin ekstrakraniyal kısmındaki taze trombus teşhis edilmiştir. Muayenesinde herhangi bir bulgu saptanmamıştır. İnternal karotisin ekstrakraniyal kısmındaki taze trombusun oldukça nadir görülmesi nedeni ile vaka takdim edilmiş ve bu konudaki literatür kısaca tartışılmıştır.

Anahtar Kelimeler: Karotis Arter, Tromboz, Cerrahi

Intraluminal thrombus in the cervical segment of the internal carotid artery is seen most often in association with atherosclerotic stenosis at cervical internal carotid artery (1, 2, 3). However, fresh thrombus of cervical internal carotid artery without atherosclerosis or with a very thin layer of atherosclerosis is extremely rare (2, 3, 4, 5). The angiographic appearance of the lesion has been well described; thrombus is most commonly seen as an elongated, smooth filling defect within the contrast medium-filled vessel. The lesion may then act as a source of emboli, leading to intracranial branch occlusion, or progress locally to complete occlusion of the internal carotid artery which can cause more severe sequelae. The optimal treatment of this situation is debatable. Both surgical and medical treatments deserve further investigation (2, 4, 5).

CASE REPORT

A 40-year-old woman was admitted to our clinic with a 3-day fluctuating history of right hemiparesis which recovered spontaneously a month before admission. There was no history of transient ischemic attacks or known medical illness. On physical examination no carotid bruit was detected. Neurological examination was intact. Routine laboratory studies and cardiac investiga-

* MD., Instructor, Ankara University, School of Medicine, Department of Neurosurgery, Ankara, Turkey
** MD., Resident, Ankara University, School of Medicine, Department of Neurosurgery, Ankara, Turkey
**** M.D., Professor, Ankara University, School of Medicine, Department of Neurosurgery, Ankara, Turkey

Received: Sept 15,2000 Accepted: Feb 08,2001

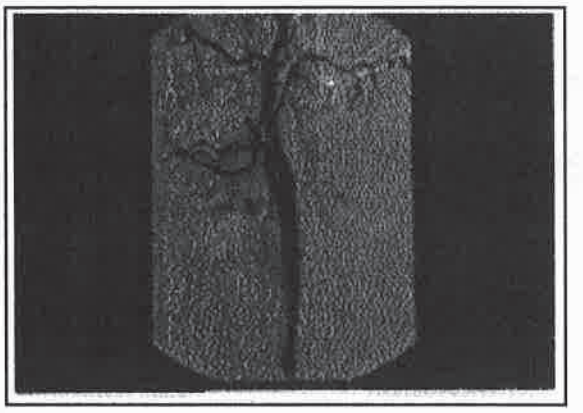

Fig 1: DSA appearance of the filling defect in internal carotid artery

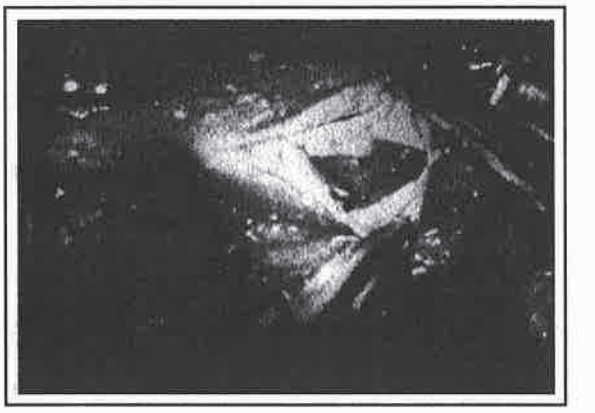

Fig 2: The peroperative apperance of the fresh trombus in internal carotid artery

tions were normal. Computerized tomography demonstrated an infarct of the left parietal region and caudat nucleus. Carotid doppler ultrasonography and digital subtraction angiography revealed a 10x15 mm intraluminal filling defect (thrombus) without significant stenosis. Emergency left carotid endarterectomy for thrombus removal was carried out to prevent fragmentation or distal propagation. In operative observation the thrombus appeared fresh with only a very thin atherosclerotic plaque. The patient has an uneventful postoperative course.

DISCUSION

Carotid circulation thrombus is an uncommon angiographic finding and is rare without associated atheroma (1, 4). The clinical significance of intraluminal thrombus within the cerebral vessels relates to the known propensity for distal embolization and progression to complete vessel occlusion (3, 5). The thrombus is usually elongated, cylindirical, or oblong and may be irregular or ball-like. Intraluminal carotid thrombus may also be associated with the so-called string sign of near occlusion, in which a nonadherent, tailing thrombus may extend up the internal carotid artery distal to a severe proximal stenosis. The actual frequency of clot identification is not high. Roberson et al. report only seven cases in 1.000 angiograms obtained for cerebrovascular atherosclerosis. Pessin et al. report seven cases in 570 angiographic studies performed for ischemic cerebrovascular disease. However, four of seven patients had severe associated carotid stenosis. The remaining three had no significant atheroma. Of all our studies, in only more than 500 angiographic studies performed for cerebrovascular disease 1 carotid thrombus was detected without significant atheroma plaque (1, 4, 5). The course of the thrombus formation is not known. A coagulopathy, although unproven, may be the best explanation despite the absence of recognized conditions such as polycythemia vera, thrombocythemia, collagen-vascular disease, estrogen treatment, hyperviscosity, and pregnancy. None of these conditions were detected in our patient. The most suitable treatment for intraluminal carotid thrombi remains a much debated question. Some authors have reported a lower morbidity in patients treated with anticoagulant or antiplatelet therapy, while some prefer anticoagulant therapy and delayed surgery if there are major underlying lesions (2, 3). Some authors, however, prefer emergency surgery (5). In our very limited experience we think when a fresh thrombosis is detected, emergency surgery should be performed, and it must be emphasized that extreme care should be taken during operation because of the propensity for distal embolization.

REFERENCES

1. Caplan L, Stein R, Patel D, Amico L, Cashman N, Gewertz B. Intraluminal clot of the carotid artery detected radiographically. Neurology 1984; 34: 1175-1181.
2. Combe J, Poinsard P, Besancenot J, Cattin F, Bonneville JF, Camelot G. Intraluminal thrombosis of the cervical internal carotid artery. Helv Chir Acta 1990; 57(2): 219-221. (Abstract)
3. Combe J, Poinsard P, Besancenot J, Cattin F, Bonneville JF, Moulin T, Henlin JL, Chopard JL, Cotte L. Free-floating thrombus of the extracranial internal carotid artery. Ann Vasc Surgery 4: 558-562.
4. Pelz DM, Buchan A, Fox AJ, Barnett HJM, Vinuela F. Intraluminal thrombus of the internal carotid arteries: Angiographic demonstration of resolution with anticoagulant therapy alone. Radiology 1986; 160: 369-373.
5. Pessin MS, Abbott BP, Pragger RJ, Batson RA, Scott RM. Clinical and angiographic features of carotid circulation thrombus. Neurology 1986; 36: 518-523.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 23, No 4, 2001 329-334

THE SPLIT NOTOCORD SYNDROME WITH MENINGOCELE AND DIASTEMATOMYELIA

Mehmet Erkan Üstün* ❖ Adnan Köroğlu* ❖ Aydan Canbilen ❖ Mustafa Cihat Avunduk*** ❖ Önder Güney* ❖ Olcay Eser* ❖ Abdullah Konuk***

SUMMARY

Split notochord syndrome of the lumbosacral spine associated with diastematomyelia, meningocele is an extremely rare congenital anomaly. This is the fifth case with no dorsal enteric opening in the literature. In this study the occurrence of such a lesion whose embryological development has not been understood yet, is discussed under the sight of the literature..

Key Words: Diastematomyelia, Lumbosacral Spine, Magnetic Resonance, Meningocele, Split Notochord.

ÖZET

Meningiyosel ve Diastematomiyelisi olan bir Split Notocord Sendromu Vakası

Meningosel ve diastomatomiyeli ile birlikte olan lumbosakral vertebra yerleşimli, split notokord sendromu oldukça ender görülen konjenital bir anomalidir. Bu olgu literatürde dorsal enterik açıklığı olmayan beşinci olgudur. Embriyolojik gelişimi henüz tam olarak anlaşılamayan bu tür olgular literatürlerin eşliğinde tartışıldı.

Anahtar Kelimeler: Diastematomiyeli, Lumbosakral Vertebra, Manyetik Rezonans, Meningosel, Split Notokord

The split notochord syndrome is a complete cleft of the vertebral column associated with severe malformations of the central nervous system and gastrointestinal tract. In 1960 Bentley and Smith (1) suggested that a primary split of the notochord leads to a dorsal herniation of the endoderm through the split (2 - 7). The neural plate responds with a similar split, creating a diastematomyelia. A majority of these cases involve the cervico-thoracic region. Lumbosacral involvement is considerably less common. Often such defects are associated with meningocele or meningomyelocele and genitourinary abnormalities (2,3,8). Nine cases have been observed toba associated with meningocele or meningomyelocele (2,3,4,7,9,10), out of the 19 human cases that involve lumbosacral region. We present a split notochord syndrome of the lumbosacral spine with diastematomyelia associated with

*Department of Neurosurgery, Faculty of Medicine. Selçuk Üniversity, Konya,Turkey

**Department of Histology & Embryology, Faculty of Medicine, Selçuk Üniversity, Konya,Turkey

***Department of Pathology, Faculty of Medicine. Selçuk Üniversity, Konya,Turkey

Received: Feb 04,2000 Accepted: April 09,2001

meningocele.

CASE REPORT

A 2-day-old, male new-born, weighing 3.0 kg was admitted to our service. He was born at full term by normal delivery. Pregnancy and family history were unremarkable; specifically, there was no history of a teratogenic exposure or consanguinity.

On examination, the baby was irritable with an initial temperature of 37,5C , but his overall condition was good. The anterior and posterior fontanelles had a normal bulging with normal frontooccipital circumference. There was a 4x4 cm meningocele pouch over the lumbosacral region, which had a soft consistency grey- yellow colour and was ruptured (with a leakage of cerebrospinal fluid). There were no cutaneous abnormalities but the lower extremities had equino varus deformities. The child moved the extremities. The anal reflex was hypoactive.

Plain films showed division of the lower lumbar (L4 and L5) spine and sacral promontories and also rudimentary bone formation inside and posterior to the spinal canal at L4 and L5 levels. There was a posterior fusion defect between L5 and S1.

Computerised tomography (CT) of the spine confirmed the plain radiographic findings, while also showing a duplication of the dural sac between L4 and S1 by a fibrotic tissue. Magnetic resonance (MR) images demonstrated the herniation of the abdominal viscera from the anterior fusion defect between L4 and sacral promontories connecting with the fibrotic tissue that divides the dural sac (Fig.1).

During surgery, after exposing the fundus of the meningocele the sac was incised. Inside the sac there was a mix tissue composed of cartilaginous and fatty tissue. The sac was excised and the defect was primarily sutured.

Histopathological examination demonstrated that cystic area was lined by intestinal (Fig.2), squamous (Fig.3) and transitional

Figure 1: Axial MR image. Double arrow ( ) pointed the herniated abdominal viscera at L5-S1 level. Single arrow (←) pointed the fibrotic tissue that divides the dural sac.

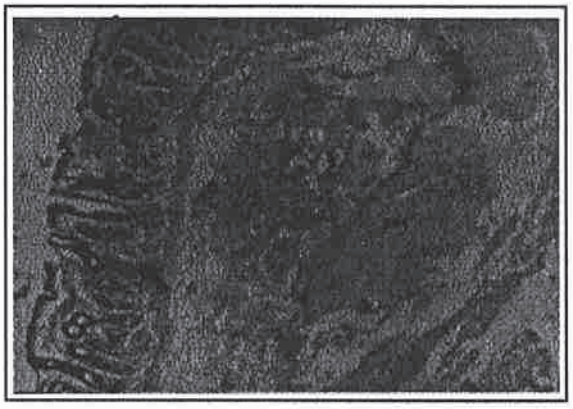

Figure 2: Intestinal epithelium (IE), smooth muscle (SM) tissue are clearly seen (HE;X10).

epithelium (Fig.4). Cyst wall contained mucinous glands (Fig.4) and smooth muscle tissue (Fig.2). Skeletal muscle, lymphoid tissue, hepatic and splenic tissue were also seen in some different areas. Hematopoetic focuses were determined in splenic tissue. Fibrous tissue (Fig.3), mature cartilaginous tissue (Fig.4), were observed in another microscopic area too. No immature or malignant cells were present. So three distinct types of mature tissues are seen: cartilaginous tissue, fibrous tissue, smooth muscle (mesodermal), squamaus epitelium (ecdodermal) , intestinal epitelium, transitional epitelium, mucinous glands (endodermal).

Figure 3: Squamous epithelium (SE), and fibrous tissue (FT) are seen (HE; X10).

Figure 4: Transitional epithelium (TE), mucinous glands (MG) and cartilaginous tissue (CT) can be seen. (HE; X10).

DISCUSSION

Many abnormalities of the gastrointestinal tract and other structures derived from endoderm, in combination with the nervous system have been described on human (5). The connection between the gastrointestinal tract and the neural structures varies from simple contact to fibrous tract, a fistula, or in severe forms an open cleft that allows the viscera to herniate from the back surface (8,11).

Many theories have been proposed to explain these complex malformations and to group them with simple anomalies like isolated neurenteric cysts, dorsal enteric fistula, meningocele or myelomeningocele (3,5,6,8,11). Theories concerning the pathogenesis of the split notochord phenomenon can be separated into six groups;

1) Beardmore and Wiglesworth (12) and also Prop et al (13) proposed an abnormal endodermal- ectodermal adhesion, with subsequent splitting of the notochord. Although this theory could explain diastematomyelia, it seems difficult to explain so many kind of endoderm derived tissues seen in pathological examination.

2) Bentley and Smith (1) proposed that the initial defect is split notochord. They hypothesized that there is a partial duplication with separation of the notochord through which a portion of the endoderm may herniate and attach to the ectoderm (2,5,6,8). This may occur at any level of the vertebral column although cervico- thoracic lesions are somewhat more frequent. In their original report, Bentley and Smith (1) described neuroenteric cysts, diverticula, and dorsal enteric fistula as communication with the vertebral column and classified them as developmental posterior enteric remnants. Persistence of the complete cleft leads to the development of a midline fistula from the gut to the back (combined anterior and posterior spina bifida) , often with herniation of bowel out of the dorsal defect (6,7). Degeneration of part of the tract could leave cords of tissue behind with the rest of the tract remaining as a sinus or cyst. Further regression of the cleft could result in diastematomyelia (5).

3) Bremer (14) suggested that presence of a persistent or accessory neurenteric canal, caused by a dorsal herniation of the endoderm is responsible from the splitting of the notochord and the neuroepithelium. The partial obliteration of the accessory neuroenteric canal from the mid-portion may cause diastematomyelia with enteric remnants located anterior and posteriorly and also disturbing the notochordial development , the axial skeleton formation may also be disturbed causing rudimentary bone formations (6,8,15,17).

4) Gardner (16) proposed that if neural tube overdistension, as a consequence of oversecretion of neural tube fluid, splits the underlying notochord and damages primitive gut, anomalies of endodermal organs may result. This theory

may explain the formation of neuroenteric cysts but not diastematomyelia.

5) Other studies suggest that an initial early teratogenic or spontaneous mutation of the developing notochord occurs leading to a split of its inferior portion. Under the stimulus of the notochordal tissue, normal vertebral bodies could then develop around both divisions of the spinal cord. The enteric yolk sac would herniate between both divisions of the spinal cord and adhere to the dorsal ectoderm or rupture into the amniotic cavity (3). This theory could also explain diastematomyelia with so many kind of endoderm derived tissues.

6) Recent theories are based upon the vascular compromise of the inferior neural structure, preventing neural tube closure.

In our case anterior and posterior spina bifida, herniation of the abdominal viscera from the anterior spina bifida, diastematomyelia caused with a fibrotic tissue and a meningocele with endodermal remnants and rudimentary bone formations exists. When a fistula or an open cleft that allows the viscera to herniate through the anterior and posterior spina bifida to the surface of the back exists it is more easy to recognize the split notochord syndrome. But as in our case when the cleft is obliterated and instead a fibrotic band exists then the anterior spina bifida and histopathological examination of the remnants leads us to the diagnosis. A careful histopathological examination of the remnants is very essential.

Split notochord syndrome with diastematomyelia and meningocele of the lumbosacral spine is extremely rare. Nineteen human cases have been previously reported as split notochord syndrome in the lumbosacral region. Of the four cases which had no dorsal enteric opening, only one has been associated with meningocele or meningomyelocele and of the 15 cases with dorsal enteric opening, 8 have been associated with meningocele or menigomyelocele (2,3,4,7,9,10). Therefore, our case is thought to be the fifth with no dorsal enteric opening and the second that has been associated with meningocele or meningomyelocele.

Management of these patients is identical in many ways to management of children with spina bifida and meningocele or meningomyelocele depending on the type and level of the spinal cord lesion. In fact, the split notochord syndrome may be seen as a more extreme variant of meningocele or meningomyelocele. Adequate cover of neural structures is important to control cerebrospinal fluid leakage and possible bacterial contamination. When an enteric communication exists, then surgical management of this lesion may be either a staged repair (2,4,6,9) or a combined single- stage correction (10). In a staged repair, it has been suggested that the treatment of enteric cysts, duplications or fistula should be performed first to avoid the contamination of neural canal. Later on the meningocele or meningomyelocele can be operated on safely (4,6). In our case as there has been no enteric communication only adequate cover of neural structures was enough. In our opinion if the meningocele is ruptured then it must be operated first.

In conclusion, it may be prudent to consider the possibility of a gastrointestinal anomaly in the patient with spina bifida, meningocele or meningomyelocele. Therefore, a careful examination of all posterior defects should be done in order to exclude a fistula or communication to the gastrointestinal tract. The split notochord syndrome is an unusual anomaly involving malformations of the intestinal tract, the vertebral column, the spinal cord and the central nervous system. As there are numerous variations, each case must be individualised.

REFERENCES

1. Bentley JFR, Smith JR. Development posterior enteric remnants and spinal malformation. Arch Dıs Child 1960; 35: 76-8
2. Gupta DK, Deodhar MC. Split notochord syndrome presenting with meningomyelocele and dorsal enteric fistula. J Pediatr Surg 1987; 22: 382- 83.
3. Hoffman CH, Dietrich RB, Pais MJ ve ark. The split notochord syndrome with dorsal enteric fistula. AJNR 1993; 14: 622-27.
4. Kiristioğlu I, Teitelbaum DH, Doğruyol H. Split notochord syndrome with prolapsed congenital colostomy. J Pediatr Surg 1998; 33: 525-28.
5. Macdonald RL, Schwartz ML, Lewils JA. Neurenteric cyst located dorsal to the cervical spine. Neurosurg 1991; 28(4): 583-88.
6. Meller JL, Loeff DS, Reyes HM. A variant of the split notochord Syndrome. J Pediatr Surg 1989; 24: (8) 733-35.
7. Pathak VB, Singh S. Double split of notochord with massive prolopsus of the gut. J Pediatr Surg 1988; 23: 1030-40.
8. Le Doux MS, Faye Petersen OM, Aronın PA ve ark. Lumbosacral neurenteric cyst in an infant. J Neurosurg 1993; 78: 821-25.
9. Faris JC, Crowe JE. The split notochord syndrome. J Pediatr Surg 1975; 10: 467-72.
10. Kahn EA, Lemmen LJ. Unusual congenital anomalies of neurosurgical interest in infants and children. J Neurosurg 1950; 7: 544-54.
11. Kramer EL, Giacoia GP. Split notochord syndrome with dorsal enteric fistule and sacral agenesis. Teratol 1988; 38: 1-5.
12. Beardmore HE, Wiglesworth FW. Vertebral anomalies and alimentary duplications. Pediatr Clin North Am 1958; 5: 457-73.
13. Prop N, Frensdorf EL, van de Stadt FR. A postvertebral entodermal cyst associated with axial deformities: A case showing the " Entodermal-ectodermal adhesion syndrome" Pediatrics 1967; 39: 555-62.
14. Bremer JL. Dorsal intestinal fistulae accesory neurenteric canal diastematomyelia. AMA Arch Pathol 1952; 54: 132-38.
15. Harris PC, Dias SM, Brock MLD ve ark. Neurenteric cysts of the posterior fossa; Recognition, Managament and Embryogenesis. Neurosurg 1991; 29(6): 893-97.
16. Gardner JW. Ovendistention of the neural tube may cause anomalies of non-neural organs. Teratol 1980; 22: 229-38.
17. Mc letchie NGB, Purves JK, Saunders RL . The genesis of gastric and certain intestinal diverticula and enterogenous cysts. Surg Gynecol Obstet 1954; 99: 135-41.

SCHATZKI RING IN CHILDHOOD

Meral Barlas** ❖ M.Emin Boleken* ❖ İ.Haluk Gökçora***

SUMMARY

The diagnostic and therapeutic management of two children of Schatzki Rings were presented. The patients admitted with symptoms of progressive dysphagia with solid food and acute food impactions with 1,5x1x1 cm olive.Proximal gastrointestinal system X-rays with barium swallow revealed Schatzki Rings two and three centimeters, respectively, above the diaphragm. Neither gastro-esophageal reflux nor hiatal hernia was detected. The rings and olive over the rings were directly visible by fiberoptic endoscopy. Biopsy specimens taken from the rings showed mixed patterns of squamous-celled and columnar-celled lining epithelium. Treatment consisted of dilatation of the esophagus under fluoroscopy.

Key Words: Schatzki Ring, Child

ÖZET

Çocuklarda Schatzki Halkası

Iki hastada Schatzki halkasının tanı ve tedavi ilkeleri tanımlandı. Bir hastada katı gıdalara karşı ilerleyici yutma güçlüğü diğerinde ise zeytin yerken oluşan akut yutma güçlüğü mevcuttu.Baryumla çekilen özofagogramlarında diyafragmanın 2 ve 3 cm proksimalinde Schatzki halkasının oluşturduğu darlık görüldü. Halka ve çiğnenmemiş zeytin fiberoptik endoskop ile gözlendi. Halkadan alınan biyopsi materyalinde çok katlı yassı hücreli epitel ve silindirik epitel saptandı. Tedavi skopi altında özofgus dilatasyonlarıyla yapıldı.

Anahtar Kelimeler: Schatzki Halkası, Çocuk

Since it was first described in 1944,a lower esophageal Schatzki Ring has remained an etiological and therapeutic enigma(1).While it has been convincingly demonstrated that the ring is identified with the esophagogastric mucosal junction and can only be found in the patients with hiatal hernia,little is known about the pathogenesis or the effectiveness of different treatment modalities(2).Theories about the origin of the ring include inflammatory, developmental and anatomical factors as the most likely events leading to a circular constriction of the esophagogastric junction(3).However,none of these theories has so far been convincingly shown to be correct.As a result of these uncertainties,causal treatment is still unknown,and the effectiveness of the palliative measures is not even completely understood.

Multiple treatment modalities have been suggested for symptomatic patients.These include endoscopic biopsy and incision of the ring,bougienage and pneumatic dilation,surgical procedures,or simple dietary measures (4-8).We present two cases of Schatzki Rings and discuss

*Resident, Department of Pediatric Surgery, Ankara University Faculty of Medicine
**Associate Professor, Department of Pediatric Surgery, Ankara University Faculty of Medicine
***Professor, Department of Pediatric Surgery, Ankara University Faculty of Medicine

Received: Sept 15,1999 Accepted: Fep 26,2001

Figure 1: Proximal gastrointestinal system X-rays with barium swallow showed a Schatzki Ring two centimeters above the diaphragm.

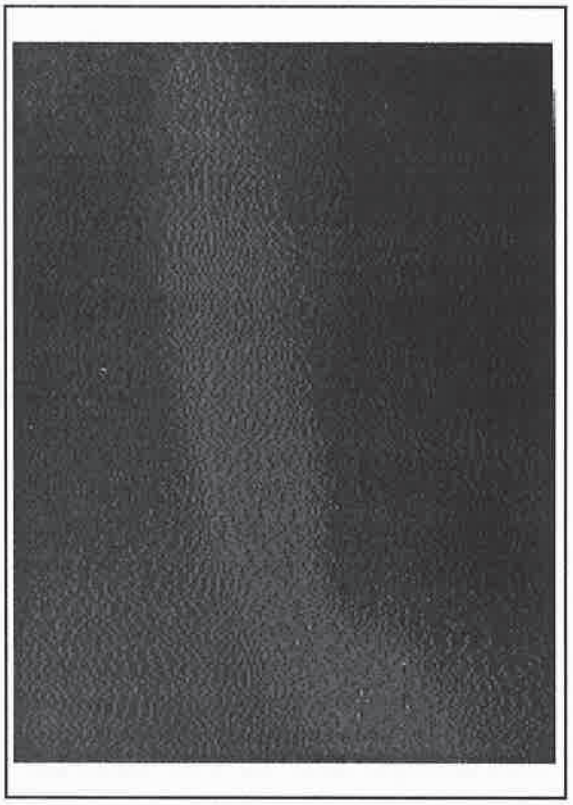

Figure 2:X-rays with barium swallow after esophageal dilatation showed a normal esophagus.

the presenting symptoms,diagnostic and treatment modalities.

CASE REPORTS

Case 1:A three-year-old girl admitted with a history of difficulty swallowing any food. Proximal gastrointestinal system X-rays with barium swallow showed a Schatzki Ring two centimeters above the diaphragm.Neither gastro-esophageal reflux nor hiatal hernia was detected (Figure-1).The Schatzki Ring and olive were detected directly by fiberoptic endoscopy using a video camera. The olive was about 1.5x1x1 cm gross and located in to the ring.A biopsy specimen of the ring showed a mixed pattern of squamous-celled and columnar-celled lining epithelium with no inflammatory findings.Dilation of the esophagus under fluoroscopy was performed twice a week for one month than monthly for one year. There has been no evidence of dysphagia in two years of followup (Figure 2).

Case 2:A four-year-old boy was admitted with a history of difficulty swallowing food.

Proximal gastrointestinal system X-rays with barium swallow showed a Schatzki Ring two centimeters above the diaphragm (Figure 3).There was no hiatal hernia or gastro-esophageal reflux.An esophagoscopy performed by fiberoptic endoscope showed a mixed pattern of squamous-celled and columnar-celled lining epithelium,with no inflammatory reaction. Dilation of the esophagus under fluoroscopy was performed twice a week for two months.No further sign of dysphagia has been detected in a follow-up period of one year (Figure 4).

DISCUSSION

Dysphagia in childhood is relatively common and can usually be diagnosed as etiologically related to either mechanical obstruction in or around the esophagus or to neuromuscular disorders of the esophagus (7,10).The pathopysiology

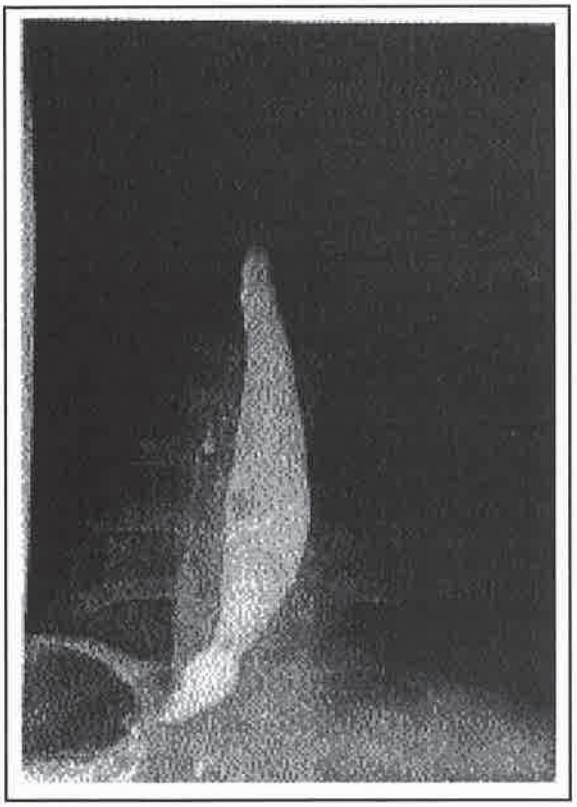

Figure 3: Proximal gastrointestinal system X-rays with barium swallow showed a Schatzki Ring three centimeters above the diaphragm.

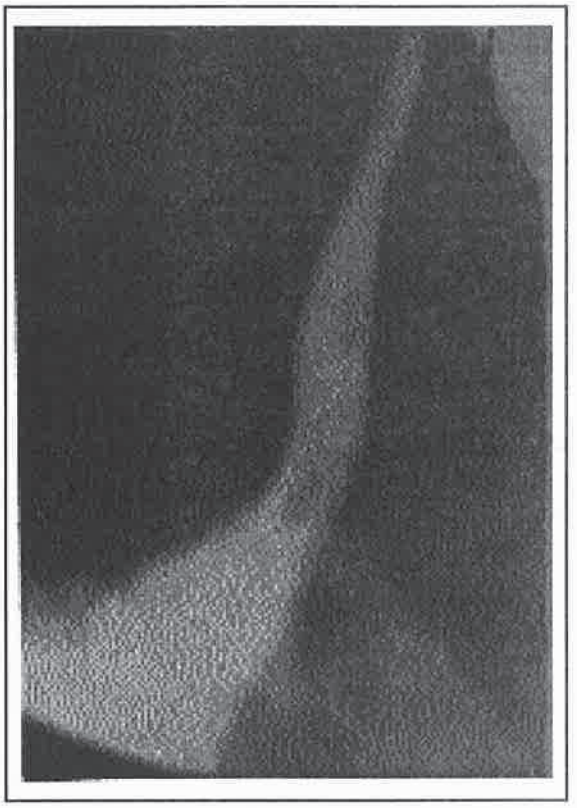

Figure 4: Proximal gastrointestinal system X-rays with barium swallow after esophageal dilatation showed a normal esophagus.

of Schatzki Rings is still controversial. One theory suggests a mucosal plication against a short lenght of the esophagus, while another involves the valve mechanism.(6).The mixed pattern of squamous and columnar epithelium on biopsy specimens in our patients supports the former theory.

Barium swallow X-rays and endoscopy are two methods of diagnosis(5,9).

Lower esophageal rings,whether symptomatic or asymptomatic,have been found in up to 18% of adult patients undergoing routine upper gastrointestinal examinations and in about 4% of patients undergoing endoscopy for dysphagia due to a benign condition (9,10).However,a Schatzki ring is a very rare entity in children.A review of the literature available in Engish revealed only two cases in over 20 years.

The age of onset of symptoms may vary.Klein et al reported a two-day-old newborn with regurgitation whose barium swallow X-ray of the proximal gastrointestinal system showed a Schatzki Ring (6).Newman et al reported a case of a twelve-year-old boy whose upper gastrointestinal radiographic series showed a lower esophageal ring approximately eight millimeters in a diameter as well as a small sliding hernia.Biopsies showed no evidence of inflammation.(8).Our cases were diagnosed by proximal gastrointestinal system X-rays and endoscopy.The discovery of an olive during endoscopy in one of our cases was demonstrative of the tight stenosis.

Rings between 13 and 20 mm in diameter are associated with a 20% incidence of obstructive symptoms in adult patients,while tighter rings almost invariaby produce episodic dysphagia or aphagia (10).The relationship between ring diameter and symptomatology is not so welldescribed in the pediatric patients,but the growth retardation and the severity of symptoms in our patients suggests that a ring of 5-7mm in diameter is tight

enough to cause severe stenosis in the pediatric population.

The treatment modality is dilatation under fluoroscopy .Previous experience indicates that only one dilatation under fiberoptic endoscope can be sufficient(6,10).Our patients were treated successfully with esophageal dilatations under fluoroscopy twice a week for onemonth plus monthly for one year and two months,respectively.No dysphagia was observed in two years of follow up.

Though it is rare in the pediatric population,a Schatzki ring should be kept in mind in the differential diagnosis of dysphagia when there is no history of caustic ingestion or other causes for the dysphagia.

REFERENCES

1-Templeton FE X-ray Examination of the Stomach:A Description of the Roentgenologic Anatomy,Physiology and Pathology of the Esophagus,Stomach and Duodenum.Chicago: University of Chicago Press,1944

2-Schatzki R,The Lower Esophageal Ring;Long Term Follow Up of Symptomatic and Asymptomatic Rings.Am J Roentgenol,1963;90:805.

3-Schatzki R,Gary J E,Dysphagıa Due to Diaphragm-Like Localized Narrowing in the Lower Esophagus (Lower Esophageal Ring),American Journal of Roentgenology, 1953; 70:911-922

4-Eckardt V F,Kanzler G,Willems D,Single Dilation of Symptomatic Schatzki Rings 'A Prospective Evaluation of its Effectiveness, Digesti ve Diseases and Sciences 1992;37:577-582

5-Kathleen Buckley,Carlo Bounomo,Khaled Husain,Samuel Nurko,Schatzki Ring in Children and Young Adults:Clinical and Radiologic Findings,Pediatric Radiology, 1998; 28:884-886

6-Klein.M D,Waltner J,Ball W,Kosloske AM,Schatzki Ring in a Newborn,Pediatrics, 1981 ;68:884-886

7-Laksmana D.Narla,Elizabeth A.Hingsbergen, Jay E.Jones,Adult Diseases in Children, Pediatric Radiology,1999,29:244-254

8-Newman S I,Caplan D B,Lower Esophageal Ring in Childhood an Unusual Cause of Dysphagıa,American Journal Gastroenterology,1980;73:165-167

9-Smith R E,Dilation of Schatzki Ring,Gastrointestinal Endoscopy,1991;37:402-406

10-Webb WA,McDaniel L,Jones L,Endoscopic evaluation of Dysphagia in 293 patients With Benign Disease.Surg Gynecol Obsted,1984; 158:152-156.

CORRECTİON

The correct titles of the two articles and Table 1 in the second paper as shown below which were published in issue number 3 volume 23, 2001.

1- "A HISTOPATHOLOGICAL STUDY OF HODGKIN'S LYMPHOMA AND ITS ASSOCIATION WITH EPSTEIN-BARR VIRUS IN TURKISH PATIENTS"

Ebru Serinsöz* , Ali Pamir** , Arzu Ensari* , Selim Erekul*
*Department of Pathology, Ankara University Faculty of Medicine
**Department of Oncology, Ankara University Faculty of Medicine

2- "ANALYSIS OF FOUR-HOUR GROWTH HORMONE PROFILES AFTER ONSET OF SLEEP IN NORMAL AND GH-DEFICIENT CHILDREN: A STANDARDIZATION OF THIS SIMPLE TEST FOR CLINICAL USE"

Gönül Öcal* , Merih Berberoğlu* , Pelin Adıyaman* ,
Ergun Çetinkaya** , Sema Akçurin*** , Nihal Memioğlu****
*Ankara Universty, Faculty of Medicine, Division of Pediatric Endocrinology
**SSK Dışkapı Children's Hospital
***Antalya Faculty of Medicine
****Dr. Sami Ulus Children's Hospital

Table 1: The clinical characteristics and GH-reserve of groups.

EMTA	Group A (n=55)	Group B (n=66)	Group C (n=19)	Significance		
				A vs B	A vs C	B vs C
Chronological Age (yr)	8.60 ± 2.40	7.89 ± 2.00	9.37 ± 1.00	NS	NS	NS
Bone Age (yr)	8.00 ± 1.00	4.30 ± 1.10	6.20 ± 0.80	$p < 0.01$	$p < 0.05$	NS
$HSDS_{CA}$	0.80 ± 0.30	-4.20 ± 0.30	-3.68 ± 0.60	$p < 0.01$	$p < 0.01$	NS
$HVSDS_{CA}$	NOT CONTROLLED	-3.60 ± 0.90	-3.80 ± 1.00	-	-	NS
L-DOPA GH peak (ng/ml)	NOTDONE	4.46 ± 1.15	14.02 ± 3.30	-	-	$p < 0.01$
ITH GH peak (ng/ml)	NOT DONE	5.70 ± 0.85	12.72 ± 4.40	-	-	$p < 0.01$
ICGH* (ng/ml/4hr)	5.77 ± 1.22 (3.33 - 8.21)**	2.14 ± 0.70	3.12 ± 0.63	$p < 0.01$	$p < 0.05$	NS
Peak Amplitude (ng/ml)	15.91 ± 2.20 (11.50 - 20.30)**	6.16 ± 1.11	6.61 ± 1.33	$p < 0.01$	NS	
Peak number (>5ng/ml)	3.09 ± 1.37 (1.15 - 6.47)**	1.10 ± 0.35	2.14 ± 1.06	$p < 0.01$	NS	NS

Group A: Control
Group B: Growth retarded patients with blunted GH response to pharmacological stimuli
Group C: Growth retarded patients with normal GH response to pharmacological stimuli
ICGH * : Integrated concentration of GH
( )** : Lower normal limit - Upper normal limit

JOURNAL OF ANKARA MEDICAL SCHOOL

VOL 23 INDEX

SUBJECT INDEX

AUTHOR INDEX

Engin Yaprak	23:04:305
Ensari Arzu	23:03:183
Erbil Mine	23:02:155
Erekul Selim	23:03:183
Erentuncay Neyyir	23:04:294
Erginay Tamer	23:01:69
Ertopçu Kenan	23:03:177
Ertürk Özcan	23:03:198
Eser Olay	23:04:318
Eskioğlu Erdal	23:02:123
Evcik Deniz	23:01:29
Evcik Deniz	23:02:137
Evirgen Oya	23:01:57
Faruk Coşkun	23:03:255
Fitol Suat	23:01:43
Fitol Suat	23:02:95
Garcia Mario	23:03:205
Gökçora Haluk	23:04:323
Gökrem Serdar	23:02:161
Gönül Engin	23:01:69
Görmüş Niyazi	23:01:11
Güleç Tülin	23:04:310
Gümüş Halil	23:01:35
Güney Önder	23:04:318
Günlemez Ayla	23:03:187
Gürdal Muharrem	23:01:9
Gürgey Erbak	23:02:155
Gürgey Erbak	23:02:149
Gürkan İlksen	23:01:49
Han Serdar	23:04:280
Hatipoğlu Selim	23:03:255
İmamoğlu Abdurrahim	23:03:227
İnan Sevinç	23:03:177
İnan Sevinç	23:03:167
Kaftan Asuman	23:03:205
Kalem Abdülçelik	23:02:117
Kara Murat	23:02:143
Karabağ Turgut	23:02:129
Karaoğuz Remzi	23:01:9
Karaoğuz Remzi	23:01:77
Kavukçu Şevket	23:02:143
Kılıç Dalokay	23:02:143
Kılınç Münire	23:03:198
Kınıklı Gülay	23:01:77
Kıynmaz Nejmi	23:03:251
Kiper Ahmet	23:03:227
Kocatürk Pelin	23:01:1
Konuk Abdullah	23:04:318
Korkmaz Mehmet	23:03:205
Köroğlu Adnan	23:04:318
Kulaçoğlu Hakan	23:03:255
Kundakçı Nihal	23:01:73
Kurtay Gülay	23:03:233
Kuyucu Necdet	23:04:258
Memeik Recep	23:01:81
Memioğlu Nihal	23:03:195
Memiş Ali	23:04:281
Mesiha Ekim	23:03:111
Moran münevver	23:03:255
Mürselov Sahin	23:01:77
Nuray Özkaya	23:02:111
Oldemir Murat	23:02:161
Onrat Ersel	23:01:29
Onrat Ersel	23:02:137
Oral Derviş	23:01:9
Oruç Tahir	23:03:255
Oskay Tuğba	23:02:149
Öcal Gönül	23:03:198
Ödev Kemal	23:02:117
Özbilgin Kemal	23:03:177
Özbilgin Kemal	23:03:167
Özcan Mutin	23:03:211
Özen Candan	23:02:129
Özkaya nuray	23:03:111
Öztürk Mehmet	23:04:281
Pamir Ali	23:03:183
Rahimov Üzeyir	23:01:77
Sabuncuoğlu Bizdem	23:02:91
Sak Serpil	23:02:143
Sakallıoğlu Ebru	23:04:275
Sakıncı Ünal	23:04:280
Sancı Muzaffer	23:03:177
Sanlı Hatice	23:02:155
Sarıfakıoğlu Evren	23:04:310
Satıroğlu Hakan	23:01:57
Sayın Topçu	23:01:77
Serinsöz Ebru	23:03:183
Şeçkin Deniz	23:04:310