Journal of Ankara Medical School

ISSN 1300-5464

Vol 24 No 2 2002

Journal Of Ankara Medical School

Cilt: 24, Sayı: 2, 2002
Vol: 24, No: 2, 2002

THE JOURNAL OF THE FACULTY OF MEDICINE
UNIVERSITY OF ANKARA

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 30.000.000 TL; 50% reductions for research fellows, practioners, etc.; 75% reductions for students, Subscription for the foreign countries: 100 $.

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
Tel: 0 (312) 310 30 30 / 207 - 330 Fax: 0 (312) 310 63 70
e-mail: tipdergi@medicine.ankara.edu.tr

ISSN 1300-5464

Desing & Preparation: ANTIP A.Ş. 0 (312) 310 63 05 - 310 33 33 / 22 53 Turgay Süslü

Constralnt: 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 Üniversitesi 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 number(s) 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: (English and Turksih) 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 and in Turkish.

Key Words: Not more than five key words should be added below the summary in alphabethical order both in English and in Turkish.

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. Photographs 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.

HISTOLOGICAL CHANGES IN RAT LIVER AFTER CHRONIC IRON-SORBITOL OVERLOAD

Meltem Özgüner* ✣ Nurşen Sayın**

SUMMARY

Iron is a metal that plays an important role in heme metabolism.This study revealed the histological changes in a new rat model after chronic iron-sorbitol overload. Experimental iron overload has been produced by intramuscular administration of iron-sorbitol 0.4 mg/g/day for two days per week, for eight weeks to 10 Sprague-Dawley rats(200-250 gr). The control group consisted of 10 Sprague-Dawley rats injected with saline. Histological sections from liver stained by hematoxylin-eosin, Perls' Prussian blue, Masson's trichrome stain and periodic acid Schiff (PAS) reagent. Microscopical findings revealed that sinusoidal cells and parenchymal cells were filled with iron deposits, and a slight fibrosis was observed with diffuse leucocyte infiltration. This experimental study revealed that the only commercial parenteral form of iron in our country, iron-sorbitol (Jectofer), could produce morphologic changes in a relatively short period of time and this model could be useful for further parenteral iron overload investigations in the future. On the whole, this study revealed to be aware of chronic iron toxicity in liver and further efforts should be directed toward the complication of chronic iron overload and the correlation of histological findings.

Key Words: *Iron-Sorbitol, Over-Load, Rat, Liver, Histology*

ÖZET

Sıçanlarda Kronik Demir-Sorbitol Yüklenmesi Sonucu Oluşan Histolojik Değişiklikler

Demir hemoglobin metabolizmasında önemli rol oynayan bir metaldir. Bu çalışmada yeni bir sıçan modelinde kronik demir-sorbitol yüklenmesinden sonra histolojik değişiklikler gösterildi.

Deneysel demir-sorbitol yüklenmesi Sprague-Dawley sıçanlarına 8 hafta boyunca haftada iki kere 0.4 mg/gr/gün kas içine uygulandı. Kontrol grubu sıçanlara izotonik serum fizyolojik enjekte edildi. Histolojik kesitler hematoksilin eozin, Perls'in Prusya mavisi, Masson'un üçlü boyası ve PAS'la boyandı. Mikroskobik bulgular; sinuzoidal ve parankim hücrelerin demirle dolu olduğunu ve yaygın diffüz lokosit infitrasyonlu hafif bir fibrozis geliştiğini gösterdi. Bu deneysel çalışma, ülkemizde bulunan tek ticari parenteral demir preparatı olan demir-sorbitolün (Jectofer), nispeten kısa bir sürede morfolojik değişiklikler oluşturabileceğini ve bu modelin, daha ileride parenteral demir yüklenmesi araştırmaları için kullanılabileceğini göstermiştir.Sonuç olarak, bu çalışma karaciğerde kronik demir toksisitesinin varlığını gösterdi ve kronik demir yüklemesi komplikasyonlarının histolojik bulgularla doğrulanması için daha ileri çalışmalar yapılması gerekliliğini ortaya koydu.

Anahtar Kelimeler: *Demir-Sorbitol Yüklemesi, Sıçan, Karaciğer, Histoloji.*

Iron is a necessary element for all living cells. Iron deficiency with or without anemia is the main cause of nutritional deficiency for human beings. With all the justified awareness of iron deficiency, attention should also be given to the potentially damaging effects of prolonged and indiscriminate iron administration (1).

Toxicity is mostly dependent on iron-induced free radical reactions and oxidative injury. Main physicopathologic effects of iron overload on liver tissue are fibrosis, porphyria cutanea tarda and hepatocellular carcinoma (2-5). Vigorous efforts at diagnosis and treatment of iron overload are essential since the pathologic effects of iron are

* Süleyman Demirel University, Medical Faculty, Department of Histology-Embryology, ISPARTA, TURKEY.
** Ankara University, Medical Faculty, Department of Histology-Embryology, ANKARA, TURKEY.

Received: May 29, 2002 Accepted: Sept. 30, 2002

totally preventable by early vigorous iron removal and prevention of iron re-accumulation (5, 6).

Effects of chronic iron sorbitol overload in Sprague-Dawney rat liver are taken into consideration histologically. Using experimental animal model, we aimed to study the only commercial parenteral form of iron in our country could produce morphological changes.

MATERIALS AND METHODS

Twenty Sprague-Dawley type albino rats, weighing 200-250 g were used. Animals were divided into two groups of ten animals each. They were housed in two different cages and fed a commercially avaliable diet; drinking water was freely provided at all times. Group I was administered saline (control group); Group II received iron-sorbitol (Jectofer, Eczacıbaşı Pharmaceutical) intramuscularly 2 days a week for 8 weeks at a dose of 0.4 mg/g/day. After completion of iron administration rats were sacrificed by high dose ether anesthesia for histological examination. Blocks of tissue were immediately fixed in 10 % neutral buffered formalin, dehydrated with a graded series of ethyl alcohol and embedded in paraffin. Sections (5 (m) were cut and stained with hematoxylin and eosin, Perls' Prussian blue method for iron pigments and Masson's trichrome stain, periodic acid Shiff (PAS) reagent. Histological slides were photographed under a Zeiss Axioscope photomicroscope.

RESULTS

It is commonly believed that more than a few ferritin particles in cell cytoplasm is a predictor of iron overload except Kupffer cell cytoplasm. Control groups showed normal lobular architecture and histology without stainable iron. After chronic iron administration, there was heavy iron deposition in all of the hepatocytes and Kupffer cells. Administration of iron-sorbitol (Jectofer) in doses of 0.4 mg/g/day distributed over a period of 8 weeks caused hepatic iron overload in rats. When the experimental group was compared with the control group (Figure 1), the most significant finding was yellowish brown depositions with hematoxylin-eosin stain (Figure 2). Depositions were abundant in all of the hepatocytes and Kupffer cells.

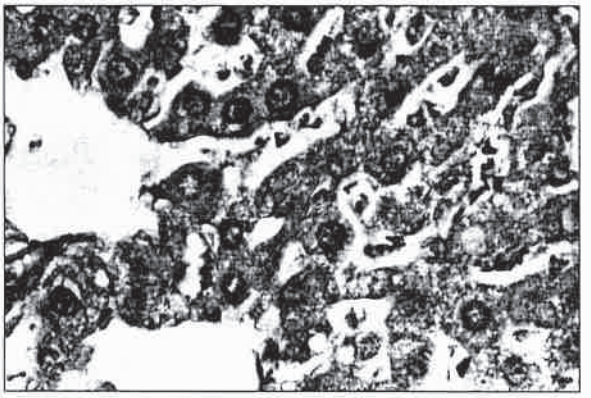

Figure 1: Control group: 5(m histologic section of liver parenchyma without stainable iron. H.E X 250.

In experimental group, yellowish-brown pigment granules were thought to be hemosiderin granulles and granul increase were adequate in all histological zones (Figure 2).

Histological sections were stained by Perl's Prussian blue method for the observation of " hemosiderin granules". Pearl's Prussian blue (ferrocyanide method) staining made Fe^{+3} apparent (Figure 3 and 4). Siderosomes containing hemosiderin granules were accepted as Prussian blue (PB) positive (+) granules. PB positive iron was present in the form of typical cytoplasmic granules and was diffuse in cytoplasm of hepatocytes (Figure 4). After iron administration, there was heavy iron deposition in all of the hepatocytes and Kupffer cells PB (+) granules were observed and in sinusoidal lining cells (Figure 4).

Masson trichrome stain showed fine, and prominent collagen fibers around the portal areas.

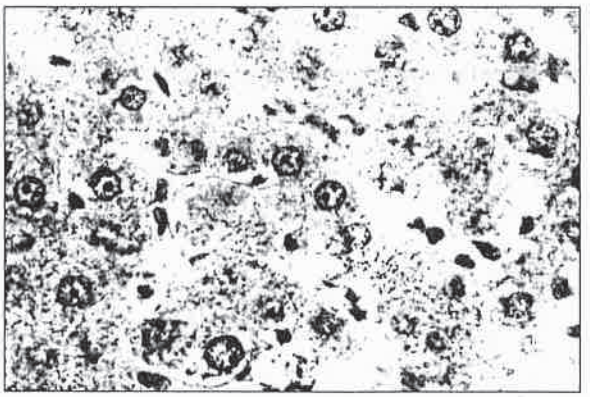

Figure 2: Experimental group: histologic section which contains yellowish brown depositions in cell cytoplasm after chronic iron overload. H.E X 250.

Comparison of the experimental group with the control group revealed a significant increase in collagen synthesis (Figure 5). Especially, in periportal areas stromal proliferation was evident (Figure 5).

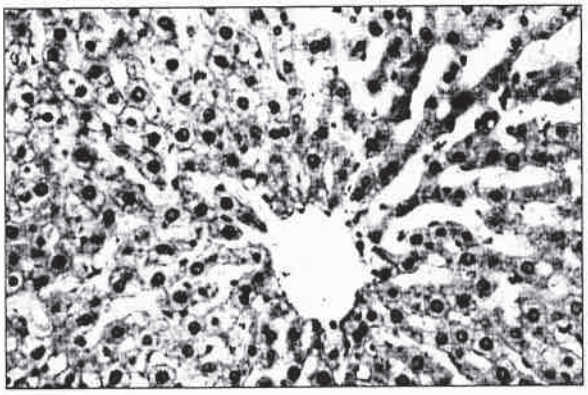

Figure 3: Control group: histologic section of hepatocytes without PB (+) granules. Pearl's Prussian Blue X 100.

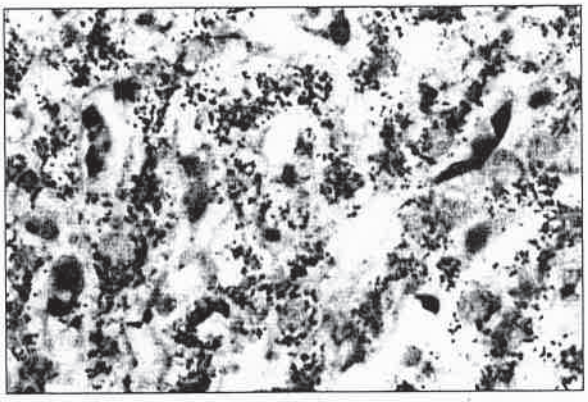

Figure 4: Experimental group: liver parenchyma containing PB (+) granules in cell cytoplasms. Pearl's Prussian Blue X 250.

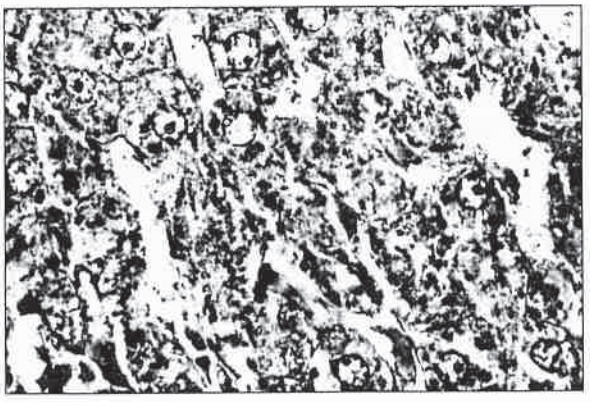

Figure 5: Experimental group: stroma with prominent collagen fibers. Masson trichrome stain X250.

PAS stain revealed the thickening of basal lamina of the sinusoids in iron overloaded rat liver. While hepatocyte cytoplasms were containing PAS (+) glycogen granules in the control group (Figure 6), hepatocyte cytoplasm was pale in color because of the heavy iron overload in the experimental group (Figure 7).

Diffuse leucocyte infiltration was apparent in the intercellular area (Figure 8). Light microscopic examination of the liver showed the characteristics of massive iron deposition in hepatocytes and Kupffer cells without significant cell necrosis.

DISCUSSION

Iron is essential for life but iron overload was shown to be toxic and potentially fatal (5).Hepatotoxicity is the most common finding in

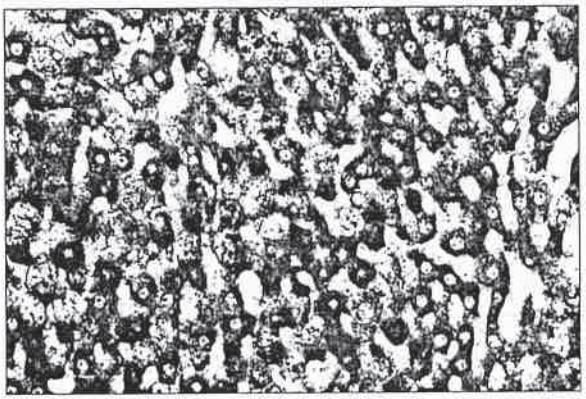

Figure 6: Control group: histologic sections containing PAS (+) glycogen granules in hepatocyte cytoplasm. PAS X 100.

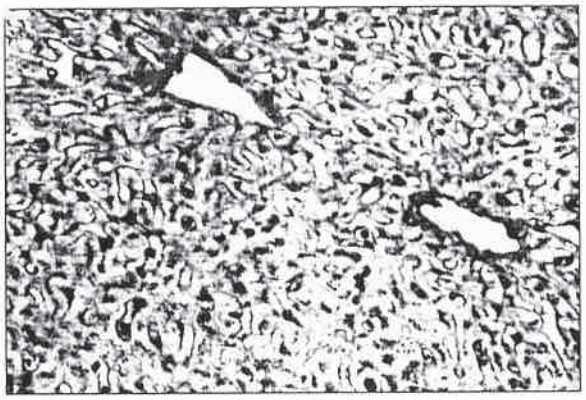

Figure 7: Experimental group: PAS staining shows basal lamina thickening and interestingly PAS (+) glycogen granules are absent in hepatocyte cytoplasm because of heavy iron overload. PAS X100.

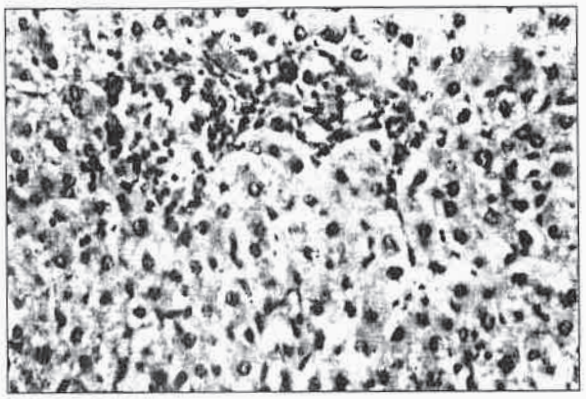

Figure 8: Experimental group: histologic sections showing diffuse leucocyte infiltration. H.E X100.

iron over-load because liver is the main recipient of the excess iron (5, 7-10).

The source of iron administered either orally or parenterally is a predictor of hepatic iron distribution and toxicity. Although increase in intestinal iron absorption as in hereditary hemochromatosis leads predominantly to parenchymal siderosis, parenteral iron overload which is produced by i.m administration of iron predominantly leads to retikuloendothelial (RE) iron deposition (11-13) and after prolonged periods of heavy iron loading, parenchymal siderosis has been demonstrated (12). The present experimental animal study also demonstrates massive iron overload in liver.

Cellular uptake of circulating excess iron results in increased formation of ferritin and hemosiderin found in highest concentrations in parenchymal tissue of several organs (e.g.liver, heart, pancreas) (9).

Carthew et al. have demonstrated that parenteral administration of iron dextran leads to parenchymal hemosiderosis, but perisinusoidal cell siderosis and fibrosis were not reported (14).

The results of Gualdi et al. indicated that, regardless of the total hepatic iron burden, selective localization of iron into liver cells (i.e, parenchymal cells) is required for the activation of the collagen expressing gene during long-term iron overload in rodents (15). Our present experimental animal model is in favour of Gualdi et al.'s study, as we also demonstrated parenchymal cell siderosis and only slight fibrosis during long-term iron administration.

Distrubution of iron in dietary iron over-loaded animal models was reported as initially confined to periportal (zone 1) hepatocytes but subsequently extended to midzonal (zone 2) and centrilobular (zone 3) hepatocytes (12).We have described pathologic features of chronic iron overload produced by parenteral administration of iron sorbitol for up to 2 months and indicated that within the liver iron deposition was present in all hepatocytes.

Both hepatocytes and RE cells are capable of iron storage but the hepatocytes metabolize enterally absorbed iron whereas RE cells metabolize the parenterally administered iron complexes first (12). Oral administration of iron would favor parenchymal siderosis but it is unlikely to induce a severe iron overload. Just in contrast, as in this experimental model; parenteral administration of iron-sorbitol for 8 weeks, favors both parenchymal siderosis and sinusoidal cell siderosis and induces a severe hepatic iron overload.

In this study the pathogenetic mechanism, which initiates the observed histopathologic features, could not be revealed. However, there are theories discussing the possibilities of oxidative injury and increased lysosomal lability by many investigators (5,10,16, 17,).

In conclusion, this experimental study revealed that the only commercial parenteral form of iron in our country, iron-sorbitol, could produce morphological changes in a relatively short period of time and this model could be useful for further parenteral iron overload investigations. Further efforts should be directed toward the complication of chronic iron overload and the correlation of histological findings.

REFERENCES

1- Iancu T.C., Ward R.J., Peters T.J. Ultrastructural observations in the carbonyl iron-fed rat an animal model for hemochromatosis. Virchows Arch 1987; 53:208-217.

2- Sheuer P.I., Willims R., Muir A.R. Hepatic pathology in relatives of patients with hemochromatosis. J Pathol Bacteriol 1962; 84:53-64.

3- Powell L.W., Halliday J.W. The liver and iron storage disorders. In: Metals and the liver. L.W Powell (ed.) New York, Marcel Dekker,1978; 145-176.

4- Good MF, Chapman ED, Powell LW, Halliday JW. The effect of experimental iron over load on splenic T-cell function. Clin Exp Immunol 1987; 68: 375-383.

5- Bonkovsky HL. Iron and the liver.The American Journal of Medical Sciences 1991; Vol. 301, No.1: 32-43.

6- Niederau C, Fischer R, Pürschel A, Stremmel W, Haussınger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. Gastroenterology 1996; 110: 1107-1119.

7- Galleanuo M, Puntarulo S. Hepatic chemiluminescence and lipid peroxydation in mild iron overload. Toxicology 1992; 76: 27-38.

8- Pietrangelo A, Gualdi R, Casalgrandi G, Geerts A, De Bleser P, Montasi G, Ventura E. Enhanced hepatic collagen type I mRNA expression in to fat storing cells in a rodent model of hemochromatosis. Hepatology 1994; 19: 714-721.

9- Britton RS et al. Pathophysiology of iron toxicity. Progress in Iron Research 1994:239-253.

10- Britton RS. Metal-induced hepatotoxicity. Seminars in Liver Disease 1996; Vol.16: 3-12.

11- Brissot P. Experimental hepatic iron over load in the Baboon: Results of a two year study. Digestive Diseases and Sciences 1983; Vol.28, No.7: 616-625.

12- Park C.H. Pathology of dietary carbonyl iron overload in rats. Lab Invest 1987; Vol. 57: 555.

13- De Sousa M. Immun cell functions in iron overload. Clin Exp Immunol 1989; 75: 1-6.

14- Carthew P. Rapid induction of hepatic fibrosis in the gerbil after the parenteral administration of iron-dextran complex. Hepatology 1991; Vol.13, No.3: 534-539.

15- Gualdi R. Excess iron into hepatocytes is required for activation of collagen type I gene during experimental siderosis. Gastroenterology 1994; 107: 1118-1124.

16- Masini A. et al.: The effect of iron overload on the mitochondrial porphyrin level in the hexachlorobenzene induced experimental porphyria. Biochem Biophy Res Comm 1988; Vol. 151: 320-321.

17- Pietrangelo A, Borella F, Casalgrandi G. Antioxydant activity of silybin in vivo during long-term iron overload in rats. Gastroenterology 1995; 109: 1941-1949.

HYPERTONIC DIURETIC INFUSION vs FRACTIONED DIURETIC USE FOR THE ACUTE RENAL FAILURE FOLLOWING OPEN HEART SURGERY AND THE ADVANTAGES OF HEMODIAFILTRATION

Neyyir Tuncay Eren* ✣ Sadık Eryılmaz* ✣ Ruchan Akar* ✣ Serkan Durdu* ✣ Hakkı Akalın*

SUMMARY

Bacground: *We planned this study to compare the effectiveness of the hypertonic diuretic infusion and fractioned diuretic use in the acute renal failure (ARF) in the early period following open-heart surgery and to study the effects of the hemodiafiltration.*

Material and Methods: *There were forty patients with impaired left ventricular function and normal preoperative renal function (creatinine < 1.5 mg/dl) who underwent open-heart surgery and developed ARF postoperatively. Hypertonic diuretic infusion was given to the first group whereas fractioned furosemide (500 mg/day) was applied to the second. Two patient groups were compared for weaning from oliguric/anuric ARF, hemodiafiltration and dialysis requirements.*

Results: *Fourteen patients in the Group I (70%), and 10 patients (50%) in Group II were weaned from ARF in the 36-48th hours (mean 39±7 h.). Six patients in Group I (30%) and 10 patients (50%) in Group II required hemodiafiltration*

Conclusions: *Hypertonic diuretic infusion use is more effective in diminishing the dialysis necessity for oliguric/anuric ARF following open-heart surgery compared to the fractioned diuretic use in the early period.*

Key Words: *Open-Heart Surgery, Depressive Left Ventricular Function, Acute Renal Failure, Hypertonic Diuretic Infusion*

ÖZET

Açık Kalp Cerrahisi Sonrasında Gelişen Akut Böbrek Yetmezliğine Hipertonik Yetmezliğinde Hipertonik Diüretik Kullanımının Karşılaştırılması ve Hemodiyafiltrasyonunun Etkisi

Amaç: *Bu çalışmayla açık kalp cerrahisi sonrası erken dönemde gelişen akut böbrek yetmezliğinde, hipertonik diüretik infüzyonu ile fraksiyone diüretik kullanımının etkinliğini karşılaştırmayı ve hemodiyafiltrasyonun etkinliğini araştırmayı planladık.*

Materyal ve Metod: *Preoperatif renal fonksiyonları normal (kreatinin <1.5 mg/dl) ve bozuk sol ventrikül fonksiyonu olan 40 hastamızda açık kalp cerrahisi sonrası akut böbrek yetmezliği (ABY) gelişti. Bir gruba hipertonik diüretik infüzyon uygulanırken diğer gruba fraksiyone furosemid (500 mg/gün) uygulandı. Her iki grubun oligürik/anürik fazdan çıkma, hemodiyafiltrasyon ve diyaliz gereksinimleri açısından karşılaştırıldı.*

Sonuçlar: *Diüretik infüzyon grubundan 14 hasta (%70), fraksiyone diüretik grubundan 10 hasta (%50) 36-48 saat sonra ABY'den çıktı. Diüretik infüzyon grubundan 6 hastada (%30), fraksiyone diüretik grubundan 10 hastada (%50) hemodiyafiltrasyon ihtiyacı oldu.*

Yorum: *Hipertonik diüretik infüzyonu kullanımı, fraksiyone diüretik kullnımına oranla, açık kalp ameliyatı sonrası gelişen oligürik/anürik ABY'de diyaliz ihtiyacını azaltmada daha etkindir.*

Anahtar Kelimeler: *Açık Kalp Cerrahisi, Sol Ventrikül Disfonksiyonu, Akut Böbrek Yetmezliği, Hipertonik Diüretik İnfüzyon*

Acute renal failure (ARF) following open-heart surgery in the early period is an important risk factor for the increments of mortality and morbidity. ARF in the postoperative period may occur due to the decrease of the renal perfusion, prolonged mechanical ventilation and low cardiac output syndrome (LOS) (1). The dialysis requirement in the early postoperative period makes the metabolic, hemotologic and hemodynamic stabilisation difficult. ARF may

* Ankara University, Medical School Cardiovascular Surgery Department.

Received: July 18, 2002 Accepted: Oct 14, 2002

occur 2-15 % of the patients with normal preoperative renal functions and depressive ventricles following surgery and in these cases mortality increases 24-70% (1). We studied the effects of hypertonic diuretic infusion, fractioned diuretic use and hemodiafiltration on the ARF following open-heart surgery in depressive left ventricular patients.

Acute renal failure requiring dialysis is an important risk factor for an early mortality after open-heart surgical procedures. Continuous infusion of the solution of mannitol, furosemide, and low-dose dopamine promoted diuresis in acute oliguric renal failure occurring in the early postoperative period in patients with adequate cardiac output and substantially decreased the need for dialysis. In contrast, intermittent doses of diuretics failed to induce diuresis and a majority of patients required dialysis. It remains to be determined whether routine infusion of the solution in the early postoperative period for acute oliguric renal failure influences the long-term mortality and morbidity in those patients who do require dialysis. (2)

MATERIALS AND METHODS:

Between January 1995 and December 2000 in Ankara University School of Medicine Cardiovascular Surgery Department 2483 patients underwent open-heart surgery. Of these 2483 patients 154 had depressive left ventricle. In this study we studied forty patients who had severe left ventricular dysfunction under elective conditions with preoperative normal renal functions and developed oliguric/anuric ARF in the postoperative period. Forty patients are divided in to two groups: Group I received hypertonic diuretic infusion whereas fractioned furosemide was given to the Group II for the treatment of ARF.

The demographic and comorbid factors of the patients are listed on Table-I and there wasn't statistically significant difference between the groups ($p>0.05$). None of the patients in both groups had any kind of renal disease and, the mean creatinine levels were 0.81±0.14 in Group I, and 0.79±0.19 in Group II. Left ventricular function and coronary arteries are evaluated by myocardial perfusion scintigraphy with dipyridamole and coronary angiography.

The patients were anaesthesied by general anaesthesia. Median sterntomy was performed to all patients. Following systemic heparinization aorta-right atrial or aorta – bicaval cannulation was performed and cardiopulmonary bypass (CPB) was started by non-pulsatile flow. Systemic hypothermia was conducted till 30-32°C. Pump flow was maintained between 2.4-2.6 L/m^2/min, blood pressure was maintained between 50-70 mmHg and the myocardial protection was achieved by antegrade cold blood cardioplegia. Mean CPB time was 150±20 min. and cross-clamp time was 100±20 min. and the number of distal anastomosis was 3.8±1.2. Intraaortic baloon pump (IABP) was inserted to 12 patients (30%)

Table-1. The classification of patients according to the demographic and comorbid factors in the hypertonic diuretic infusion (Group I) and intermittent furosemide (Group II) groups.

	GROUP I (n=20)	GROUP II (n=20)	*p* value
Age (years)	67.1±2.9	65.7±3.1	*>0.05*
Female/male ratio	%60	%65	*>0.05*
Ejection fraction (%)	20±3.8	22±3.5	*>0.05*
Creatinine levels (mg/dl)	0.81±0.14	0.79±0.19	*>0.05*
Hypertension	55%	60%	*>0.05*
Diabet	6 (30%)	5 (25%)	*>0.05*
Peripheral vascular disease	3 (15%)	2 (10%)	*>0.05*

who couldn't be weaned from CPB peroperatively. Whole patients have received dobutamine 8-10 μ/kg/min, and also 1μ/kg/min nitroglycerine infusion. We have administered adrenaline and calcium infusion for maintaning effective systemic arterial pressure. Antibiotic proflaxis was achieved by cefazolin 3x1g/day. The patients were monitorized in the intensive care unit (ICU) concerning the hemodynamic parameters (cardiac index, central venous pressure, systemic mean arterial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, systemic and pulmonary vascular resistance) and hourly urine output. Whole blood count, activated clotting time (ACT), electrolytes, BUN, creatinine, arterial blood gases and ECG were obtained for all of the patients.

Hourly urine output below 30 ml accepted as oliguria, while below 17 ml accepted as anuria. More than 0.5 mg increment of creatinine or more than 50% increment of creatinine compared to the preoperative levels in the oliguria/anuria detected patients were accepted as ARF.(1) The patients were in low cardiac output syndrome for 8-10 hours postoperatively (mean 8.2±4.2) and the hemodynamic parameters were recorded (Table-2) We immediately inserted IABP on these 28 patients in ICU. One patient (3.57%) who inserted IABP had pulseless, cold and pail leg in the side of IABP. We have moved IABP to the another leg and we have made embolectomy to the privious IABP side. IABP of the extubated patient were removed 2.2±1.2 hours later after the extubation on average.

The preoperatively normal renal functioned patients underwent operation under non-pulsatile CPB. 32 patients (80%) underwent CABG while 8 patients (20%) underwent CABG and concomitant mitral ring annuloplasty for ischemic mitral failure (2°-3°). The patients who were in low cardiac output in the 8-10th hours postoperatively and developed ARF in the early period (mean 13.4±15.2th hours) were randomised into two groups. While hypertonic diuretic infusion (500 cc 3% Nacl containing 500 mg Furosemide, 20 g. mannitol, 50 cc 30% Dextrose) was administered to 20 patients (group 1), fractioned furosemide was administered to the remaining 20 patients (group 2). Hypertonic diuretic infusion was adjusted for 24 hrs. while the total dose of the furosemide was adjusted as 500 mg/day. Hemodynamic parameters were recorded in the two groups (Table-3). For all of the patients that have been devoleped ARF in ICU we have made renal artery doppler ultrasonography and we haven't seen any insufficiency in the flow of the renal artery. Controlled veno-venous hemodiafiltration (Baxter Hemoconcent, REF HO 7000) by a roller pump (Masterflex L/S 7518-10 Cole-parmer Instrument Company) combined with reverse flow peritoneal dialysis solution (2.27%) was performed for the patients who maintaned ARF in spite of the two regimens begining in the 36-48th hrs. (mean 41±4 h.) and lasting till 96 ± 5 hrs. postoperatively. The flow of the hemodiafiltration was adjusted as 100-150 ml/min. Heparin was administered in a 200-400 IU/hr dose to the prefilter line and ACT was maintaned over 200/sn. Veno-venous filtration

Table-2. Hemodynamic parameters of the patients in the early postoperative period.

	GROUP I	GROUP II	p value
Cardiac index (L/min/m^2)	1.2±0.2	1.2±0.3	>0.05
Systemic vasculary resistance (dyn/sec/m^2)	1800±100	1875±75	>0.05
Pulmonary vasculary resistance (dyn/sec/m^2)	120±8	145±9	>0.05
Mean arterial pressure (mm-Hg)	55±11	58±13	>0.05
Pulmonary capillary wedge pressure(mm-Hg)	14±1.3	15±1.5	>0.05
Central venous pressure (mm-Hg)	11±2	12±3	>0.05

Table-3. Hemodynamic parameters of the patients after during ARF.

	GROUP I	GROUP II	p value
Cardiac index (L/min/m^2)	1.7±0.2	1.8±0.3	>0.05
Systemic vasculary resistance (dyn/sec/m^2)	1100±100	1125±75	>0.05
Pulmonary vasculary resistance (dyn/sec/m^2)	90±8	85±9	>0.05
Mean arterial pressure (mm-Hg)	75±15	78±15	>0.05
Pulmonary capillary wedge pressure (mmHg)	12±1.3	11±1.5	>0.05
Central venous pressure (mm-Hg)	8±2	8±2	>0.05

was performed by a dual lumen catheter (JOKA Kathetertechknik GmbH 11 F Fem.Catheter Kit.) inserted to the femoral vein.

Statistical Analysis

The differences between the two groups were evaluated by γ^2 and Fischer's test. When the *p* value was <0.05, the difference between the groups was accepted as significant.

RESULTS:

There was no statistically significant difference between the two groups concerning the hemodynamic parameters (p>0.05). The mean creatinine levels of the patients to whom hypertonic diuretic infusion was administered following ARF was between 1.5-2.3mg/dl. Totally 500 mg Furosemide was administered to both group of patients in the first 8-10th hrs. Although hemodynamic parameters revealed low cardiac output findings, the urine outputs of the patients were more than 1 ml/kg/h. In the end of this 8-10 hours period LOS recovered to normal. 14 patients (70%) weaned from oliguric/anuric state after hypertonic diuretic infusion administration in the average 36-48th hrs (mean 41±4 h) and were extubated.

Veno-venous hemodiafiltration by a non-pulsatile roller pump was performed for 6 patients (30%) in this group who were under mechanical ventilation because of the ongoing oliguric/anuric state despite hypertonic diuretic infusion and hyperkalemia, metabolic acidosis and volume overload in the 36-48th hrs. (mean 41±4 h.) postoperatively in the ICU. Hemofiltration was performed with 2.27% peritoneal dialysis solution with reverse flow. 5lt/24 hrs peritoneal dialysis solution was used for this procedure.

Hypertonic diuretic infusion was continued for these patients, but the furosemide content was diminished to 500 mg/dl. Diuresis started in all of the patients in the 72-96th hrs. (mean 85.2±95.5 h.) and they were weaned from the oliguric/anuric state. Hemodiafiltration was terminated at this stage. The patients were extubated in the 98.4±4 hr. on average. Hyperglicemia occurred due to the glucose content of the peritoneal dialysis solution in the 4 patients (20%) who were diabetic preoperatively and the blood glucose levels were regulated and kept below 140 mg/dl by regular insulin infusion. The patients who developed hypotension during hemodiafiltration procedure were managed by the temporary cessation of the filtration, volume loading and short-duration adrenaline infusion (250 ml 0.9% NaCl containing 4 mg adrenaline and 40 ml %10 calcium). All of the patients in this group were weaned from ARF on the postoperative 1st week and the decreases of the creatinine values were noted. The avarage creatinine values of the patients were 1.1±0.2 mg/dl in the end of the 1st week.

The creatinine levels of the fractioned furosemide used patients were between 1.6-2.2 mg/dl. Furosemide was administered to this group of patients as 500 mg/24 hrs. 10 patients (50%) were weaned from ARF in the 36-48th (mean 39.3±7.4 h.). Hemodiafiltration was performed for the remaining 10 entubated patients because of

the ongoing oliguric/anuric state and hyperkalemia, metabolic acidosis and volume overload. 5lt/24 hrs the same peritoneal dialysis solution was used for this procedure.

Fractioned furosemide administration was continued in 500mg/24 hrs dose to the patients to whom we performed hemodiafiltration. Hyperglicemia, which occurred in 5 preoperatively diabetic patients, was regulated to keep the blood glucose level below 140 mg/dl by regular insulin infusion. 6 patients (30%) weaned from the oliguric/anuric state and were free of the hemodiafiltration requirement. These patients were extubated within several hours. 4 patients (20%) were taken into hemodialysis schedule for ongoing oliguric/anuric state and hyperkalemia, metabolic acidosis and volume overload till the end of the 2nd week. Renal functions of the 2 patients in this group returned to normal in the 3rd postoperative week and the mean creatinine levels decreased to 1.2± 0.2 mg/dl. The remaining 2 patients' renal functions didn't return to normal and they were concerned as chronic renal failure (CRF) and were taken to hemodialysis schedule. One of them died on the 28th, and the other died on the 39th day due to sepsis and multiorgan failure.

There was significant difference between the two groups comparing the hemodiafiltration requirement and progression to CRF. The results of the hypertonic diuretic infusion group were superior compared to the other one (Figure-1).

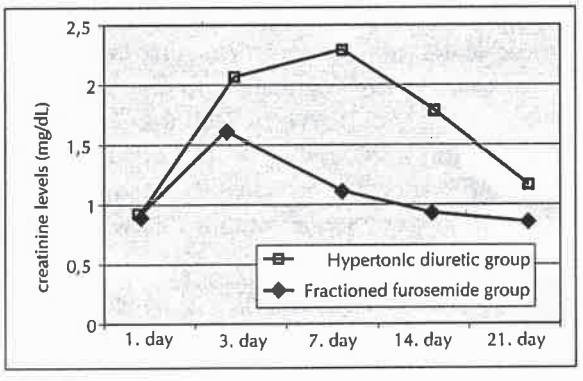

Figure 1: The creatinine levels of the two groups (p>0.05)

DISCUSSION:

ARF may occur due to the decrease of the renal perfusion without cellular damage. Prerenal renal failure refers to the failure due to renal perfusion decrease while the tubular and glomerular functions remain normal; the one due to the obstruction in the urinary outflow tract is named as postrenal failure; and renal originated one is known as intrinsic renal failure (1).

The continuous infusion of the solution of furosemide (0.6 mg to 0.85 mg/kg/h) with simultaneous administration of mannitol (0.06 gm to 0.08 gm/kg/h) and renal doses (2–3 mcg/kg/min) of dopamine promoted diuresis in acute postoperative renal dysfunction with adequate postoperative cardiac output. Diuresis occurred both in patients with preoperative normal renal function and preoperative renal dysfunction and significantly decreased the need for postoperative dialysis. Diuresis was also observed in renal dysfunction complicating pigment nephropathy (ie, nephropathy induced by increased load of myoglobin and hemoglobin pigments in blood), which may occasionally complicate surgery of acute Type I aortic dissection using periods of circulatory arrest. Despite hyperosmolarity of the solution, consequent to its administration, there was improvement in pulmonary gas exchange with a decrease in edema of all tissues including the myocardium. (2)

Cardiopulmonary bypass (CPB) has negative effects on renal physiology due to non-pulsatile flow properties (3), insufficient renal perfusion (4), and the effect of free hemoglobin released as a result of hemolysis (5). CPB leads to the decrease of the organ perfusion increasing the vasomotor tonus. The most important reason of ARF following CPB is renal affarent arteriolar vasoconstriction. Angiotensin II levels were detected high in non-pulsatile CPB, this leads to renal arterial vasoconstriction and hemolysis occurring during CPB causes toxic effects in the renal microvascular structure. The location of the reperfusion injury is also important in the occurrence of renal damage in CPB. Neutrophylls extravasated of the vasculary endothelial structure following ischemia move to the ischemic tissue

(6). The complement cascade activates after neutrophyl chemotaxis; and leads to the release of active oxygen radicals, protease, elastase, myeloperoxidase from the neutrophylls and these lead to the occurrence of the renal damage (7).

Renal vasoconstriction; desquamation of the renal tubular cells and renal tubular obstruction occurs due to the aforementioned effects of CPB (8). This pathology appears as oliguric/anuric acut renal failure clinically (9). Our patient group had low cardiac output as an additional risk factor accompanying the deleterious effects of CPB. The patients stayed in low cardiac output despite the inotropic support 8-10 hrs. (mean 8.2± 4.2). ARF occurred in the 13.4± 15.2 postoperative hrs. although there was no hemodynamic problem.

There are various treatment modes of ARF following open-heart surgery. Renal dose dopamine infusion that we administer to any patient groups leads to renal arteriolar vasodilatation and increases the renal blood flow and glomerular filtration rate (10,11). Using calcium channel blockers can cease vasoconstriction, caused by the free calcium ions by increasing the tonus of the vascular smooth muscle cells. For this reason, calcium-blocking agents may be used for the treatment of ARF for renal vasodilation aim like dopamine (9).

Off-pump cardiac surgery has removed the deleterious effects of the CPB on the kidneys. Thus the postoperative ARF occurrence rate was diminished noteworthy (12). The protective effects of mannitol and furosemide in the ischemic renal injury were shown (13). The combined early use of the hypertonic agents, of mannitol and furosemide is effective in the treatment of the oloiguric/anuric ARF by increasing the urine amount (14). Renovasculary and functional effects of furosemide and mannitol are to increase the renal blood flow and solid discharge (15). We increased the osmolarity of the diuretic solution by adding 30% Dextrose and 3% NaCl. While without this addition the osmolarity of the diuretic solution was 440 mOsm/L, with this addition the osmolarity increased to 570 mOsm/l.

Dialysis is used for the treatment of the hypervolemia, electrolyte imbalance and the metabolic acidosis in ARF (16). Hemodialysis, as a dialysis method was reported by Kramer in 1977 (17). The superiorities of hemofiltration to hemodialysis are the 90% urea elimination, it doesn't lead to leukopenia as a result of the confrontation of the blood with capillary hemofilter, non-alteration of complement levels and it doesn't increase bleeding risks as small amounts of heparin is used (18). Uremic symptoms, electrolyte imbalance and hypervolemia are prevented by the continuous use of hemofiltration and thus the mortality due to ARF is decreased (19,20). Mannitol and furosemide infusion diminishes the postoperative dialysis requirements of the patients with or without normal preoperative renal functions (21).

We achieved the weaning from ARF and the decrease of the dialysis requirement of the patients who had normal preoperative renal functions and developed ARF due to low cardiac output in the postoperative early period with the combined use of the diuretic infusion composed of hypertonic solutions and renal dose dopamine. In addition we achieved to resume the normal renal functions of the patients with metabolic acidosis, electrolyte imbalance and volume overload by controlled, reverse flow peritoneal dialysis solution combined with veno-venous hemodiafiltration by improving the renal functions and diminished the hemodialysis requirement progressing to CRF noteworthy. We noted statistically significant worse results in the intermittent furosemide using patients concerning the hemofiltration and hemodialysis requirement, weaning from ARF, progression to CRF compared to the hypertonic diuretic used group. We believe that hypertonic diuretic infusion, renal dose dopamine and hemodiafiltration are effective treatments for the ARF due to low cardiac output following open-heart surgery.

REFERENCES

1- R. Thadhani, MD, M. Pascaul, MD, and J. V. Bonventre,MD, PHD. Acute renal failure. *N Engl J Med 1996:1448-1460.*

2- S. Sirivella, MD, I. Gielchinsky, MD, V. Parsonnet, MD. Mannitol, furosemide, and dopamine infusion in postoperative renal failure complicating cardiac surgery. *Ann Thorac Surg* 2000;69:501-506.

3- Ravitch MM: A Century of Surgery: 1880-1980. *Philadelphia, Lippincott, 1981, vol 2, p889.*

4- Stott RB, Ogg CS, Cameron JS, Bewick M: Why the persistently high mortality in acute renal failure? *Lancet 1972; 2: 75.*

5- Baslov JT, Jorgensen HE: Survey of 499 patients with acute anuric renal insufficiency. *Am J Med 1963; 34:753.*

6- Springer TA. Traffic signals for lymphocte recirculation and leukocyte emigration: the multistep paradigm. *Cell 1994; 76: 301-14.*

7- Weisman HF, Bartow T, Leppo MK, et al. Soluble human complemant receptor type 1: in vivo inhibitor of complement supressing post-ischemic myocardial inflamation and necrosis. *Science 1990; 249: 146-51.*

8- Brezis M, Rosen S. Hypoxia of the renal medulla – its implications for dissease. *N Engl J Med 1995; 332: 647-55.*

9- Bonventre JV. Mechanism of ischemic acute renal failure. *Kidney Int 1993; 43: 1160-78.*

10-Lindner A, Cutler RE, Goodman G. Synergism of dopamine plus furosemide in preventing acute renal failure in the dog. *Kidney Int 1979; 16: 158-66.*

11-AT Tang, A El-Gamel, B Keevil, N Yonan, and AK Deiraniya. The effect of renal-dose dopamine on renal tubuler function following cardiac surgery: assessed by measuring retinal binding protein (RBP). *Eur J Cardiothorac Surg 1999; 15:717-21.*

12-Raimondo A, MD, Clinton TL, FRCS, Malcom JU, FRCS, Walter JG, MD, and Gianni DA, FRCS. On-pump Versus Off-Pump Coranary Revascularization: Evaluation of Renal Function. *Ann Thorac Surg 1999; 68: 493-8.*

13-Mohaupt M, Kramer HJ. Acute ischemic renal failure: review of interventions. *Ren Fail 1989-90; 11: 177-85.*

14-Liberthal W, Levinsky NG. Treatment of acute tubuler necrosis. *Semin Nephrol 1990; 10: 571-83.*

15-Levinsky NG, Bernard DB, Johston PA: Mannitol and loop diüretics in acute renal failure. *Philadelphia, Saunders, 1983, pp 712-722.*

16-Kleinknecht D, Jungers P, Chanard J, et al: Uremic and nonuremic complications in acute renal failure: evaluation of early and frequent dialysis on prognosis. *Kidney Int 1972; 1: 190.*

17-Kramer P, Wiggu W, Rieger J, et al: Arteiovenous hemofiltration: a new and simple method for treatment of overhydrated patients resistant to diüretics. *Klin Wochenschr 1977;55:1121.*

18-Stokke T, Kramu P, Schrader J, et al: Continous arteriovenous hemofiltration. *Anesthesiol* 1982; 31: 579.

19-Conger JO: A controlled evaluation of prophylactic dialysis in posttraumatic acute renal failure. *J Trauma 1975; 15: 1056.*

20-Srikrishana S, MD, Isaac G, MD, and Victor P, MD. Mannitol, Furosemide, and Dopamine Infusion in Postoperative Renal Failure Complicating Cardiac Surgery. *Ann Thorac Surg 2000; 69: 501-6.*

21-Paul B, MD, Han KT, MD, Rinaldo B, MD, Jonathan B, MD, et al: Early and Intensive Continous Hemofiltration for Severe Renal Failure After Cardiac Surgery. *Ann Thorac Surg 2001; 71: 832-7.*

A RARE CRANİOFACİAL CLEFT: TESSIER NO. 7: A RETROSPECTIVE ANALYSIS

Serdar Gökrem* ✣ Orhan Murat Özdemir* ✣ Arda Katırcıoğlu* ✣ Zeynep Şen* ✣ Atilla Ersoy* ✣ Zeki Can* ✣ Murat Emiroğlu* ✣ Serdar Gültan*

SUMMARY

In this report we present a retrospective analysis of our craniofacial cleft cases, classified as Tessier no. 7.

Key Words: *Rare Craniofacial Clefts, Tessier No. 7*

ÖZET

Nadir Görülen Bir Kraniofasiyal Yarık: Tessier No. 7: Retros, Rektif Bir Analiz

Bu yayında nadir görülen fasiyal yarıklardan, Tessier No. 7 olarak sınıflandırılan vakalarımızın retrospektif bir analizi bildirilmiştir.

Anahtar Kelimeler: *Nadir Görülen Fasiyal Yarıklar, Tessier No. 7*

The Tessier No. 7 cleft is the least rare seen atypical craniofacial cleft. The incidence of the malformation is reported to be between 1: 3000 and 1: 5642 births (1). Males are more frequently affected than females. Bilateral involvement is rare.

It has been termed as hemifacial microsomia (1), craniofacial microsomia (2), first and second branchial arch syndrome and otomandibular dysostosis (1).

Clinical expression is variable. A preauricular skin tag can be present in microform cases. In it's complete form, cleft begins as a macrostomia at the oral commissure and continuous across the cheek toward a microtic ear. All soft tissues may be underdeveloped on affected site. Osseous manifestations also cover a wide range.

MATERIALS AND METHODS

Five patients with Tessier No. 7 treated in our clinic, during the last 17 years, were evaluated. The age of admission was between 4 months to 12 years of age. All patients were female. There was no family history (Table 1).

Table 1: Age and sex distribution of the patients.

Sex	Age	Family History
Female	4 months	(-)
Female	7 months	(-)
Female	11 months	(-)
Female	2 years	(-)
Female	12 years	(-)

There patients had the lateral fascial cleft on the left oral commisure and two had the deformity on the right (Figure 1a, Figure 2a, Figure 3a). Two patients had pretragal skin tag as associated deformity (2a, 3b). One of these two patients had bilateral prominant ear deformity and left, Puzansky type Ia hypoplastic mandibular ramus additionaly (Figure 3c). All patients were classified as type Ia, according to Harvold classification. Correction of the macrostomia was done according to Skoog technique (Table 2).

* Ankara University, Medical School Department of Plastic and Reconstructive Surgery.

Received: March 25, 2002 Accepted: Oct. 09, 2002

Table 2: Clinical presentation of the patients

Site of the lateral cleft	Associated Deformities	Classification (According to Harvold)	Operative Technique
R	(-)	Type Ia	Skoog
L	Preauricular skin tag	Type Ia	Skoog
R	(-)	Type Ia	Skoog
L	(-)	Type Ia	Skoog
L	Preauricular skin tag, bilateral prominent ear, left hypoplastic mandibular ramus (Pruzansky type Ia)	Type Ia	Skoog

OPERATIVE TECHNIQUE

After the excision of preauricular skin tag (Figure 3d) oral commisures were reconstructed with the technique desciribed by Skoog (3).

After the proposed oral commisure is marked, a surgical oral commisure is created laterally because of the expected postoperative contraction. A dot is placed opposite on the lower lip (Figüre 1b, Figure 3e). After the vermillion turnover flap is prepareted oral mucosa is closed (Figure 3f). Upper and lower muscle bundles are skeletonized and divided and upper bundle is sutured over lower one. Skin closure is done according to Z-plasty principles (Figure 3g). In one patient skin is closed primarily (Figure 2b).

RESULTS

During the postoperative follow-up period we didn't see any problem (Figure 1c, Figure 2c, figure 3h).

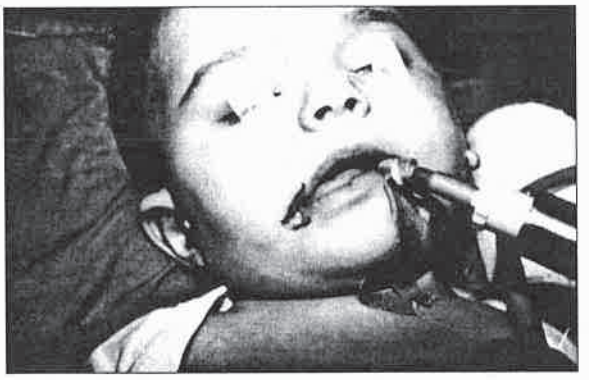

Figure 1b: Preoperative planning

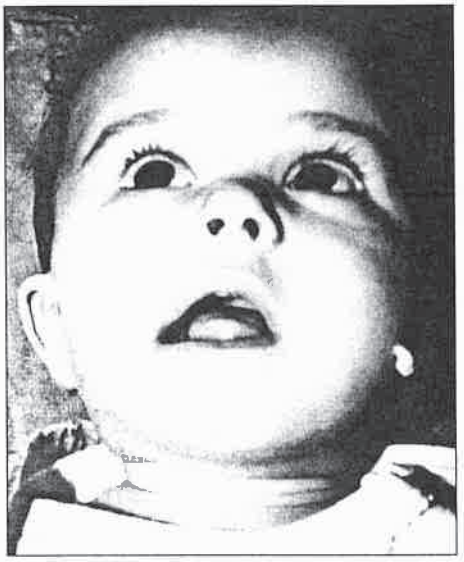

Figure 1a: Preoperative appearance of the cleft

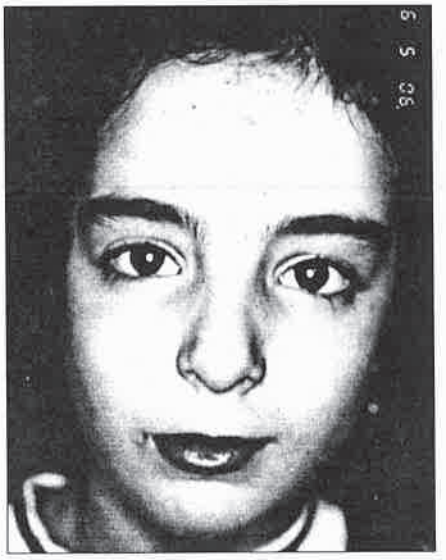

Figure 1c: Late postoperative result

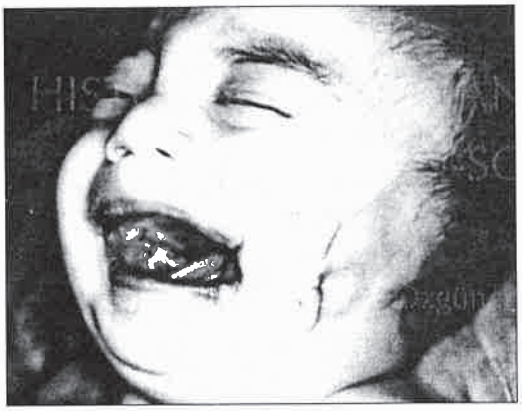

Figure 2a: Preoperative appearance of the cleft and the preauricular skin tag

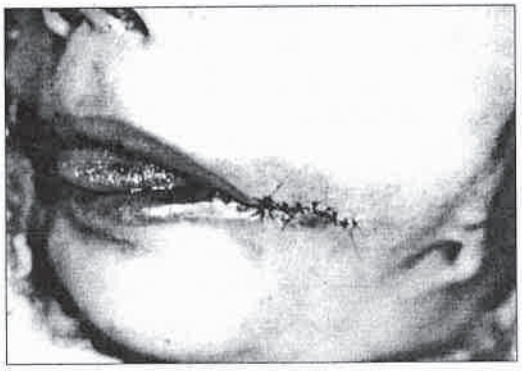

Figure 2b: Intraopeartive view

Figure 2c: Late postoperative result

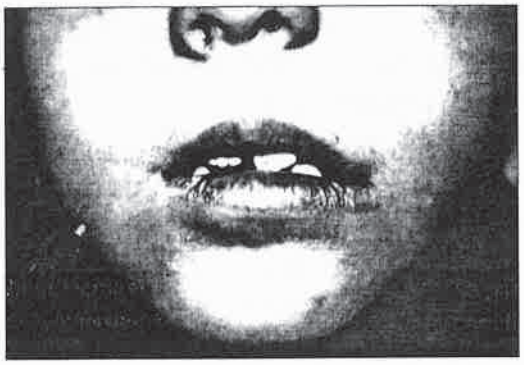

Figure 3a: Preoperative appearance of the cleft

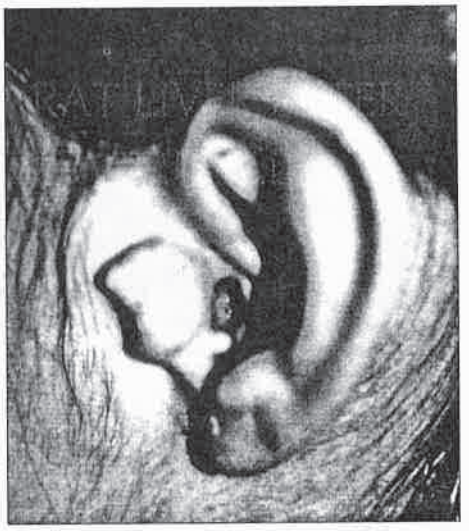

Figure 3b: Preoperative appearance of the preauricular skin tag

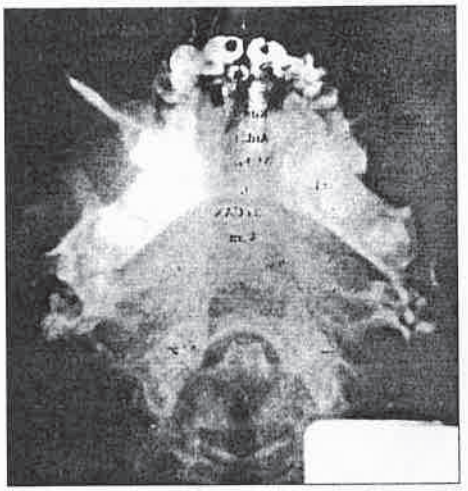

Figure 3c: Radiographic appearance of the hypoplastic ramus mandibula

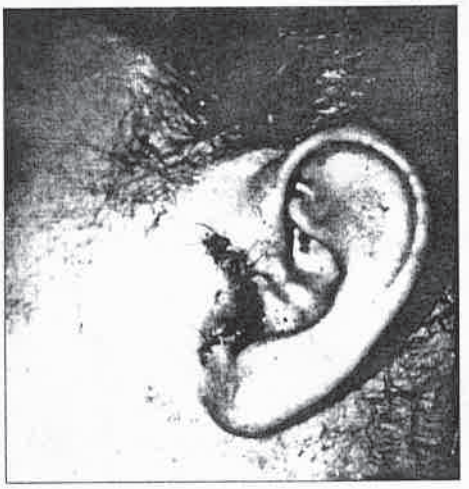

Figure 3d: Excision of the preauricular skin tag

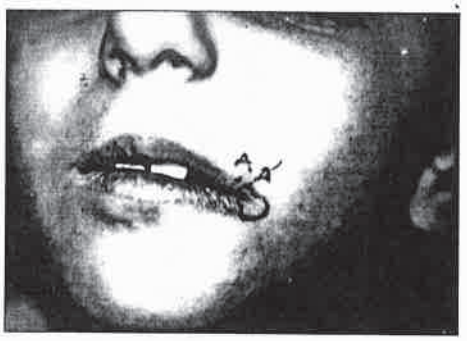

Figure 3e: Preoperative planning

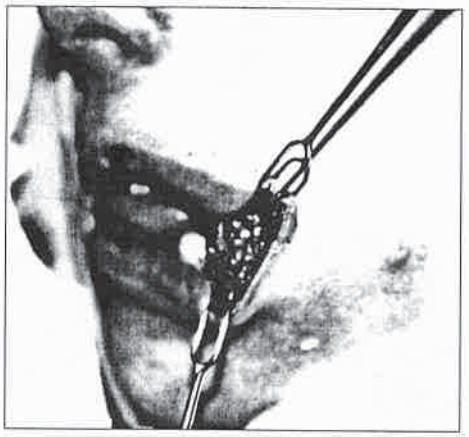

Figure 3f: Closure of the oral mucosa

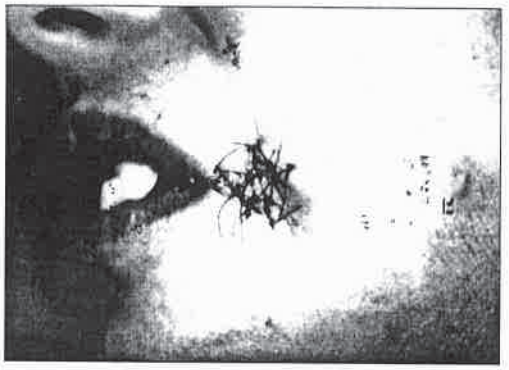

Figure 3g: Closure of the skin according to z-plasy principles

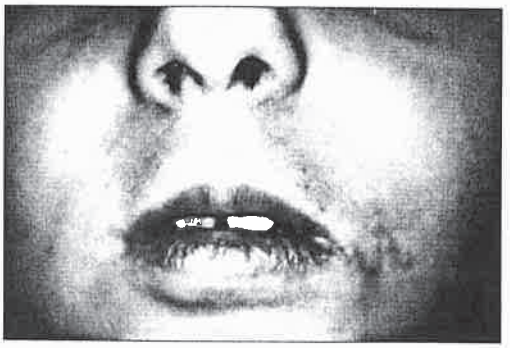

Figure 3h: Late postoperative result

DISCUSSION

Although this deformity is seen more frequently in males, all of our patients were interestingly, female.

As previously mentioned this syndrome shows wide variety in pathologic expression.

According to Pruzansky (4) mandibular deficiency may be classified as;

Type I: Mild hypoplasia of the ramus, and the body of the mandibula is minimally or slightly affected.

Type II: The condyle and ramus are small; the head of the condyle is flattened; the glenoid fossa is absent; the condyle is hinged on a flat, often convex, infratemporal surface; the coronoid process may be absent.

Type III: The ramus is reduced to a thin lamina of bone or is completely absent.

Maxilla, zygomatic complex, the temporal bone and the frontal bone may be hypoplastic. Orbit is often reduced in all dimensions.

One of our patients had Pruzansky Type Ia mandibular deformity.

On the affected site preauricular skin tags are common and the skin, the subcutaneous tissue, tongue, soft palate mimic muscles and muscles of mastication may also be hypoplastic.

Two of our patients had preauricular skin tag.

Absence of the facial nerve function in the distribution of the marginal mandibular branch is seen approximately %25 of patients, with weakness of other components (5). There were no problems associated with facial nerve in our patients. Involvement of the auricle occurs in most of cases and varies from near normalcy to complete absence. One of our patients had prominent ear deformity.

There are some classification systems of the syndrome. Harvold, Vargervik and Chierici proposed following classification (6):

Ia. Unilateral facial underdevelopment without microphtalmos or ocular dermoids but with or without abnormalities of vertebrae, heart or kidneys.

Ib. Similar to type I (a) except for the presence of microphtalmos.

Ic. Bilateral asymmetric type in which one site is more severely involved.

Id. Complex type that doesn't fit the above but doesn't display limp deficiency, frontonasal phenotype or ocular dermoids.

II. Limp deficiency type-unilateral or bilateral-with or without ocular abnormalities.

III. Frontonasal type. Relative unilateral underdevelopment of the face in the absence of hypertelorism with or without ocular dermoids and vertebral cardiac or renal abnormalities.

IV. (A) Unilateral or (B) Bilateral. Goldenhard type with facial underdevelopment in association with ocular dermoids, with or without under lid coloboma.

All of our patients were classified as Type Ia.

All treatment plans must be customized according to the needs and the age of the individual patient.

Under two years of age:

Excision of preauricular skin tag and correction of macrosomia by commisuroplasty.

Two to six years of age:

In children with severe reduction in the vertical height of mandibular ramus distraction osteogenesis may be performed.

In the patients with a Pruzansky Type III deformity a preliminary costochondral rib graft reconstruction should be performed at the age of four.

In patients with bilateral craniofacial microsomia bilateral mandibular distruction can be performed at the age of two years.

Six to fourteen years of age:

This is the period of orthodontic treatment and facial soft tissue augmentation.

Beyond the fourteen years of age:

Limited autogenous bone grafting of the deficient portions of the craniofacial skeleton, combined LeFort I osteotomy, bilateral mandibular ramisection and genioplasty, bilateral mandibular advencement in patients with mild to moderate mandibular micrognathia and microvascular free flap soft tissue augmentation of the soft tissues may be considered.

REFERENCES

1. Grabb and Smith's, Plastic Surgery 5th edition, Philedelphia-New York, Lippincott-Raven, 1997.
2. Converse, J. M., et al. Craniofacial microsomia. In J. M. Converse (ed.), Reconstructive Plastic Surgery (2nd ed.) Philadelphia: W. B. Saunders, 1977, P. 2359.
3. Skoog T G: Plastic Surgery. 1974, Almquist – Wiksell International, Stockholm.
4. Pruzansky S. Not all dwarfed mandibles are alike. Birth Defects 5: 120, 1969.
5. Mulliken, J. B., Kaban, L. B. Analysis and treatment of hemifacial microsimia? in childhood. Clin. Plast. Surg., 14:91, 1987.
6. Harvold, E. P., Vargervick, K., Chierici G. Treatment of hemifacial microsomia. New York: A. R. Liss, 1983.

SONOGRAPHY GUIDED PERCUTANEOUS NEPHROSTOMY: SUCCESS RATES ACCORDING TO THE GRADE OF THE HYDRONEPHROSIS

Eriz Özden* ✣ Önder Yaman* ✣ Tarkan Soygür* ✣ Çağatay Göğüş* ✣ Zafer Tokatlı* ✣ Orhan Göğüş*

SUMMARY

Percutaneous nephrostomy (PCN) procedure can be performed with ultrasonography (US) or fluoroscopy. We undertook a retrospective analysis of 58 PCN's performed only by US guidance with the aim of evaluating the grade of hydronephrosis that is enough to establish the procedure without fluoroscopy. In 48 patients, 58 PCN procedures were performed using the Seldinger technique under US guidance. The procedure had a success rate of %50 in grade 1, %85 in grade 2 and %95 in grade 3 hydronephrosis. In patients with grade 2 and 3 hydronephrotic kidneys, PCN can be performed safely using only US guidance.

Key Words: *Hydronephrosis, Percutaneous Nephrostomy, Ultrasound*

ÖZET

Perkütan Nefrostomi Yerleştirilmesi

Perkütan nefrostomi katateri yerleştirilmesi (PCN) işlemi ultrasonografi (US) veya fluoroskopi eşliğinde uygulanabilir. Kliniğimizde sadece US kılavuzluğunda yapılan 58 PCN işlemini retrospektif olarak inceleyerek, işlemin fluoroskopi eşliğine gerek kalmadan yapılabilmesi için gerekli hidronefroz düzeyini belirlemeyi amaçladık. 48 hastaya 58 adet PCN işlemi, US eşliğinde Seldinger yöntemi ile uygulandı. Başarı oranları: grade 1 düzeyinde hidronefrozda %50, grade 2' de % 85, grade 3'te %95 idi. Sonuçlarımıza göre; grade 2 ve 3 düzeyinde hironefrotik böbrekli hastalarda, PCN sadece US eşliğinde güvenli bir şekilde yapılabilir.

Anahtar Kelimeler: *Hidronefroz, Perkütan Nefrostomi, Ultrasonografi*

Percutaneous nephrostomy catheter (PCN) placement was initially described by Goodwin in 1955 (1). Its main indication is drainage of the obstructed collecting system (2). PCN is a procedure that is preferred for its low mortality and complication rates and for not requiring general anesthesia (2). While selection of the initial needle puncture site and entrance to the pelvicalyceal system (PCS) is generaly done with ultrasonography (US) guidance, fluoroscopy has been preferred for guide wire and catheter manipulations (3). PCN with only US guidance has been reported in pregnant women and children to avoid radiation exposure (4-7).

As there are only a few reports in the literature about US guided PCN and none of them had reported definitive criteria on patient selection, we retrospectively searched our US guided PCN series to find out the grade of hydronephrosis that allows satisfactorly PCN placement with only US guidance.

MATERIALS AND METHODS

During a two year period (2000- 2001), 58 PCN's on 48 patients (9 women, 39 men, age; 20-76 years, mean 52 years) were performed. Bilateral procedures were undertaken in 10 patients.

Indications were; obstruction due to urolithiasis or malignancy, ureteropelvic or ureterovesical stenosis and preoperative decompression of the dilated collecting system.

* Ankara University, Department of Urology.

** Presented At; Uroradiology Symposium April 2002, Çeşme-Turkey.

Received: July 16, 2002 Accepted: Sept. 06, 2002

We classifed the grade of hydronephrosis as follows; mild PCS dilatation: grade 1, moderate PCS dilatation and normal parenchyma : grade 2, severe PCS dilatation with a large pelvis and significant calyceal dilatation and parenchymal thinning: grade 3 hydronephrosis (8, 9). Of the 58 kidneys, four were grade 1, 34 were grade 2 and 20 were grade 3 hydronephrotic.

SSA 250A Toshiba US system with 3.5 MHz sector transducer was used to guide the procedure. All PCN's were performed by the same radiologist and an assistant using the Seldinger technique, with sterile technique under local anesthesia. Patients were positioned lateral or prone- oblique and under US guidance, an 18 G needle is placed into a lower pole calyx. A J tip guidewire is introduced via the needle lumen into the renal pelvis and than the needle is removed. After the dilatation of the tract with three dilators, a 7 or 8 F catheter is introduced and the guidewire is removed. During the procedure, all manuevers are continiously monitored with US. Correct catheter position is determined by free urine drainage or nephostography when needed.

RESULTS

In four grade 1 hydronephrotic kidneys, there were two satisfactory catheter placement and the success rate is % 50. In 34 grade 2 hydronephrotic kidneys, we placed 29 catheters satisfactorily and the success rate is % 85. We placed 19 catheters in 20 patients with grade 3 hydronephrosis (% 95 success rate), and the overall success rate is % 86.

Major complications occured in three patients (% 5). These were two perirenal hematoma and one postprocedure sepsis. In eight procedures (% 13.7) catheter dislodgement occured and two cases (% 3.4) required catheter exchange because of blockage.

DISCUSSION

PCN placement is a safe and rapid procedure to drain obstruced collecting system (4). While in the earlier series intravenous contrast media and fluoroscopy have been used to viualize the PCS, now US is generally being used (10, 11). But after the entrance to the PCS with US guidance, fluoroscopy is preferred for visualizing the guidewire and catheter manuevers (3).

PCN with C armed fluoroscopy assistance does not expose patient to high radiation doses but as radiation has no threshold dose, even the minimal exposure must be avoided if possible (12). US guided PCN has advantages of not including radiation and not requiring IV contrast media usage. There are only a few reports in the literature on US guided PCN using Seldinger technique (4,13). Gupta and associates reported a success rate of % 91.1 for 273 PCN's with US guidance, but did not defined hydronephrosis grades (4).

In our series, our success rate for grade 1 hydronephrotic kidneys were % 50. Despite poor visualization of the PCS, PCN were attempted because of emergency in these cases and this is the reason of the low case number. Two catheters were placed satisfactorily but in the other two patients, poor visualization caused by the insufficiently dilated calyces did not allow the needle to be accessed into the PCS.

Our success rate was % 85 in grade 2 hydronephrotic kidneys (34 /29). Of the five cases that could not be achieved satisfactory placement , in two, we could not obtain access to the PCS and in one case urine drainage was achieved after catheter placement but we detected at nephrostography that one of the side holes of the catheter was out of the PCS. These three cases were because of inadequacy of US guidance. In one case, the procedure was stopped because of intracalyceal hemorrhage and in one because of fibrotic tissue that did not allow needle manuevers. These two attempts are a failure but not caused by US guidance and with these two accepted out of the study group, the real success rate of US guidance rises to % 91 in grade 2 hydronephrosis. But this is still under the % 96-100 reported success rates of fluoroscopy guided procedures (2, 14).

In the grade 3 hydronephrotic group, our success rate was % 95 (20/ 19). In only one case the procedure was stopped and this was because of dense fibrotic tissue and pain intolerance of the patient, not caused by US guidance. If we accept this case out of the study group, the success rate of US guidance rises to % 100 in grade 3 hydronephrosis and is in the same range with fluoroscopy guided procedures (14).

The potential complications of PCN are; sepsis, perirenal hematoma, urinoma formation, perforation of a viscus, pyopneumothorax or minor complications like dislodgement or obstruction of the catheter (15).The incidance of significant complications with fluoroscopy guided PCN has been estimated to be %1- 4 (16,17). In our series, there were two perirenal hematoma and one postprocedure sepsis and this % 5 incidance of significant complications are not significantly higher than fluoroscopy guided procedures. There were eight (% 13.7) catheter dislodgement and two (% 3.4) catheter blockages that required exchange of catheter in our series and these rates are in correlation with reported %7- 14 minor complication rates of fluoroscopy guided procedures (2, 17, 18).

In conclusion, our results indicate that; US guided PCN has high success rates in grade 2 and especially in grade 3 hydronephrosis and must be the procedure of choice in selected, adequately visualized grade 2 and all grade 3 hydronephrotic kidneys.

REFERENCES

1. Goodwin WE, Casey WC, Woolf W. Percutaneous trocar (needle) nephrostomy in hydronephrosis. JAMA 1955; 157: 891-4.
2. Kaskarelis IS, Papadaki MG, Malliarki NE, et al. Complications of percutaneous nephrostomy, Percutaneous insertion of üreteral endoprosthesis and replacement procedures. Cardiovasc Intervent Radiol 2001; 24: 224-28.
3. Zegel HG, Pollack HM, Banner MP, et al. Percutaneous nephrostomy. Comparision of sonographic and fluoroscopic guidance. AJR 1981; 137: 925-7.
4. Gupta S, Gulati M, Shankar K, et al. Percutaneous nephrostomy with real – time sonographic guidance. Acta Radiologica 1997; 38: 454 – 457.
5. Trewhalla M, Reid B, Gillespie A, et al. Percutaneous nephrostomy to relieve renal obstruction in pregnancy. Br J Radiol 1991; 64: 471- 2.
6. VanSonnenberg E, Casola G, Talner LB, et al. Symptomatic renal obstruction or urosepsis during pregnancy. Treatment by sonographically guided percutaneous nephrostomy. AJR 1992; 158: 91- 4.
7. Von der Recke P, Nielsen MB, Pedersen JF. Complications of ultrasound guided nephrostomy. A 5 year experience. Acta Radiol 1994; 35: 452- 4.
8. Judith AW Webb. The renal collecting system. In: Cosgrove D, Meire H, Dewburry K, eds. Abdominal and General Ultrasound, 1993; Vol 2: 471.
9. Fernbach SK, Maiselz M, Conway JJ. Ultrasound grading of hydronephrosis: introduction to the system used by the society for fetal urology. Pediatr Radiol 1993; 23: 478 – 480.
10. Saxton HM. Percutaneous nephrostomy. Technique. Urol Radiol 1981; 2: 131- 9.
11. Dubuisson RL, Eichelberger RP, Jones TB. A simple modification of real – time sector sonography to monitor percutaneous nephrostomy. Radiology 1983; 146: 232.
12. Bush WH, Brannen GE, Gibbons RP, et al. Radiation exposure to patients and urologists during percutaneous nephrostolithotomy. J Urol 1984; 132: 1148 – 52.
13. Gupta DK, Chandrasekhram VS, Srinivas M, et al.Percutaneous nephrostomy in children with ureteropelvic junction obstruction and poor renal function. Urology 2001; 57: 547 – 550.
14. Le Roy AJ, May GR, Bender CE, et al. Percutaneous nephrostomy for stone removal Radiology 1984; 151: 607- 612.
15. Watson RA, Esposito M, Richter F, et al. Percutaneous nephrostomy as adjunct management in advanced upper urinary tract infection. Urology 1999; 54: 234 – 39.
16. Prister RC, Papanicolau N, Yader K. Diagnostic, morphologic and urodynamic antegrade pyelography. Radiol Clin North Am 1986; 24: 561- 71.
17. Stables DP. Percutaneous nephrostomy; techniques, indications and results. Urol Clin North Am 1982; 9: 15-29.
18. Nolsoe C, Nielsen L, Torp-Pedersen S, et al. Major complications and deaths due to interventional ultrasonography: a review of 8000 cases. J Clin Ultrasound 1990; 18: 179-184.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 24 No 2, 2002 73-82

Na^+, K^+–ATPASE: A REVIEW

Aslıhan Aydemir Köksoy*

SUMMARY

The enzymatic manifestation of the sodium pump is the Na^+, K^+-ATPase. This enzyme, found in all mammalian cell membranes, is necessary for proper cellular function since it helps to preserve the ionic gradients across the cell membrane and thus the membrane potential and osmotic equilibrium of the cell. This review aims to inform the reader about the molecular regulation of the sodium pump expression and function, as well as providing insight on the role of the sodium pump as an ion regulator and a signaling protein in mammalian cells.

Keywords: *Sodium Pump, ATPase, Protein Expression, Ouabain, Signaling*

ÖZET

Na^+, K^+ Atpase

Na^+, K^+-ATPazın enzimatik gösterimi sodyum pompası olarak da bilinir. Bu enzim tüm memeli hücrelerinin membranlarında bulunmaktadır. Soyum pompası hücre membranının iki tarafındaki iyon gradientlerinin düzenlenmesi ve korunmasından sorumlu ana protein olarak karşımıza çıkar ve bu nedenle hücrelerin düzgün çalışması, membran potansiyelinin ve ozmotik dengenin korunması için mutlaka gereklidir. Bu derleme memeli hücrelerinde sodyum pompasının ekspresyonu ve fonksiyonunu düzenleyen moleküler mekanizmalar yanında sodyum pompasının bir iyonik regulatör ve sinyalci protein olarak rolü hakkında bilgi vermeyi amaçlamaktadır.

Anahtar Kelimeler: *Sodyum Pompası, ATPaz, Protein Ekspresyonu, Ouabain, Sinyal İletimi*

All eukaryotic animal cells have high extracellular sodium and high intracellular potassium, a reverse of the situation seen outside the cells. A typical cell keeps a resting membrane potential of -70 mV. Potassium ions will tend to flow out of the cell, since their equilibrium potential (-91 mV) is more negative than the transmembrane potential. Sodium ions have a very strong force driving them into the cell, since both the chemical and electrical gradients (equilibrium potential of +64 mV) favor Na^+ uptake. The enzymatic manifestation of the sodium pump is the Na^+, K^+-ATPase. This enzyme, found in all mammalian cell membranes, is necessary for proper cellular function since it helps to preserve the ionic gradients across the cell membrane and thus the membrane potential and osmotic equilibrium of the cell [1]. The enzyme pumps $3Na^+$ and $2K^+$ ions against their concentration gradient, at the expense of an ATP molecule. The transport of $3Na^+$ for $2K^+$ across the membrane, through the means of the sodium pump, maintains transmembrane gradients for the ions and produces a convenient driving force for the secondary transport of metabolic substrates such as amino acids and glucose. In addition the nonequivalent transport is electrogenic and leads to the generation of a transmembrane electrical potential allowing cells to become excitable.

The ATPase family:

Sodium pump belongs to the family of P-ATPases along with the sarcoplasmic reticulum and plasma membrane Ca^{+2} ATPase and H^+, K^+ ATPase of stomach and colon in vertebrates. P-type ATPase superfamily, differs structurally and

* Ankara University, Medical Department of Biophysics.

Received: March 08, 2002 Accepted: May. 20, 2002

functionally from both the F-type ATPases (ATP-synthases present in prokaryotes, chloroplasts, and mitochondria) and V-type ATPases (e.g., the H+ pump located in vacuolar membranes of eukaryotic cells)[2]. The widely distributed class of P-type ATPases is responsible for the active transport of a variety of cations across cell membranes. They are found in both prokaryotic and eukaryotic cells, and are used for transporting H^+, Na^+, Mg^{2+}, K^+, Ca^{2+}, Cu^{2+}, and Cd^{2+}. All of these enzymes use the hydrolysis of ATP to drive the transport of cations against an electrochemical potential. The P-type designation refers to the unique characteristic of these enzymes in forming a transient phosphorylated aspartyl residue during the catalytic cycle [3]. Accompanying the phosphorylation-dephosphorylation process, the P-type ATPases bind, occlude, and transport ions by cycling between two different cation-dependent conformations, called E1 and E2. The precise molecular mechanisms that couple the hydrolysis of ATP to the conformational changes and the translocation of ions remain unknown. Of the P-type ATPases only the Na^+, K^+-ATPase is specifically inhibited by cardiac glycosides [4]. The eukaryotic P-type ATPases can be subdivided into two groups. One group of eukaryotic P-type ATPases consists only of a single subunit, designated alpha, and includes the sarco-endoplasmic reticulum Ca^{+2} ATPase (SERCA), the plasma membrane Ca^{+2}-ATPase, and the H^+-ATPase found in yeast and plants. The other group of the eukaryotic P-type ATPase family contains an additional subunit, beta; and includes the gastric H^+, K^+-ATPase and the Na^+, K^+-ATPase [5].

Structure of the sodium pump:

The sodium pump molecule is a heterooligomer composed of alpha and beta subunits and both of the subunits are required for enzymatic activity. Individual genes for the alpha and beta subunits of Na^+, K^+-ATPase are under complex regulation. Alpha subunits are composed of ~1018 residues (~110 kDa). Beta subunits are smaller compared to alpha, consisting of about ~300 residues (~55 kDa). They have three glycosylation sites and several conserved S-S bridges in the extracellular domain [6]. The experiments concerning sodium pump biosynthesis and subunit oligomerization showed that each subunit has distinct mRNA and subunits are synthesized independent of each other [7]. Regulation of the gene expression for each isoform and formation of various combinations of a-b complexes are tissue specific and controlled developmentally [8]. The studies showed that a and b subunits assemble during or very soon after synthesis in the ER [9]. Unassembled a subunits are retained in the ER [10], and both of the subunits are mutually dependent on each other to be transported out of the ER [11]. The summary of gene expression for each isoform is given in **Table.1.** **Figure 1** shows the alpha and beta subunit. **Figure 2** shows the sodium pump cycle.

Table 1. Human Na+, K+ ATPase isoforms. Data from the genome database of National Center for Biotechnological Information.

Isoform	Gene	Human Chromosome	Locus	Specific Expression
a1	ATP1A1	1 p13-11	476	Constitutive, ubiquitous. Dominant in epithelia of kidney, intestine and glands
a2	ATP1A2	1 q21-23		Muscle, heart, brain
a3	ATP1A3	19q12-13.1		CNS, brain
a4	ATP1A4			Testis, spermatozoa
b1	ATP1B1	1 q22-25	481	Ubiquitous, like a1 subunit
b2	ATP1B2	17p	482	Muscle, adhesion molecule of glial cells (AMOG) in brain
b3	ATP1B3	3 q22-23	483	Mostly in neural tissue
g	ATP1G	11q23		Kidney

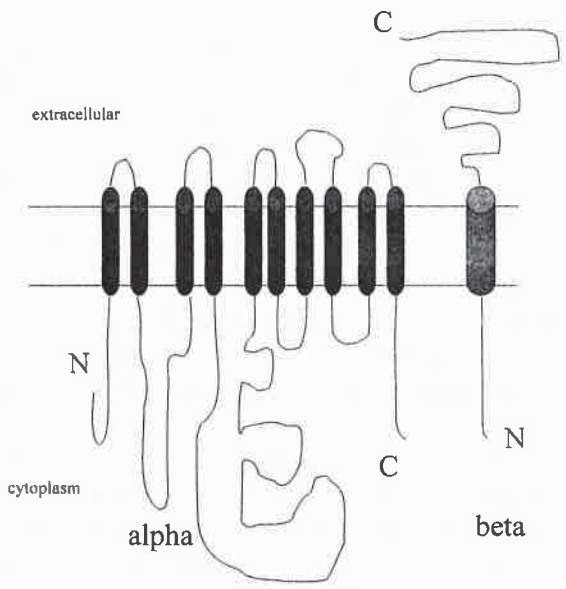

Figure 1. The Na^+, K^+–ATPase. The sodium pump is composed of alpha (catalytic) and beta subunits arranged in a 1:1 stoichiometry.

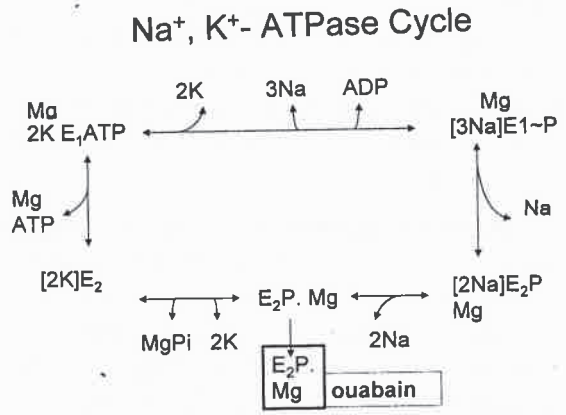

Figure 2. The sodium pump cycle and ouabain as an inhibitor, binding to a special conformation of the pump E2P.Mg.

a-Subunit: Alpha is the catalytic subunit that contains the binding sites for cardiac glycosides, ions and ATP and the transient phosphorylation site (an aspartate residue, D369) [3]. Throughout the animal kingdom the amino acid sequence of a subunit is highly conserved. So far, four alpha isoforms are defined in mammalian cells. Each subunits expression is controlled by its own gene, which is expressed in a tissue and cell specific manner. The N and C termini of the protein are located intracellularly and the protein has 10 transmembrane domains and 2 large intracellular loops. The smaller loop resides between transmembrane domains H2-H3, and the larger loop is between H4-H5. The larger cytoplasmic loop is the site for phosphorylation and ATP binding [12].

Alpha 1 seems to be ubiquitously expressed and has been found in all tissues investigated so far [13]. Alternative splicing of the a1 results in the polypeptide, a-1T, that has the first 554 amino acids a1 and a retained 27 amino acids from intron sequence. a1T has been shown in canine vascular smooth muscle cells [14]. Whether this truncated form functions in vivo remains to be determined. The **alpha 2** isoform is expressed in skeletal muscle, adipocytes and brain, and in small amounts in heart [15]. The **alpha 3** isoform is found mainly in nerves and brain but also in heart tissue [15]. The **alpha 4** isoform is found only in testis. Across species the degree of identity for the a1 and a2 isoforms is ~92% and is over 95% for a3 [16]. There is also a high degree of identity (87%) among the a1, a2 and a3 isoforms [17]. a-subunit has 63% amino acid sequence homology to H^+,K^+-ATPase of gastric mucosa and 30% to Ca^{+2}-ATPase of SR [18]. The sensitivity of the sodium pumps to the pump ligands, depends on the subunit isoforms that compose the pump and the species, cells and tissues the proteins are expressed (discussed below).

b-Subunit: Beta subunits are glycoproteins, which have a short cytoplasmic tail, one transmembrane segment, and a large, glycosylated extracellular segment. Thus, they belong to the class II integral membrane proteins, which also include human IgE and transferrin receptors [19]. Although the function of the beta subunit is not completely understood, its presence and heterodimerization with the alpha subunit is essential for the enzyme to be expressed and function. Beta subunits have been shown to alter the susceptibility of the alpha subunits to proteolytic enzymes. There is evidence that suggests they act as chaperones to stabilize the correct folding of the alpha subunits and facilitate their delivery to the membrane [20]. There are three known beta subunits for the sodium pump.

Beta 1 is expressed in all tissues. The **beta 2** isoform appears to be identical to adhesion molecule on glia (AMOG) and is expressed primarily in glia and brain [21]. **Beta 3** expression was detected in skeletal muscle, lung and brain [22]. The similarity of amino acid sequence of beta subunits is high among mammalian species (~90%) but lower across species or between different beta isoforms (~60%) in contrast to alpha subunits [23].

Beta subunits possesses 3 S-S bridges and 3 to 7 N-linked sugar chains on their extracellular domain; necessary for the proper folding and functioning of beta subunits as well as their interaction with the alpha sununit [6]. The sodium pump consists of a- and b-subunits in a 1:1 ratio. Although alpha subunit has the major binding sites for ions, ligands and ATP; beta subunits also participate in formation of the binding sites for ligands and modulate the ion transport function of the pump [24,25]. Experimental evidence suggests that the b subunit interacts with the a subunit at multiple sites, which are located in the ectodomain, the transmembrane, and the cytoplasmic domain [26,27]. The interaction between the a and the b subunit is important in the function of the Na^+, K^+-ATPase as inferred from the observation that reduction of a disulfide bond existing between Cys 158 and Cys 175 of the b-subunit results in loss of enzyme activity of the purified enzyme [6]. Under experimental conditions there does not seem to be a preference of a given alpha subunit for a particular beta. However the expression of pumps composed of different alpha and beta subunit combinations are controlled in a tissue specific manner. [13]. The a1b1-isozyme is ubiquitous and constitutively expressed and it maintains the Na^+ gradients driving the active transcellular transport in kidney and intestine. Targeted disruption of the a1 and a2 isoforms in mice confirm the necessity of sodium pump function for the life of a mammalian cell [28]. The affinity of the sodium pump isozymes to ions, ATP and ouabain are determined in a tissue specific way.

Regulation of pump expression:

The concentration of Na^+, K^+-ATPase in tissues varies largely with around a 160,000 fold difference between the lowest (erythrocytes) and the highest (brain cortex) concentrations. The vascular smooth muscle is in the lower range of the spectrum with very limited concentration of pumps (400,000-700,000 pumps/cell); ~100 times lower than that seen on heart and skeletal muscle [29,30]. Cellular regulation of pump expression can be controlled by rate of synthesis of the pump subunits and delivery to the membrane. Environmental and hormonal factors can increase the sodium pump activity per cell by mainly three mechanisms: 1) Through increasing the turnover of pumps that are already present in the membrane (short term regulation) [31]; 2) Through insertion of more pumps to the cell membrane [31] ; 3) Through increasing the transcription or translation (i.e. synthesis) of pump subunits (long term regulation) resulting in increased pump sites in the membrane [32,33]. The second mechanism seems to be an intermediate mechanism of regulation in cells with a pool of pre-formed pumps, where new pumps are delivered to the membrane when needed [29,34]. Thus, the synthesis, translocation and the regulation of the enzymatic turnover of the pumps in the membrane define the long, intermediate and short term control of sodium pump activity, respectively.

Short-term regulation occurs within minutes to hours. In this process, a faster or slower transport of ions per pump for a given time is achieved through modulating the turnover rate of the existing pumps via PKA, PKC or PKG phosphorylation [31]. Conditions that raise intracellular sodium [35], and also hormonal and growth factor stimulation are, known to increase pump turnover [36,37]. Several serine residues on the alpha subunit have been identified for their role in pump modulation. Phosphorylation of Ser943 of rat a1 subunit by PKA decreases Na^+,K^+-ATPase activity in some cells [38,39], Phosphorylation of Ser11, 16 or 18 by PKC results in activation [40,41] or inhibition [42] of the pump activity depending on the cell type. PKG has also been reported in sodium pump regulation although its actual phosphorylation site on the pump is not yet defined [37]. **Long-term regulation** defines transcriptional and translational regulation of pump expression, where there is mRNA and/or

protein synthesis of pump subunits and it generally occurs over days. Studies of such pump up-regulation often use agents (e.g. ouabain, sodium ionophore) or conditions (low K^+ treatment) that inhibit pump function and challenge the cells to up-regulate functional pump subunits to eliminate the increased intracellular Na^+ [43]. The physiological stimuli for long term regulation of pumps are serum and hormones [44] which increase intracellular sodium besides activating specific signaling cascades. The majority of the hormones exert a positive effect on the pump activity by increasing the synthesis of new a and b subunits. This response involves the interaction of the hormone-receptor complex with the specific hormone response element on a or b subunit gene promoter [45].

Less is known about the increase in pump activity by translocation, which occurs much more quickly, compared to transcriptional and translational regulation. Few studies have suggested the presence of a cytoplasmic pool of sodium pumps, ready for delivery to the membrane. In some cases the translocation of the pumps to the membrane were induced by phosphorylation of the pump subunits by PKC [34,46]. In general intracellular transport and translocation can be inhibited by agents that breakdown the actin filaments and microtubules such as colchicine, cytochalasin D or nocodazole [47] or by inhibitors of PI3K that regulate the protein transport machinery [29].

An increased degradation of alpha subunits is observed when they fail to couple with a beta. This suggests that beta subunit availability is also important for pump expression [9]. There are several pathological situations (inactivity, cardiac insufficiency, myotonic dystrophy) and experimental models (hypokalemia, diabetes) where the tissue expression of sodium pumps is reduced as a result of the condition, further jeopardizing the function of the organ. For example during heart failure, the heart becomes more sensitive to the effect of cardiac glycosides (due to a decrease in the number of pump sites) [48]. Thus, the regulation of pump function and expression is very important for treatment and possible prevention of these diseases.

Sodium pump as a receptor of digitalis and digitalis like factors:

Na^+, K^+-ATPase is known to be the receptor for the cardiac glycoside family, which includes ouabain and digoxin, and is specifically inhibited upon binding with these substances (Figure 2). For this reason the cardiac glycosides have been and still are successfully used in the treatment of cardiac failure. Cardiac glycosides inhibit the pump activity by binding to the extracellular site of the enzyme [49]. As mentioned above, the sodium pump consists of a- and b-subunits in a 1:1 ratio and the generally accepted view is that one ouabain binds to one a-b dimer [50]. Because each sodium pump molecule binds only one molecule of digitalis glycoside, [^{3}H]- labeled glycosides (ouabain) are frequently used for the quantification of sodium pumps in homogenates, cells and tissues.

Although the amino acid residues that affect ouabain binding are found in the first transmembrane and extracellular regions of the alpha subunit, the binding site for cardiac glycosides and ouabain is composed of multiple functional groups. It has been shown both by affinity labeling and expression of mammalian subunits in yeast cells that, beta subunit participates in ouabain binding [50,51]. The amino- and the carboxy- termini of the alpha subunit contribute to the ouabain sensitivity along with several other residues and the loss of any particular one does not completely prevent binding [52]. The Kd of the human a1 isoforms for ouabain are reported as $\sim 10^{-7}$–10^{-8} M [53] whereas the Kd of rat a1 isoforms are $\sim 10^{-6}$–10^{-4} M [54].

The mechanism of action of the cardiac glycoside family is such that the binding of the glycoside inhibits the Na^+, K^+-ATPase, reducing sodium extrusion from cardiac muscle. The increase in intracellular Na^+, reduces the extrusion of Ca^{+2} from the cell via the Na^+/Ca^+ exchanger [28]. This raises the intracellular calcium content and triggers calcium release from the sarcoplasmic reticulum, which results in an increase in force of contraction of cardiac muscle [55].

The presence of a globulin-bound, circulating endogenous factor in hypertensive patients, which

can bind and inhibit the sodium pump has been known for a long time [56,57]. Isolation of this factor from human plasma and its identification as the endogenous digitalis like factor (EDLF) or "endogenous ouabain" shed a new light to the role and regulation of the sodium pump. The EDLF is starting to be recognized as an endogenous regulator of sodium pump function, as it has been suggested to play an important role in development of salt induced hypertension [58]. Physiological circulating concentrations of endogenous ouabain are reported as less than 1nM (~0.5nM)[59]. These concentrations can be expected to inhibit only a very small fraction of the sodium pumps at a time. However, their constant presence in the cellular environment may increase their impact on the cellular function. Under circumstances where a considerable number of pumps are inhibited, the cell will be forced to compensate for the loss in sodium pump function by expressing more pump sites. Information in the literature suggests cellular proliferation and regulation of sodium pump expression are related to some extent. Several studies demonstrated an increase in sodium pump activity prior to DNA synthesis in the cell cycle [60] and during tissue regeneration [61]. Interestingly ligands of the sodium pump, mainly ouabain (at micromolar concentrations), has been shown to induce signaling and proliferation in rat astrocytes [62], cardiomyocytes [63] and lymphocytes [64] and vascular smooth muscle cells [65].

Conclusion:

Jens Christian Skou published his early studies about the identification and characterization of an ATPase, namely the Na^+, K^+ - ATPase in 1957 [66] and was awarded the Nobel Prize in Chemistry in 1997 for his work on the sodium pump. Fortyfive years after its discovery the research about the clinical and therapeutic importance of sodium pump is still evolving, providing more intriguing results every year. The main basic function of the sodium pump is to maintain the Na^+ and K^+ gradients across the plasma membrane. Thus, membrane potential, nutrient uptake, intracellular volume and pH are all regulated by proper function of the sodium pump. Gene expression of the sodium pump subunits is tissue specific and controlled by hormones as well as growth factors. Understanding the mechanisms underlying short and long term regulation of the pump is essential for analyzing the adaptation of cells and tissues to the endocrine and electrolyte status of the organism, as well as the developing treatment for pathophysiological conditions caused by failure of this. Digitalis, a cardiotonic steroid has been used for treatment of heart failure for hundreds of years. The demonstration of an endogenous circulating factor that correlated with blood pressure of donors and inhibited the Na^+, K^+-ATPase, was a first in developing the paradigm of a group of digitalis like substances whose physiological and pathophysiological functions are just beginning to be delineated thus whether EDLF is friend or foe, remains yet to be determined.

REFERENCES

1. Skou JC, Esmann M: **The Na,K-ATPase.** *J Bioenerg Biomembr* 1992, **24**:249-261.
2. Sachs G, Munson K: **Mammalian phosphorylating ion-motive ATPases.** *Curr Opin Cell Biol* 1991, **3**:685-694.
3. Ohtsubo M, Noguchi S, Takeda K, Morohashi M, Kawamura M: **Site-directed mutagenesis of Asp-376, the catalytic phosphorylation site, and Lys-507, the putative ATP-binding site, of the alpha-subunit of Torpedo californica Na+/K(+)-ATPase.** *Biochim Biophys Acta* 1990, **1021**:157-160.
4. Repke KR, Sweadner KJ, Weiland J, Megges R, Schon R: **In search of ideal inotropic steroids: recent progress.** *Prog Drug Res* 1996, **47**:9-52.
5. Axelsen KB, Palmgren MG: **Evolution of substrate specificities in the P-type ATPase superfamily.** *J Mol Evol* 1998, **46**:84-101.
6. Beggah AT, Jaunin P, Geering K: **Role of glycosylation and disulfide bond formation in the beta subunit in the folding and functional expression of Na,K-ATPase.** *J Biol Chem* 1997, **272**:10318-10326.
7. Geering K: **Biosynthesis, membrane insertion and maturation of Na, K-ATPase.** *Prog Clin Biol Res* 1988,:19-33.
8. Jewell EA, Shamraj OI, Lingrel JB: **Isoforms of the alpha subunit of Na,K-ATPase and their significance.** *Acta Physiol Scand Suppl* 1992, **607**:161-169.
9. Geering K, Beggah A, Good P, Girardet S, Roy S, Schaer D, Jaunin P: **Oligomerization and maturation of Na,K-ATPase: functional interaction of the cytoplasmic NH2 terminus of the beta subunit with the alpha subunit.** *J Cell Biol* 1996, **133**:1193-1204.
10. Beguin P, Hasler U, Staub O, Geering K: **Endoplasmic reticulum quality control of oligomeric membrane proteins: topogenic determinants involved in the degradation of the unassembled Na,K-ATPase alpha subunit and in its stabilization by beta subunit assembly.** *Mol Biol Cell* 2000, **11**:1657-1672.
11. Ackermann U, Geering K: **Mutual dependence of Na,K-ATPase alpha- and beta-subunits for correct posttranslational processing and intracellular transport.** *FEBS Lett* 1990, **269**:105-108.
12. Lingrel JB, Kuntzweiler, T: **Na+,K+-ATPase.** *J. Biol. Chem.* 1994, **269**:19659-19662.
13. Lingrel JB, Young RM, Shull MM: **Multiple forms of the Na,K-ATPase: their genes and tissue specific expression.** *Prog Clin Biol Res* 1988,:105-112.
14. Allen JC, Pressley TA, Odebunmi T, Medford RM: **Tissue specific membrane association of alpha 1T, a truncated form of the alpha 1 subunit of the Na pump.** *FEBS Lett* 1994, **337**:285-288.
15. Juhaszova M, Blaustein MP: **Na+ pump low and high ouabain affinity alpha subunit isoforms are differently distributed in cells.** *Proc Natl Acad Sci U S A* 1997, **94**:1800-1805.
16. Shull GE, Young RM, Greeb J, Lingrel JB: **Overview: amino acid sequences of the alpha and beta subunits of the Na,K-ATPase.** *Prog Clin Biol Res* 1988,:3-18.
17. Blanco G, Mercer RW: **Isozymes of the Na-K-ATPase: heterogeneity in structure, diversity in function.** *Am J Physiol* 1998, **275**:F633-650.
18. Shull GE, Lingrel JB: **Molecular cloning of the rat stomach (H+ + K+)-ATPase.** *J Biol Chem* 1986, **261**:16788-16791.
19. Kawamura M, Noguchi S: **Structure and function of the beta subunit of (Na,K)ATPase.** *Prog Clin Biol Res* 1988,:93-98.
20. Kawamura M, Noguchi S: **Possible role of the beta-subunit in the expression of the sodium pump.** *Soc Gen Physiol Ser* 1991, **46**:45-61.
21. Avila J, Alvarez de la Rosa D, Gonzalez-Martinez LM, Lecuona E, Martin-Vasallo P: **Structure and expression of the human Na,K-ATPase beta 2-subunit gene.** *Gene* 1998, **208**:221-227.
22. Appel C, Gloor S, Schmalzing G, Schachner M, Bernhardt RR: **Expression of a Na,K-ATPase beta 3 subunit during development of the zebrafish central nervous system.** *J Neurosci Res* 1996, **46**:551-564.
23. Kawakami K, Nojima H, Ohta T, Nagano K: **Molecular cloning and sequence analysis of human Na,K-ATPase beta- subunit.** *Nucleic Acids Res* 1986, **14**:2833-2844.
24. Jaunin P, Jaisser F, Beggah AT, Takeyasu K, Mangeat P, Rossier BC, Horisberger JD, Geering K: **Role of the transmembrane and extracytoplasmic domain of beta subunits in subunit assembly, intracellular transport, and functional expression of Na,K-pumps.** *J Cell Biol* 1993, **123**:1751-1759.
25. Jaisser F, Jaunin P, Geering K, Rossier BC, Horisberger JD: **Modulation of the Na,K-pump function by beta subunit isoforms.** *J Gen Physiol* 1994, **103**:605-623.
26. Geering K, Jaunin P, Jaisser F, Merillat AM, Horisberger JD, Mathews PM, Lemas V, Fambrough DM, Rossier BC: **Mutation of a conserved proline residue in the beta-subunit ectodomain prevents Na(+)-K(+)-ATPase oligomerization.** *Am J Physiol* 1993, **265**:C1169-1174.

27. Hasler U, Crambert G, Horisberger JD, Geering K: **Structural and functional features of the transmembrane domain of the Na,K-ATPase beta subunit revealed by tryptophan scanning.** *J Biol Chem* 2001, **276**:16356-16364.

28. James PF, Grupp IL, Grupp G, Woo AL, Askew GR, Croyle ML, Walsh RA, Lingrel JB: **Identification of a specific role for the Na,K-ATPase alpha 2 isoform as a regulator of calcium in the heart.** *Mol Cell* 1999, **3**:555-563.

29. Aydemir-Koksoy A, Allen JC: **Regulation of Na(+) pump expression by vascular smooth muscle cells.** *Am J Physiol Heart Circ Physiol* 2001, **280**:H1869-1874.

30. Kjeldsen K, Bjerregaard P, Richter EA, Thomsen PE, Norgaard A: **Na+,K+-ATPase concentration in rodent and human heart and skeletal muscle: apparent relation to muscle performance.** *Cardiovasc Res* 1988, **22**:95-100.

31. Bertorello AM, Katz AI: **Short-term regulation of renal Na-K-ATPase activity: physiological relevance and cellular mechanisms.** *Am J Physiol* 1993, **265**:F743-755.

32. Nemoto J, Muto S, Ohtaka A, Kawakami K, Asano Y: **Serum transcriptionally regulates Na(+)-K(+)-ATPase gene expression in vascular smooth muscle cells.** *Am J Physiol* 1997, **273**:C1088-1099.

33. Songu-Mize E, Liu X, Stones JE, Hymel LJ: **Regulation of Na+,K+-ATPase alpha-subunit expression by mechanical strain in aortic smooth muscle cells.** *Hypertension* 1996, **27**:827-832.

34. Hundal HS, Marette A, Mitsumoto Y, Ramlal T, Blostein R, Klip A: **Insulin induces translocation of the alpha 2 and beta 1 subunits of the Na+/K(+)-ATPase from intracellular compartments to the plasma membrane in mammalian skeletal muscle.** *J Biol Chem* 1992, **267**:5040-5043.

35. Allen JC, Navran SS, Seidel CL, Dennison DK, Amann JM, Jemelka SK: **Intracellular Na+ regulation of Na+ pump sites in cultured vascular smooth muscle cells.** *Am J Physiol* 1989, **256**:C786-792.

36. Girardet M, Geering K, Gaeggeler HP, Rossier BC: **Control of transepithelial Na+ transport and Na-K-ATPase by oxytocin and aldosterone.** *Am J Physiol* 1986, **251**:F662-670.

37. McKee M, Scavone C, Nathanson JA: **Nitric oxide, cGMP, and hormone regulation of active sodium transport.** *Proc Natl Acad Sci U S A* 1994, **91**:12056-12060.

38. Satoh T, Cohen HT, Katz AI: **Different mechanisms of renal Na-K-ATPase regulation by protein kinases in proximal and distal nephron.** *Am J Physiol* 1993, **265**:F399-405.

39. Fisone G, Cheng SX, Nairn AC, Czernik AJ, Hemmings HC, Jr., Hoog JO, Bertorello AM, Kaiser R, Bergman T, Jornvall H, et al.: **Identification of the phosphorylation site for cAMP-dependent protein kinase on Na+,K(+)-ATPase and effects of site-directed mutagenesis.** *J Biol Chem* 1994, **269**:9368-9373.

40. Feraille E, Beguin P, Carranza ML, Gonin S, Rousselot M, Martin PY, Favre H, Geering K: **Is phosphorylation of the alpha1 subunit at Ser-16 involved in the control of Na,K-ATPase activity by phorbol ester-activated protein kinase C?** *Mol Biol Cell* 2000, **11**:39-50.

41. Pedemonte CH, Pressley TA, Cinelli AR, Lokhandwala MF: **Stimulation of protein kinase C rapidly reduces intracellular Na+ concentration via activation of the Na+ pump in OK cells.** *Mol Pharmacol* 1997, **52**:88-97.

42. Chibalin AV, Pedemonte CH, Katz AI, Feraille E, Berggren PO, Bertorello AM: **Phosphorylation of the catalyic alpha-subunit constitutes a triggering signal for Na+,K+-ATPase endocytosis.** *J Biol Chem* 1998, **273**:8814-8819.

43. Liu X, Hymel LJ, Songu-Mize E: **Role of Na+ and Ca2+ in stretch-induced Na(+)-K(+)-ATPase alpha-subunit regulation in aortic smooth muscle cells.** *Am J Physiol* 1998, **274**:H83-89.

44. Ewart HS, Klip A: **Hormonal regulation of the Na(+)-K(+)-ATPase: mechanisms underlying rapid and sustained changes in pump activity.** *Am J Physiol* 1995, **269**:C295-311.

45. Horisberger JD, Rossier BC: **Aldosterone regulation of gene transcription leading to control of ion transport.** *Hypertension* 1992, **19**:221-227.

46. Songu-Mize E, Jacobs, M., Shreves, A.: **Acute cyclic stretch induces upregulation of the Na+ pump of aortic smooth muscle cells in culture by cytoplasmic translocation.** *FASEB J. Abstr Book I* 1999,:351.355.

47. Nakamura M, Sunagawa M, Kosugi T, Sperelakis N: **Actin filament disruption inhibits L-type Ca(2+) channel current in cultured vascular smooth muscle cells.** *Am J Physiol Cell Physiol* 2000, **279**:C480-487.

48. Shamraj OI, Grupp IL, Grupp G, Melvin D, Gradoux N, Kremers W, Lingrel JB, De Pover A: **Characterisation of Na/K-ATPase, its isoforms, and the inotropic response to ouabain in isolated failing human hearts.** *Cardiovasc Res* 1993, **27**:2229-2237.

49. Lingrel JB, Van Huysse J, O'Brien W, Jewell-Motz E, Askew R, Schultheis P: **Structure-function studies of the Na,K-ATPase.** *Kidney Int Suppl* 1994, **44**:S32-39.

50. Hansen O: **Interaction of cardiac glycosides with (Na+ + K+)-activated ATPase. A biochemical link to digitalis-induced inotropy.** *Pharmacol Rev* 1984, **36**:143-163.

51. Eakle KA, Kim KS, Kabalin MA, Farley RA: **High-affinity ouabain binding by yeast cells expressing Na+, K(+)- ATPase alpha subunits and the gastric H+, K(+)-ATPase beta subunit.** *Proc Natl Acad Sci U S A* 1992, **89**:2834-2838.

52. Palasis M, Kuntzweiler TA, Arguello JM, Lingrel JB: **Ouabain interactions with the H5-H6 hairpin of the Na,K-ATPase reveal a possible inhibition mechanism via the cation binding domain.** *J Biol Chem* 1996, **271**:14176-14182.

53. Crambert G, Hasler U, Beggah AT, Yu C, Modyanov NN, Horisberger JD, Lelievre L, Geering K: **Transport and pharmacological properties of nine different human Na, K- ATPase isozymes.** *J Biol Chem* 2000, **275**:1976-1986.

54. Ridge K, Rutschman,D. E., Factor, P., Katz, A.I., Bertorello,A.M., Sznajder, J.: **Differential expression of Na-K-ATPase isoforms in rat alveolar epithelial cells.** *Am. J. Physiol.* 1997, **273**:L3246-L3255.

55. Grupp I, Im WB, Lee CO, Lee SW, Pecker MS, Schwartz A: **Relation of sodium pump inhibition to positive inotropy at low concentrations of ouabain in rat heart muscle.** *J Physiol* 1985, **360**:149-160.

56. Kramer HJ: **Natriuretic hormone - a circulating inhibitor of sodium- and potassium- activated adenosine triphosphatase. Its potential role in body fluid and blood pressure regulation.** *Klin Wochenschr* 1981, **59**:1225-1230.

57. Hamlyn JM, Ringel R, Schaeffer J, Levinson PD, Hamilton BP, Kowarski AA, Blaustein MP: **A circulating inhibitor of (Na+ + K+)ATPase associated with essential hypertension.** *Nature* 1982, **300**:650-652.

58. Blaustein MP: **Endogenous ouabain: role in the pathogenesis of hypertension.** *Kidney Int* 1996, **49**:1748-1753.

59. Vakkuri O, Arnason SS, Joensuu P, Jalonen J, Vuolteenaho O, Leppaluoto J: **Radioiodinated tyrosyl-ouabain and measurement of a circulating ouabain- like compound.** *Clin Chem* 2001, **47**:95-101.

60. Ando K, Omi N, Shimosawa T, Takahashi K, Fujita T: **Effects of ouabain on the growth and DNA synthesis of PC12 cells.** *J Cardiovasc Pharmacol* 2001, **37**:233-238.

61. Simon FR, Fortune J, Alexander A, Iwahashi M, Dahl R, Sutherland E: **Increased hepatic Na,K-ATPase activity during hepatic regeneration is associated with induction of the beta1-subunit and expression on the bile canalicular domain.** *J Biol Chem* 1996, **271**:24967-24975.

62. Murata Y, Matsuda T, Tamada K, Hosoi R, Asano S, Takuma K, Tanaka K, Baba A: **Ouabain-induced cell proliferation in cultured rat astrocytes.** *Jpn J Pharmacol* 1996, **72**:347-353.

63. Kometiani P, Li J, Gnudi L, Kahn BB, Askari A, Xie Z: **Multiple signal transduction pathways link Na+/K+-ATPase to growth- related genes in cardiac myocytes. The roles of Ras and mitogen- activated protein kinases.** *J Biol Chem* 1998, **273**:15249-15256.

64. Marakhova, II, Vinogradova TA, Toropova FV: **Na/K-pump and the cell response to mitogenic signal: regulatory mechanisms and relation to the blast transformation of human blood lymphocytes.** *Membr Cell Biol* 2000, **14**:253-261.

65. Aydemir-Koksoy A, Abramowitz J, Allen JC: **Ouabain-induced signaling and vascular smooth muscle cell proliferation.** *J Biol Chem* 2001, **276**:46605-46611.

66. Skou JC: **The influence of some cations on an adenosine triphosphatase from peripheral nerves.** *Biochem Biophys Acta* 1957, **23**:394-401.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 24, No 2, 2002 83-86

CARCINOID TUMOR ARISING IN A MATURE CYSTIC TERATOMA

Ebru Serinsöz* ✣ Ayşe Sertçelik* ✣ Cem Atabekoğlu ✣ İlkkan Dünder****

SUMMARY

Although dermoid cysts (Mature cystic teratoma) of the ovary are almost always benign tumors, the rare development of cancer deserves emphasis. A case of carcinoid tumor of insular type is presented. The small focus of carcinoid tumor was found incidentally in a resected dermoid cyst. Histologically, the tumor had thick fibrous septa among the cell nests. The tumor revealed argyrophylia by Grimelius satin. The immunohistochemical studies demonstrated positivity for Chromogranin A, Synaptophisin, NSE, Prostatic Acid Phosphatase (PAP) and Substance-P. This case is considered to be a rare ovarian carcinoid arising from a dermoid cyst without an association of struma ovarii. Immunohistochemistry will be helpful in demonstrating the neuroendocrine nature of the tumor cells.

Key Words: *Carcinoid tumor, Dermoid cyst*

ÖZET

Matür Kistik teratom İçerisinde Gelişen Karsinoid Tümör

Overin dermoid kistleri hemen daima benign tümörler olmasına karşın, nadir de olsa malignite gelişimi üzerinde durulması gereken bir noktadır. Bu makalede insular tipte bir karsinoid tümör olgusu sunulmaktadır. Dermoid kist nedeniyle rezeke edilen bir overde rastlantısal olarak küçük bir karsinoid tümör odağı saptanmıştır. Histolojik olarak, tümör hücreleri arasında kalın bağ dokusu septumlar bulunduğu tesbit edilmiştir. Grimelius özel boyası ile tümör hücrelerinde argirofili saptanmıştır. İmmünhistokimyasal olarak tümör hücrelerinin Chromogranin A, Synaptophisin, Nöron Spesifik Enolaz (NSE), Prostatik Asid Fosfataz (PAP) ve Substance P eksprese ettiği izlenmiştir. Bu olgu, dermoid kist içerisinde gelişen ve struma ovarii ile ilişkisi olmayan nadir bir ovarian karsinoid olarak değerlendirilmiştir. Bu tip olgularda immünhistokimyasal inceleme tümörün nöroendokrin natürünün ortaya konulmasını sağlayacaktır.

Anahtar Sözcükler: *Karsinoid tümör, Dermoid kist.*

Mature cystic teratomas (dermoid cyst) make up almost 20% of all ovarian neoplasms. Although they are almost always benign tumors, the rare development of cancer deserves emphasis. The most common malignant change in a dermoid cyst is squamous cell carcinoma, followed by adenocarcinoma and carcinoid tumor (1-3). Primary of ovarian carcinoid tumors are uncommon and the majority of them are associated with mature cystic teratomas (4). Robboy et al (5) divided these tumors into three types: the insular type, trabecular type, and strumal carcinoid type. We report herein a case of insular carcinoid tumor arising from a mature cystic teratoma, which was examined by histological and immunohistochemical methods.

Case report

A 52 year old Turkish woman was admitted to İbn-i Sina Hospital because of an abdominal mass which she had noticed years ago. Physical examination revealed a palpable mass in the

* Ankara University, Medical School Resident in Department of Pathology.

** Ankara University, Medical School Resident in Department of Obstetrics and Gynecology.

*** This case was presented at the 2nd Balkan Congress of Oncology, 10-14 September 1998, İzmir, Turkey.

Received: June 15, 2001 Accepted: Sept 20, 2001

pelvic region. Serum tests, plain abdominal X-ray film revelad no abnormality. Ultrasonography showed a cystic lesion in the right ovary with a focal small solid area corresponding to an ovarian dermoid cyst. The tumor was extirpated and no other abnormalities were found. The patient is now alive and healthy without postoperative therapy and shows no evidence of distant methastasis.

Pathological findings

Macroscopically the tumor measured 13x9x6cm and was multilobulated. At the cut surface, the tumor had a greasy content composed of keratin, sebum and hairs and showed a focal solid area. Many sections, especially from the solid area, were taken and stained routinely with H-E. Special stains such as PAS and Grimelius were also applied. Microscopically, the tumor was a typical dermoid cyst composed of skin and appandages, respiratory epithelium and connective tissue (Figure 1a). A small, slightly irregular lesion measured 9mm in the largest diameter was found incidentally. This focus had an appearance similar to that of carcinoid tumors elsewhere; solid nests of small, round cells (Figure 1b). There was an abundant fibrous stroma. The tumor cells had scant, slightly eosinophylic cytoplasm and round nucleus with finely dispersed chromatin. No mitotic figures were present. Grimelius stain revealed the argyrophilia in the cytoplasm of the tumor cells.

Immunohistochemically Chromogranin A, Synaptophisin, NSE, PAP and Substance-P markers have been studied. The tumor showed positivity with all of the markers with varying profile of staining. NSE, Choromogranin A and Synaptophisin showed a diffuse positivity while PAP and Substance-P were focally positive.

Discussion

Several authors have reported that cystic teratomas constitute 15 to 20 % of all ovarian tumors (6). Altough dermoid cysts of the ovary are almost always benign tumors, primary malignancy arising in these cysts rarely encountered, about 1.5% (6), despite the presence of embryonic structures in these neoplasms. Primary ovarian carcinoid arising in a cystic teratoma is an uncommon neoplasm but its probably more frequent than it has been reported to be. Our case has an importance from that point of view. In this case the patient did not have any symptoms that would be related to carcinoid syndrome while all the other reported cases in the literature (6-9) up to date have presented with one or more of the characteristic symptoms related to carcinoid syndrome. The tumor has been detected incidentally in our case. The tumor showed immunreactivity for Chromogranin A, Synaptophisin, NSE, PAP and Substance-P, a common finding for all the other classical carcinoid tumors. As this is a malignancy, it would give rise to a poorer prognosis than a mature cystic teratoma.

This experience showed us to give more importance while taking sections from the solid parts of an dermoid cyst to increase the data about primary ovarian carcinoids arising in a mature cystic teratoma and make a clear consideration about its prognosis.

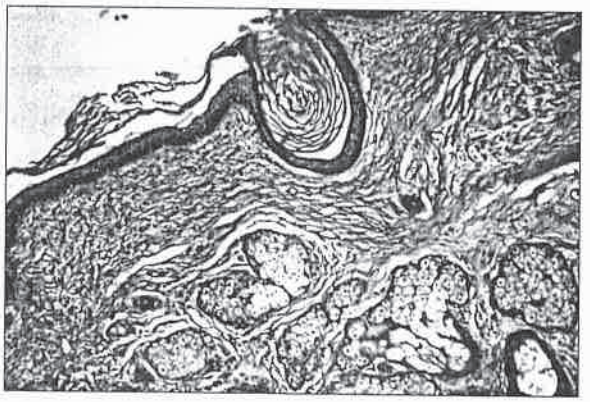

Figure 1a: Low power view of the dermoid cyst with skin and appandages (H&Ex100)

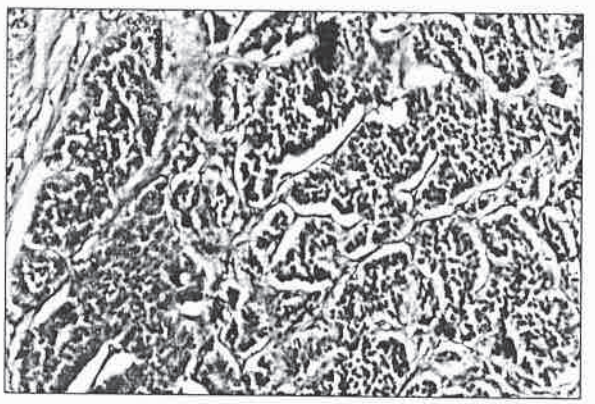

Figure 1b: Solid nests of small, round cells in the carcinoid tumor focus (H&Ex250).

REFERENCES

1. Climie ARW, Heath LP. Malignant degeneration of benign cystic teratomas of the ovary. Review of the literature and report of a chondrosarcoma and carcinoid tumor. Cancer 1968; 22:824-9.
2. Hirakawa T, Tsuneyoshi M, Enjoji M. Squamous cell carcinoma arising in a mature cystic teratoma of the ovary. Clinicopathological and topographic analysis. Am J Surg Pathol 1989; 13: 397-405.
3. Palmer PE, Bogojavlensky S, Bhan AK, Scully RE. Prolactinoma in wall of ovarian dermoid cyst with hyperprolactinemia. Obstet Gynecol 1990; 75: 540-43.
4. Scully RE. Carcinoid. In Tumors of the Ovary and Maldeveloped Gonads (Atlas of Tumor Pathology, 2nd series, Fascicle 16). Armed Forces Institute of Pathology, Washington, D.C., 1979: 274-283.
5. Robboy SJ, Scully RE, Norris HJ. Primary trabecular carcinoid of the ovary. Obstet Gynecol 1977; 49: 202-207.
6. Fukuda T, Ohnishi Y, Terashima T, Iwafuchi M, Itoh S. Peptide Tyrosine-positive ovarian carcinoid tumor arising from a dermoid cyst. Acta Pathologica Japonica 1991; 41(5): 394-400.
7. Sidhu J, S·nchez RL. Prostatic Acid Phosphatase in strumal carcinoids of the ovary: An immunohistochemical study. Cancer 1993; 72: 1673-81.
8. Kephart SB, Jackson CE, Caylor HD. Argentaffinoma (carcinoid) in a benign cystic ovarian teratoma. Report of a case. Obstet & Gynecol 1960; 15: 93-97.

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 24, No 2, 2002 87-90

MULTINODULAR GOITER PRESENTING AS A RETROPHARYNGEAL MASS: A CASE REPORT

Çetin Atasoy* ✣ A. Tuba Karagülle* ✣ Serdar Akyar*

SUMMARY

Multinodular goiter not uncommonly grows substernally causing symptoms related to compression of the trachea and/or esophagus. However, cephalad extension of a goitrous thyroid gland is rare, and retropharyngeal thyroid tissue has been reported only scarcely in the literature. We describe radiographic and computed tomographic findings in an elderly patient presenting with dysphonia and dysphagia due to a large retropharyngeal goiter compressing the larynx and hypopharynx. This rare condition must be considered in the differential diagnostic list of retropharygeal masses.

Key Words: *Thyroid Gland - Goiter - Computed Tomography*

ÖZET

Multinodüler Guatr

Multinodüler guatrın substernal uzanımına bağlı özofagus veya trakeada kompresyon sık karşılaşılan bir durumdur. Ancak guatrın asendan uzanımı oldukça enderdir. Bu olgu bildirisinde, retroorofarenjeal uzanım göstererek larinks ve hipofarinkste kompresyona neden olan multinodüler guatrın direkt grafi ve bilgisayarlı tomografi bulgularını sunduk.

Anahtar Kelimeler: *Tiroid Bezi-Guatr-Bilgisayarlı Tomografi*

Goitrous enlargement of the thyroid gland usually presents as a non-tender anterior neck mass. Asymptomatic patients may be treated medically, which often reduces the size of the gland or avoids progression of the disease. Neglected or ineffectively treated cases may grow beyond the confines of the gland, which primarily occurs caudally into the mediastinum. Cranial extension of the goiter into the retropharygeal space is a very rare phenomenon, which, to our knowledge, has been described in only five patients previously (1-4). In this paper, we present a patient with multinodular goiter with a large retropharyngeal component.

Case Report:

A 78-year-old male patient living in a moderately iodine-deficient environment (5) presented with dysphagia, a change in the quality of voice, and a swelling in the neck. Physical examination revealed a large mass in the right anterior cervical triangle extending down to the supraclavicular region, which was soft, mobile, nontender and nonpulsatile on palpation. Endoscopic examination showed a smooth submucosal mass which protruded into the lumen of the oropharynx and obliterated the right piriform sinus. Lateral radiography of the nasopharynx demonstrated prevertebral soft tissue swelling causing marked anterior displacement of the larynx and trachea (Figure 1). Computed tomography (CT) showed a diffusely enlarged thyroid gland with a heterogenous contrast enhancement. The right lobe of the gland extended medially to the left of the midline behind the oropharynx, remarkably narrowing the right

* Ankara University, Medical School, Department of Radiology.

Received: April 04, 2001 Accepted: July 12, 2001

piriform sinus and the laryngeal vestibule (Figure 2). The gland showed minimal intrathoracic extension. Sagittal reformations displayed the compromise of the airway lumen by the retropharyngeal thyroid tissue to a better advantage (Figure 3). Thyroid function tests showed the patient to be euthyroid. At surgery the thyroidal mass could easily be removed. The pathological examination revealed multinodular colloidal goiter. The postoperative course was uneventful. The preoperative symptoms were relieved after surgery. Postoperatively the patient became hypothyroid and was placed on thyroid replacement therapy.

Discussion:

When sufficiently large, goitrous thyroid glands usually grow down into the mediastinum or retroesophageal space. Extension cranially into the retropharyngeal region is extremely uncommon (1-4). Though most of the reported retropharyngeal goiters were due to direct extension, an occasional case was caused by ectopic thyroid tissue in this region (1). The patient presented herein also exemplifies direct cephalic growth of the thyroid gland into the retropharyngeal space.

The thyroid gland is normally situated in the pretracheal space, which is continuous inferiorly with the mediastinum and posteriorly with the retrovisceral space located behind the pharynx and esophagus. An enlarged thyroid gland may grow in either of these two directions. Extension caudally into the mediastinum forms the well-known substernal goiter, causing symptoms related to compression of the airway and/or esophagus. In a minority of the patients, mediastinal extension is followed by growth superiorly behind the oro-hypopharynx, which may produce dysphagia and dysphonia. In our patient the goitrous thyroid grew predominantly cephalad markedly narrowing the hypopharynx and larynx, with only minimal intrathoracic extension. His symptoms were presumably caused by the large retropharyngeal component.

Most of the retropharyngeal thyroid glands are histologically multinodular goiters (2-4), as in our patient. Only one patient had Hashimoto thyroiditis (1). The condition generally affects the

Figure 1. Lateral neck radiography shows prevertebral soft tissue swelling causing anterior displacement of the larynx and trachea.

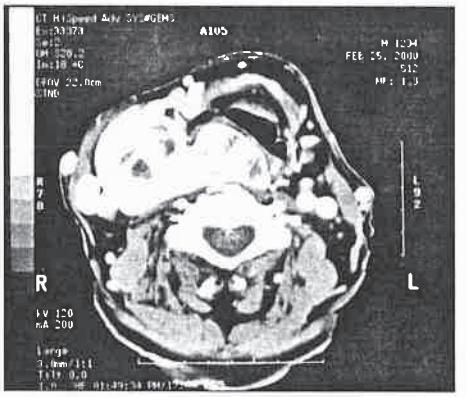

Figure 2. Contrast enhanced axial CT section at the level of the hyoid bone shows medial extension of the right lobe of the thyroid gland partially obliterating the right piriform sinus and laryngeal vestibule.

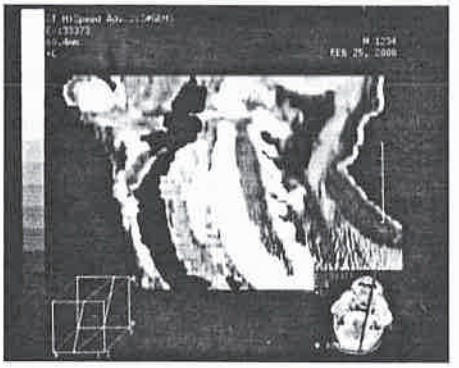

Figure 3. Sagittal reformatted CT image demonstrates the contrast enhanced thyroidal tissue in the prevertebral space with the displaced and narrowed laryngeal lumen.

elderly, probably because the goitrous enlargement has to be neglected for a long period of time to attain a sufficient size. The formerly reported three patients were euthyroid (2,4). One of the remaining two was hypothyroid and the other was hyperthyroid (1,3). This patient was also an elderly with normal thyroid function tests.

Retropharyngeal goiters are generally treated surgically. In only one of the reported patients thyroid suppression therapy was used and resulted in symptomatic improvement (4). Because of the enormous size of the retropharyngeal component, our patient was also referred for surgery and the thyroid tissue could easily be extirpated with relief of symptoms.

In summary, the possibility of retropharyngeal as well as mediastinal extension of the thyroid gland must also be considered in elderly goitrous patients living in iodine deficient environment with symptoms suggesting compression of the airway or esophagus. Indeed, the principal cause of the symptoms may be due to the retropharyngeal component rather than the substernal part, as was the case in this patient. CT examination, which in this context must cover both the neck and upper mediastinum, can easily confirm the thyroidal nature of the retropharyngeal mass due to its characteristic density and contrast enhancement properties.

REFERENCES

1. Kenyon GS, Robb PJ. Hashimoto's disease presenting as an unusual retropharyngeal mass. Clin Oncol 1981; 9:159-164.
2. Soboroff BJ. An unusual retropharyngeal mass. Trans Am Acad Ophthalmol Otolaryngol 1977; 84: 136-138.
3. Som PS, Sugar JMA. Retropharyngeal mass as a rare presentation of a goitre: CT findings. J Computed Assist Tomogr 1991; 15: 823-825.
4. Berenzholz LP, Segal S, Kessler A. Goitre presenting as a oropharyngeal mass: an unusual finding in the elderly. J Laryngol Otol 1999; 113: 170-171.
5. Erdoğan G, Erdoğan MF, Delange F, Sav H, Güllü S, Kamel N. Moderate to severe iodine deficiency in three endemic goiter areas from the Black Sea region and the capital of Turkey. Eur J Epidemiol, in press, 2001.

ABDOMINAL TUBERCULOSIS MIMICKING MALIGNANCY: A CASE REPORT

Aydın Yağmurlu* ✣ Günce Tolasa* ✣ Banu Yağmurlu** ✣ İ. Haluk Gökçora* ✣ Hüseyin Dindar

SUMMARY

A 3-year-old male child was admitted with fever, anorexia and abdominal pain for the past two months. Presumptive diagnosis leads to malignancy. Biopsy-aimed laparotomy was conducted. Laparotomy findings suggested the diagnosis of abdominal tuberculosis. Acid-fast bacilli in the peritoneal fluid and a positive culture determined confirmation of abdominal tuberculosis. Histopathological examination revealed a granulomatous inflammatory process, which compatible with tuberculosis. Anti-tuberculoses treatment was started immediately.

Although modern imaging techniques were used, this rare infectious disease mimics malignancy, and lead to a more aggressive innovation. The authors recommend minimally invasive surgery for to avoid unnecessary laparatomy.

Key Words: *Abdominal Tuberculosis, Childhood*

ÖZET

Maligniteyi Taklit Eden Abdominal Tüberküloz

3 yaşında erkek hasta iki aydan beri süregelen ateş, iştahsızlık ve karın ağrısı yakınmaları ile kliniğimize başvurdu. Malign bir lezyon olabileceği düşünülerek biyopsi amaçlı laparotomi uygulandı. Laparotomi bulguları abdominal tüberküloz ile uyumlu bulundu. Abdominal tüberküloz tanısı peritoneal sıvıda asidorezistan basil ve kültür sonucunun pozitif gelmesi ile doğrulandı. Histopatolojik incelemede ise tüberküloz ile uyumlu olan inflamatuar granülamatöz reaksiyon saptandı. Antitüberküloz sağaltımına hemen başlandı.

Ender görülen bu enfeksiyöz hastalık maligniteyi taklit ederek daha invaziv bir girşimin uygulanılmasına yol açmıştır. Yazarlar, minmal invaziv cerrahi girişimler kullanılarak gereksiz laparatomiden kaçınılabileceğini vurgulamaktadırlar.

Anahtar Kelimeler: *Abdominal Tüberküloz, Çocukluk Çağı*

With the recent resurgence of tuberculosis infections, the interest in abdominal tuberculosis (TB) has been reviewed. Abdominal TB presenting with nonspesific findings and may mimic a multitude of gastrointestinal disorders. It still remains as a diffucult disease to diagnose out of the operating room (1,2).

The following report highlights one such case, where a malignant process was primarily considered depending on initial findings. And also emphasizes the role of minimally invasive surgery for to change the attitudes in such kind of cases.

Case Report

A 3-year-old male child was admitted to the hospital with fever, anorexia and abdominal pain, since two months. Physical examination revealed the existence of 3-4 submandibular microlymphadenopathies, BCG vaccination scar was missing. The white blood cell (WBC) and erythrocyte sedimentation rate were 5000 /mm^3 and 20 mm/h, respectively. The chest x-ray was normal with no suspect of an infection. A hypoecoic pseudo-capsule formation with size 2.5 x 1.5 x 1.5 cm. was observed on the ultrasonography (US), which displaced bowel

* Ankara University, Medical School, Department of Pediatric Surgery.
** Ankara University, Medical School, Department of Radiology.

Received: Jan 15, 2001 Accepted: Sept 20, 2001

segments ventrally. Abdominal computerized tomography (CT) revealed a cyst or hypodense bisegmental structure of 3 × 2 × 2 cm. and mesenteric lymph nodes on the abdominal mid-plane (Figure-1a). It was assumed that the cyst or bisegmental structure had mesenteric placement, and its borders could not be distinguished from the bowel wall, accompanying peritoneal thickening was also observed (Figure-1b). Depending on these findings, biopsy-aimed laparotomy was conducted with the suspicion of a malignant process. During laparotomy the overall bowel surface was covered with white micronodules). There was a centrally necrosed mass of 4 × 3 × 2 cm. placed in the mesenteric origin and lots of mesenteric lymph nodes. Incisional biopsy was performed from the lesion. Samples were taken from the peritoneal fluid for cytologic analysis and microbiological culture. Postoperative period was uneventful. According to the laparotomy findings the diagnosis of abdominal tuberculosis was established. Acid-fast bacilli in the peritoneal fluid and a positive culture result determined confirmation of abdominal tuberculosis infection. Histopathological diagnosis revealed a granulomatous inflammatory process, compatible with TB. Anti-tuberculosis treatment was started immediately.

Discussion

Abdominal TB was a common disease among the Industrial Countries at the turn of the 20th century. During the ensuing decades, there was a steady decline in incidence attributed to improvements in nutrition, living conditions and the development of the specific drug therapies. By the 1970s, it was rarely seen in industrialized countries, and most reports dealt with its incidence in immigrant and third world populations (1). Although after a period, a steady decline in the incidence of tuberculosis, a resurgence of the disease has occurred since the mid 1980's. Numerous studies have reported an increasing frequency in the patients infected with HIV and in undeveloped or developing countries. This situation has been exacerbated by the increasing number of multidrug-resistant strains of M. Tuberculosis (2). TB can be seen in all age and socio-economic groups in undeveloped countries. It should be considered in the differential diagnosis of the acute abdomen. The main symptom is abdominal swelling in 82%. Other symptoms are fever (74%), weight loss (62%), abdominal pain (58%), and diarrhoea (16%). Seventy five percent of the patients have abdominal tenderness. An abnormal chest radiograph is found in 48% but active pulmonary tuberculosis in only14% (3).

Although most cases of abdominal TB are thought to be due to a pulmonary cause. Post-mortem studies have found intestinal involvement in %80 of patients who die of pulmonary TB. Almost all cases of abdominal TB are caused by Mycobacterium tuberculosis. Mycobacterium bovis has been almost eliminated by public health measures but may be a rare cause of primary

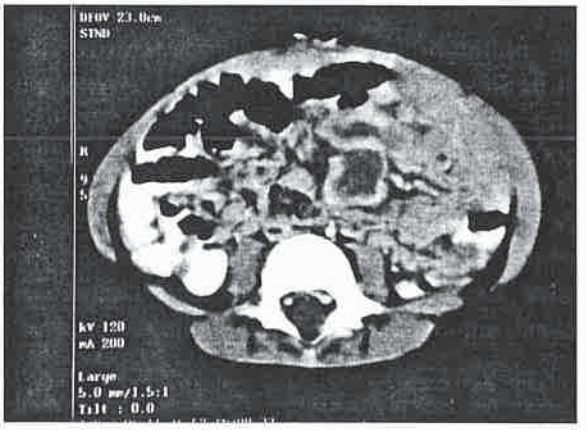

Figure-1a: Hypodense bisegmental structure and mesenteric lymph nodes were observed on the abdominal midplane in computerized tomography.

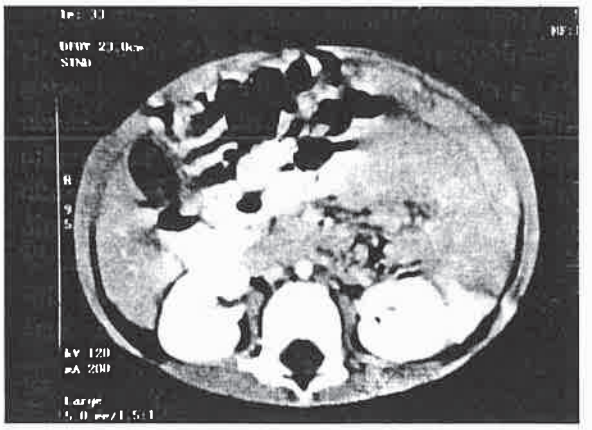

Figure-1b: Peritoneal thickening and the massy appearence undistinguishable from the bowel wall observed in computerized tomography.

intestinal tuberculosis, which is due to direct ingestion of infected material (3). The intestinal mucosa responds with an inflammatory exudate that may progress to an area of ulceration. The natural course of intestinal TB follows three patterns: ulcerative, hypertrophic, and ulcerohypertrophic. In the ulcerative form, transverse ulcer occurs perpendicular to the bowel axis and may bleed, perforate, or form fistulas. In the less common hypertrophy form, a mass or multiple nodules with or without caseous necrosis and may mimic malignant neoplasms such as lymphoma or carcinoma and may cause obstruction (2,4,5).

The diagnosis of abdominal TB is diffucult especially in children due to its vague clinical picture, and therefore the diagnosis is often delayed. The most common forms of abdominal TB in children are adhesive peritonitis and nodal disease. Strictures are uncommon, and the hypertrophic form is rare (3,6).

Our patient was admitted to the hospital for his fever, anorexia and abdominal pain, which have all been continuing for two months. At the beginning, anti-parasitic medical drug treatment was started with the suspicion of parasitic infestation. Routine laboratory tests provided non-specific data. Abdominal CT and US was performed as radiological studies. It was assumed that the cyst or bisegmental structure had mesenteric placement, and its borders could not be distinguished from the bowel wall. The patient could not be diagnosed preoperatively. During laparotomy, partial omental thickening, white micronodules covering almost the entire bowel surface and a $4 \times 3 \times 2$ cm mass placed at the mesenteric origin were observed. As a result of all the above findings, the case was diagnosed as abdominal TB, during operation. This macroscopic form, which is rarely encountered in the childhood, was histologically compatible with the hypertrophic form.

Should CT show intraabdominal tuberculosis, laporatomy can be avoided and less invasive methods such as laparascopy may be used. Also with the use of abdominal paracenthesis the diagnosis could be accurately made, but laparoscopy could give a better exposure to whole abdominal cavity, and tissue sampling. Laparotomy must be used for complications such as obstruction, perforation, abscess, and fistulization. The authors offer explorative laparotomy or laparoscopy with unexplained process, because of differential diagnosis for hypertrophic form such as lymphoma, various forms peritoneal carcinomatosis, and peritoneal mesothelioma (7).

The abdominal TB, which has recently come to issue with HIV infections in the developed countries, has never lost its importance in the developing or undeveloped countries, should be kept in mind and considered by the clinician. This case is thus reported, since we believe that this hard-to-diagnose disease can be successfully treated if marked early enough.

REFERENCES

1. Amber A.G., Unsup K. The Reappearance of abdominal tuberculosis. Surg. Gynecol. Obstret. 1991;172: 432-6
2. Hossein J., Mindelzun R.E., Olcott E.W.Levitt D.B. Still the great mimicker:Abdominal tuberculosis. AJR 1997; 168:1455-60
3. Niall O.A. Abdominal tuberculosis.World J. Surg. 1997;21:492-9
4. Clifford YK, Schmit PJ, Petrie B, Thompson JE: Abdominal tuberculosis: The surgical perspective. The American Surgeon. 1996; 62:10, 865-8
5. Ab Del Bagi M, Karawi AA: Ultrasound diagnosis of "Dry Type" ileocecal tıberculosis: A case report. Hepatogastroenterol. 1997:1033-6
6. Veeragandham RS, Lynch FP, Canty TG, Collins DI, Dankner WM: Abdominal tuberculosis in children: Review of 26 cases. J Ped Surg. 31:1; 170-6
7. Apaydın B., Paksoy M., Bilir M., Zengin K., Sarıbeyoğlu K., Taskin M. Value of diagnostic laparoscopy in tuberculous peritonitis. Eur J. Surg 1999;165:158-63

JOURNAL OF ANKARA MEDICAL SCHOOL Vol 24, No 2, 2002 95-98

LIPOMATOUS HAMARTOMA A RARE REASON OF ENDOBRONCHIAL OCCLUSION

Murat Güvener* ✣ Mustafa Yılmaz* ✣ Şanser Ateş** ✣ F. Tanzer Serter* ✣ Murat Özkan* ✣ İlhan Paşaoğlu*

SUMMARY

We reported a case of an endobronchial lipomatous hamartoma which occluded the bronchus of left lower lobe.

Endobronchial lipomatous hamartoma is a very are benign tumor of the tracheobronchial tree. The medical literature in English by year up to 2000 reported only 56 cases of endobronchial and endotracheal lipoma. Actually, most of them were endobronchial lipomatous hamartomas, there were only a few cases of endobrochial true lipomas published in literature. Differentiation between endobronchial lipomatous hamartomas and endobronchial lipomas has not been made in the literature. This difference change was implied in this case report. Diagnosis and treatment were discussed.

Key Words: *Bronchial Occlusion, Endobronchial Lipomatous Hamartoma, Surgical Treatment*

ÖZET

Sol Alt Lob Bronşunu Tıkayan Endobronşiyal Lipomatöz Hamartom Vakası

Endobronşiyal lipomatöz hamartom, trakeobronşiyal ağacın nadir görülen, benign bir tümörüdür. İngilizce literatürde, 2000 yılına kadar bildirilmiş 56 endobronşiyal ya da endotrakeal lipom vardır. Gerçekte, bunların çoğu endobronşiyal lipomatöz hamartomlardır, sadece birkaç gerçek endobronşiyal lipom yayınlanmıştır. Literatürde endobronşiyal lipomatöz hamartom ile gerçek lipomlar arasındaki ayırım yapılmamıştır. Bu çalışmada, bu değişiklik vurgulanmış, tanı ve tedavi yöntemleri tartışılmıştır.

Anahtar Kelimeler: *Bronşiyal Oklüzyon, Cerrahi Tedavi, Endobronşiyal Lipomatöz Hamartom, Cerrahi Tedavi*

Most tumors of the tracheobronchial tree are malignant in nature. Benign endobronchial tumors are rare and there is considerable confusion regarding the nomenclature and classification. Less than 1% of lung tumors are benign and of these, hamartomas are the most common (1). Endobronchially located hamartomas are rare and account for only 1.,4% of all pulmonary hamartomas in a recent analysis (2). Endobronchial hamartomas arise from major bronchi (3). They are composed of mixture of bronchial components (4) and they are described by thethe principal mesenchymal component (chondromatous, lipomatous or mixed mesenchymal) (1). Frequently cartilaginous elements predominate in most of them, but a few may contain predominantly adipose tissue or bone. Cytogenetic studies have identified recombinations of chromosomal bonds 6p21 and 14q24, supporting the view that hamartomas represent clonal mesenchymal neoplasms (4).

The diagnosis may be suggested by endoscopic aspects, but reliable distinction from a carcinoid or another benign bronchial tumor often is not possible even with biopsies. In the presence of endobronchial lipomatous hamartoma or lipoma, CT may reveal endobronchial tumor with fat density (4).

* Hacettepe University, Faculty of Medicine. Department of Thoracic and Cardiovascular Surgery.

Received: May 09, 2001 Accepted: Sept 06, 2001

Due to their benign nature, endobronchial lipomas-hamartomas should initially be treated endoscopically. However more frequently endobronchial hamartomas are excised via bronchotomy, another effective and easily performed technique is cryotherapy. Endobronchial laser therapy can also be used (3).

Early endoscopic examination is important for detection of these tumors before the lung distal to the obstruction is irreversibly destroyed. The risk of lung cancer higher in patients with hamartoma than the general population (5). If irreversible lung damage has occured because of chronic obstruction and suppuration, pulmonary resection may be indicated.

Differentiation of benign endobronchial tumors from malignant lesions are of clinical importance.nterest.

CASE REPORT:

A 40-years-old man was admitted to our hospital with a history of productive coughing with expectoration. He has been smoking for 20 years, 1 pack per day. His chest X-rays showed bronchiectatic left lower lobe together with subtotal atelectasis, the CT scan revealed an occlusion in the left lower lobe bronchus. The tumor density could not been discriminated. A well circumscribed, bright yellow tumor with mucosal capillary vessels on surface, moving with respiration and obstructing the bronchus of the left lower lobe was seen by fiberoptic bronchoscopy. Biopsy specimen was not obtained because a punchtaking biopsy from this bronchial tumor that was seen as a vascular mass might cause a bronchial bleeding. Our experience in taking biopsy from vascular tumors by using current bronchoscopic tecniques was not appropriate enough. The left lower lobe with its bronchus was resected because the tumor caused to bronchiectasisa and atelectasis. The tumor was considered as malignant rather than benign. Pathological examination revealed exactly the benign characteristics of the lesion. The diagnosis was endobronchial lipomatous hamartoma. Histopathologically, the tumor was consisted predominantly of mature fat cells, a little cartilage and epithelial components. No atypical cells were found (Fig. 1).

One year after the operation, the patient was living his normal life. Control bronchoscopy revealed normal findings without any recurrences.

DISCUSSION:

Endobronchial lipomatous hamartomas are named as endobronchial lipomas by some authors, presence of small quantities of other tissues like cartilage or epithelial components within the lipoma is of little clinical importance. Both are rare benign mesenchymal tumors occuring most commonly in the left main stem bronchus of middle aged male smokers and similar clinical progresses are observed (4). On the other hand, if we classify this tumor as lipoma, we must accept these definitions: 1. They orginate from fatty tissue that is normally present in the tracheobronchial tree, both in the tissue external to the cartilage plates and to a lesser extent in the intersititial tissue of the submucosa (6). 2. They are usually pediculated tumors with a narrow stalks composed of mature fat cells and covered with normal respiratory epithelium. (7,8). 3. True

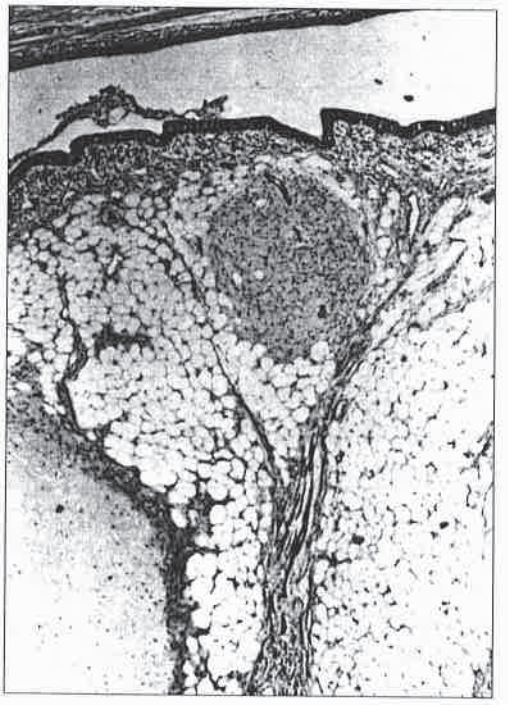

Figure 1: Microscopic section of the endobroanchial lipomatous hamartoma. The tumor was consisted predominantly of mature fat cells, a little cartilage, and epithelial components were present. Mature adipose tissue is covered by respiratory epithelium (H. E. stain X100).

lipoma is (encapsulated and consist only of fat cells) in this classification (9). 4. There is no risk of malignant transformation and no risk of recurrence (6-9). As a result, pathologically, "lipoma" is not a proper definition, the tumor is placed in the gray zone (hamartomas) near the lipoma.

The present tumor was defined as an endobronchial lipotamous hamartoma but not as a lipoma. After the histological examination, the tumor was reported to be composed of a little cartilage, predominantly adipose tissue containing mesenchymal tumor, _a hamartoma.

REFERENCES

1. John LCH, Wallis J, Edmondson SJ. Endobronchial chondromatous hamartoma: A rare cause of lobar collapse treated by endoscopic removal. J Thorac Cardiovasc Surg 1992; 103: 1226-7.
2. Gjevre JA, Myers JL, Prakash UBS. Pulmonary hamartomas. Mayo Clin Proc 1996; 71: 14-20.
3. Şahin AA, Aydiner A, Kalyoncu F, Tokgozoglu I, Barış YI. Endobronchial hamartoma removed by rigid bronchoscope. Eur Respir J 1989; 2: 479-80.
4. Stey CA, Vogt P, Russi EW. Endobronchial lipotamous hamartoma; a rare cause of bronchial occlusion. Chest 1998; 113: 254-5.
5. Ribet M, Jaillard-Thery S, Nuttens MC. Pulmonary hamartoma and malignancy. J Thorac Cardiovasc Surg 1994; 107: 611-4.
6. Doğan R, Ünlü M, Güngen Y, Moldibi B. Endobronchial lipoma. Thorac Cardiovasc Surgeon 1988; 36: 241-3.
7. Box K, Kerr KM, Jeffrey R, Douglas JG. Endobronchial lipoma associated with lobar bronchiectasis. Respiratory Medicine 1991; 85: 71-2.
8. Pinero A, Gimenez A, Lax FG, Parrilla P. Hemoptysis caused by an endobronchial lipoma. J Thorac Cardiovasc Surg 1996; 111: 1104-5.
9. Jensen MS, Petersen AH. Bronchial lipoma. Three cases and review of the literature. Scand J Thor Cardiovasc Surg 1970; 4: 131-4.