Journal of Ankara Medical School

ISSN 1300-5464

Vol. 25 No. 1 2003

Journal Of Ankara Medical School

Cilt: 25, Sayı: 1, 2003
Vol: 25, No: 1, 2003

THE JOURNAL OF THE FACULTY OF MEDICINE
UNIVERSITY OF ANKARA

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Journal Of Ankara
Medical School

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IDEAS OF EDITORS OF MEDICAL JOURNALS ON PUBLICATION ETHICS (*)

Belma Akşit* ✣ Berna Arda**

SUMMARY

This study has been carried out to make an assessment of situation regarding the publication ethics from the editorial point of view . In international literature, there are not any articles under the subtitle 'publication ethics' based on honesty of the authors and questioning it through a variety of samples. On the other hand, it is possible to see a number of articles dealing with the ethics of research and publication, samples of cheating faced in this process and responsibilities of editors . In Turkey when similar topics are brought up and discussed, a publication ethics which only focus on researcher and potential author awareness and in turn which finds it enough to express only their ethical responsibilities is dominant . In the light of this context, expressing the concept of editorial ethics by editors themselves , from their point of view and though their own ideas will serve to make up for this demand. This article devoted to discuss editorial ethics in the light of a limited survey's findings.

Key Words: *Scientific Ethics, Research Ethics, Publication Ethics, Editorial Ethics.*

ÖZET

Tıp Dergi Editörlerinin Yayın Etiği Konusundaki Görüşleri

Bu çalışmada, yayın etiği konusu tıp dergi editörlerinin görüşleri ışığında tartışılmaktadır. Uluslararası literatürde de yayın etiği başlığı altında temelde yazarların dürüstlüğünü merkeze koyan ve farklı örneklerle gündemde tutan bir yaklaşım bulunmaktadır. Öte yandan araştırma ve yayın etiği bağlamında editöryal sorumluluğun yerini vurgulayan ancak az sayıda makaleye rastlanmaktadır. Türkiye'de de benzer başlıklar benzer biçimde tartışılmakta, yayın etiği kavramı hemen hemen sadece araştırıcıların ya da potansiyel yazarların dürüstlüğü ve sadece onların etik sorumlulukları üzerine inşa edilmektedir. Bu bağlamda editörlerin kendilerinin editöryal etik konusundaki düşüncelerini almak konuya farklı bir bakış açısı getirecektir. Bu çalışma, editoryal etik konusunu sınırlı bir araştırmanın verileri ışığında tartışmaya ayrılmıştır.

Anahtar Kelimeler: *Bilim Etiği, Araştırma Etiği, Yayın Etiği, Editöryal Etik.*

Scientific publications, no doubt, play an important role in dissemination of medical knowledge, putting forward new aspects through discussion and making new scientific contributions. The peak level of articles by Turkish scientists in international science is a concrete result of the quality efforts made through years. However, leaving aside our quantitative position, it is necessary to come up with new ways of solutions, realize what to be regarded as problems and handle our publication process in terms of quality so as to put this process in a better position in ethical aspect as much as possible. This study has been carried out to make an assessment of situation regarding the publication ethics from the editorial point of view which is an important figure in publication process. In international literature, there are not any articles under the subtitle 'publication ethics' based on honesty of the authors and questioning it through a variety of samples. On the other hand, it is possible to see a number of articles

(*) *This article based on a poster which has presented by B. Arda "Editorial ethics, in the light of a restricted survey from Turkey." 5th World Congress of Bioethics. London, England, 21 - 24 Sept. 2000 and an oral presentation which has presented by B Akşit 2001 National Congress of Medical Ethics, Cappadocia, 18 – 20 Oct. 2001.*

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Received: *April 10, 2003* Accepted: *April 28, 2003*

dealing with the ethics of research and publication, samples of cheating faced in this process and responsibilities of editors (1-6). In Turkey when similar topics are brought up and discussed, a publication ethics which only focus on researcher and potential author awareness and in turn which finds it enough to express only their ethical responsibilities is dominant (7-9). In this context, there are few articles which put forward 'editorial ethics' and underline the necessity to meet the demand for such articles mentioned above (10-12). In the light of these realities, expressing editorial ethics by editors themselves, from their point of view and though their own ideas will serve to make up for this demand.

Methodology

1. General information about the journals : A questionnaire was prepared consisting of 7 parts including information about the publication policy of the journal, referees, authors, personal characteristic of the editor, editorship and the board.
2. It is a descriptive one. The questionnaire was sent to all the editors of journals in the Turkish Medical Index , which is organized by Scientific and Technical Research Council of Turkey, in April 2000. 87 journal editors were sent the questionnaires and 41 of them completed and sent them back (47%) and answered questionnaires were evaluated. The data were analyzed through SPSS.

Findings

A) General information about journals

Analyzed their years of publication, the journals published for a long time have a high percentage. The journals published between the years 1980-1984 had a low circulation, however, from 1984 onwards this ratio increased substantially. The journals published 3 or 4 times a year were the majority. (87.8%)

Nearly 40 % of the editors expressed that subscription fee, donation and ads were benefited and 25% of them said that they benefited from foundations/associations. Only 20 % of them said that their journal was sponsored and nearly 10% of them left the question unanswered. 'Foundations' and 'Universities' were the most terms used by the editors who mentioned any sponsorship. 37% of the journals were mentioned to take ads. Medical firms and medical industry constituted the basis of these ads.

12% of the editors did not answer the question about how many copies were published. Among the ones who answered the question, nearly 67% expressed that their journals had a publication of 500-2000.

B) Publication policy

With regard to the questions of 'the content and how it is determined', answers such as 'whether it is a product of a unique study and whether it is consistent with the specific content of journal' were given. In addition 'whether more than 50% of the articles is based on a real study or not in a volume' or 'whether the article complies with norm and content of journal' were underlined. In 56% of the journals giving answers authors were required to submit an invitation letter and in 93% of the journals they were required to sign and submit application forms before the article was published. Regarding awareness in ethical subjects, in 63% of the journals authors were asked for the approval of the ethical board and in only 17% of the journals a copy of the approval taken from subjects was required to be submitted. When asked the ratio of turned down articles sent in 1999, those who gave the answer '15% or fewer' constituted 35% of the answers; those who gave the answer '16-25%' constituted 22% of the answers; those who gave the answer '26-51%' constituted 24% of the answers. Different ideas were put forward about the articles refused by the editors themselves and published in another journal. The answers like 'it shouldn't be published at all', 'not appropriate', 'unfortunate' had the highest ratio with 46%. When the answer 'I'll inform the editor of the situation' was added, this ratio increased and the ratio was more than half of the answers. 78% of the journals had an editorial letter column and

90% of the journals focused on research based articles.

'Publication of unauthorized knowledge, cases, samples and data without the consent of the original authors' and 'Citation without reference' were the most common situations which didn't comply with the publication ethics. Following these answers were 'publication of an article in more than one journal' and 'listing of people who didn't contribute to the research'.

C) Information about referees

88% positive answers were given to the question whether there were certain principles about appointment of referees. 85% of those who answered the question gave the answer 'being an important and well-known figure in his field/his experience and scientific reliability'. 9% of the participants underlined the importance of the titles of the referee. 95% of the journals participating in the study expressed that 'their referee had evaluation criteria to be followed'. Referees were not paid in any of the journals. Average period of review and editing was as follows: 60% of the participants gave the answer 'shorter than a month' and 32.5% of the participants gave the answer '1 –2 months'.

D) Information about authors

In 83% of the journals there was no limitation to the articles per each author and in 86% of the journals authors were required to sign and submit an approval form. In 88% of the journals the authors were not required to pay any fee and in none of the journals authors were paid any royalty. In 20% of the journals authors were required to subscribe to journals. The author profiles of journals were interesting as well. It was determined that there was almost no information about their age, sex and academic situation.

E) Personal information about editors

The age range of editors was nearly equaled as under and over 50. Female/male ratio was 1/3 and professors were the majority in distribution of academic titles. Those who were editors for less than 4 years constituted 46% of all editors.

F) Information about editorship

9.8% of the participants didn't answer the question 'Is there a job description for editors?' and 65% of those who answered the question said 'yes'. 40% of participants said that they did not know how it was described and there was no significant distribution among those who answered the question. 60% of them gave answers such as 'being responsible for all kinds of work' which was an ambiguous answer. Only 18% said that 'scientific incentive is emphasized'. The ratio of the editors who said that 'they read every single article submitted' was 41,5%. 'The criteria of acceptance' were as follows: when 130 answers were evaluated at the rate of 30,8% 'referee reports'; at the rate of 27,7% 'being not published in any other journal; at the rate of 27,7% 'editor's own point of view'; and at the rate of 13.8% 'the ideas of the publication board' were obtained. When asked the phases at which the editors would intervene, the answers received were extremely interesting. In that, the answer 'spelling can be corrected' was at the rate of 30,4%, the answer 'it can be returned or adjourned' at the rate of 23,2%, the answer ' tables can be corrected' at the rate of 23,2%, the answer 'references can be crossed out' at the rate of 13,1%, the answer 'the editors can intervene at any phase' at the rate of 9,1%, the answer ' the editor cannot intervene at any phase in ethical aspect' at the rate of 0,9%. It was significant that only one editor drew attention to the ethical concern.

G) Information about the publication board

The number of people in the publication board was given as '5 people or fewer' at the rate of 47,5 %. When the frequency of the board meeting was asked, the most frequent answer was 'once or twice a month'. In one fourth of the journals, no answer was given to the question 'Is there a job description for the members of the board?'; in one fourth of the journals, the answer was 'No'; the rest gave the answer 'Yes'. No satisfactory answer could be obtained to the question 'What is the job description of the board?'. The rate of editors who said that 'there is a job description' but didn't make any definite

explanation was nearly 50,0%. Those who answered said 'evaluation of referee reports', 'each member is responsible for his own field', 'determination of referee', ' determination of publication policy' . More than 70% of the members of the board also supervised in their own fields. There were few answers about the function of the board members in accepting articles. (Unknown 21,7%). The distribution of those who answered was as follows : 'They express their ideas' (41,8%); 'they reach unanimous decision' (22,6%); 'they have no function' (22,6%); 'they make positive reference' (6,5%); 'they decide whether the phases are completed or not' '(6,5%).

H) The preference criteria of a journal

When asked the most determining factor for the preference of a journal, the majority of editors who answered underlined that a journal should be satisfactory in scientific aspects. On the other hand they also underlined that the originality of the article offering new horizons to the reader and print quality were the other factors for preference. The surprising point was that only one answer was given about the question whether a journal should comply with the ethical principles.

Discussion

- The fact that only one-third of journals started to come out before 1980 and the fact that there has been an ever growing increase in the number of journals since that date are due to the amendments in laws to adjust academic conditions in universities and requirement of publishing articles for academic promotion.
- It is clearly seen that journals are sponsored by medical industry through ads.
- In 93% of the journals authors are required to sign and submit an acceptance form before their articles are published in journals. And this is very concerning. In recent years an article written in Turkey ignited a discussion 'the rights to be an author'. Considering this article, it can be concluded that this subject does not draw enough attention which it really deserves. So, the rate being so high is beyond being plausible.
- The fact that editors of journals require (at the rate of 63%) authors to submit an ethical board approval justifies the Regulation of Medical Research passed in 1993 which reads as 'ethical board is compulsory'.
- This study shows that medical journals are deeply affected by the regulation taken by the Scientific and Technical Research Council of Turkey in 1994 that Medical Journals are to cover researches.
- Under the title 'Conditions which are inconsistent with the publication ethic of the journal' editors underline the following : 'Publication of unauthorized knowledge, cases, samples and data without the consent of the original authors' and 'citation without reference' and the ratio comes to 40%. However, when scientific reliability concept is considered, this rate is expected to be higher.
- 95% of the editors express that there are evaluation criteria which referees have to follow, however, when analyzed in detail it is a matter of concern that either some editors give no answer or some say 'referees are left free'.
- It is virtually impossible to draw a framework for the job description of editors through the given answers. The answers vary from 'being responsible for all kinds of work' to 'scientific incentive is emphasized'.
- And with regard to editorial authority the answers vary from 'correcting spelling mistakes', 'crossing out references' to 'intervening at any phase'.
- Ambiguity about the job description of publication board and not realizing the importance of it is the same as the case of the editorship.

It is clear that there is an urgent need for clearing away the ambiguity about the job description of the editors and publication board and clarifying the authority of and scope of intervention by editors and also there is need for producing quality and original research by taking into consideration certain standards.

Another point here to be emphasized is what problems the requirement of international publication for academic promotion may bring about in Turkey in scientific field and how this recent change should be dealt with.

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Acknowledgements: Thanks to Turkish Medical Association for financial support and to all the members of ex ECTMA (1996- 2001) for their intellectual contributions on preparing of questionnaire.

CHANGES IN PERICENTRIN LOCALIZATION DURING MEIOSIS

Olcay Semiz* ✣ Alp Can*

SUMMARY

The centrosome in oocytes, an acentriolar aggregate of centrosomal material, is regulated in a dynamic manner throughout the process of meiotic maturation. Recently, it has been demonstrated that meiotic spindle assembly is likely regulated by chromosomal and microtubule/microtubule associated modulators. Given the importance of centrosomal role in spindle assembly, we aimed to assess the distribution of the eintegral centrosomal protein, pericentrin, during the course of meiotic maturation. Distribution of pericentrin during meiotic progression was examined by the serial confocal images in z-axis. It was also evaluated after exposure of oocytes to some pharmacological agents (i.e. Taxol and Methylbenzimidazole Carbamate) that perturb spindle and/or centrosomal integrity. We examined pericentrin in various shapes and locations during different meiotic stages (i.e. arcs, rings, fractures etc.). After taxol exposure, pericentrin incorporation into both spindle poles and cytoplasmic centrosomes was increased. Treatment of oocytes with MBC, a potent drug that has been previously shown to disrupt spindle poles in meiotic oocytes, influenced early events such as chromosome capture and spindle assembly, and altered the number and distribution of cytoplasmic centrosomes. In conclusion, the dynamic reorganization of pericentrin and changes in centrosome microtubule nucleation capacity are involved in critical cell cycle transitions during meiotic maturation.

Key Words: *Centrosome, Pericentrin,Meiosis*

ÖZET

Mayoz Sırasında Perisentrin Yerleşimindeki Değişimler

Ovositte, sentrozomal materyalin sentriyol dışı birikimi olan sentrozom; mayotik gelişim sırasında dinamik bir şekilde düzenlenir. Son zamanlarda mayoz mekiğinin oluşumunda, kromozomların ve mikrotübülüs/mikrotübülüs ilişkilerini düzenleyen moleküllerin rolleri olduğu gösterildi. Mekiğin oluşumunda sentrozomun önemli bir rolü olduğu bilindiğinden, bu çalışmada ~220 kD'lik önemli bir sentrozom proteini olan pericentrinin dağılımını ortaya koymayı amaçladık. Mayoz sırasındaki perisentrin dağılımı, z-aksında alınan seri konfokal görüntülerle incelendi. Aynı incelemede, ovositler mekik ve/veya sentrozom düzenlenimini bozan bazı farmakolojik ajanlara (örneğin: Taxol ve Metilbenzimidazol karbamat) maruz bırakıldıktan sonra da incelemeler gerçekleştirildi. Mayozun değişik evrelerinde perisentrinin çeşitli şekil ve yerlerde (örneğin: yay, halka, parçacık) bulunduğu gözlendi. Taxol uygulanmasından sonra, her iki mekik kutpu ve sitoplazmik sentrozomlarda perisentrin kütlesi arttı. Ovositlere, mekik kutuplarını bozmakta etkili olduğu önceden gösterilmiş bir ilaç olan MBC'nin uygulanması, kromozom yakalanması ve mekik oluşumu gibi olayları etkiledi ve sitoplazmadaki sentrozomların sayı ve dağılımlarını değiştirdi. Sonuç olarak, mayoz sürecinde perisentrinin dinamik düzenlenimi ve sentrozom mikrotübülüs nükleasyon kapasitesindeki değişiklikler, mayoz sürecindeki kritik hücre döngüsü geçişleriyle ilişkilidir.

Anahtar Kelimeler: *Sentrozom, Perisentrin, Mayoz*

Centrosomes; play a role function as dynamic regulators of spatial organization in dividing and non-dividing cells. As the major microtubule organizing centre (MTOC) of somatic cells, their dublication, positioning, and composition have become prominent subjects of study with respect to cell cycle control (1), mitotic spindle bipolarity (2) and the symmetric (mitosis) or asymmetric partitioning of various organelles (3) and chromosomes (4). In animal oocytes, centrosomes differ from their somatic counterparts with lacking centrioles. Centrosomes presumably subserve the function of organizing cytoplasm during the growth and differentiation of animal cells. They are associated with meiotic spindles in avrious

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Received: *April 25, 2003* Accepted: *May 26, 2003*

species but their exact contribution to spindle morphogenesis and cell cycle progression remains unclear. While the cell cycle regulators are localized to the meiotic spindle mounting evidence suggests that α-tubulin, dyneins and chromatin are necessary and sufficient determinants of meiotic spindle formation and function (5,6) to the exclusion of centrosomes.

This study addresses the function of oocyte centrosomes by examining the distribution of the intrinsic protein pericentrin (7) to the meiotic spindle and cytoplasmic centrosomes. The question of cytoplasmic organization is approached by investigating cytoskeletal and biosynthetic determinants of centrosome organization after treatment of *in vitro* matured mouse oocytes with selective pharmacological agents. Towards resolving centrosome functions in meiosis, pericentrin organization has been elucidated by confocal fluorescence microscopy at various times during meiotic progression. In this study, we have revealed that spindle centrosomes change in their microtubulus (MT) binding under normal and experimental conditions.

Materials and Methods

Collection and Culture of Mouse Oocytes- Oocytes were obtained from 19-21-day old Balb-C mice injected 48 hr earlier with 5 IU of equine chorionic gonadotropin (Sigma Che.Co. USA). Cumulus-enclosed oocytes (COCs) were transferred in collection medium (Eagle's MEM with Hanks salts and Hepes supplemented with 100 IU/ml penicillin, 100mg/ml streptomycin and 0.3% BSA). Oocytes were cultured for various periods of time in Eagle's MEM supplemented with Earle's salts, 2mM glutamine, 0.23mM pyruvate, 100 IU/ml penicillin, 100 mg/ml streptomycin and 0.3% BSA. After removal of cumulus cells by gentle pipetting, oocytes were fixed and extracted for 20 minutes at 37°C in a microtubule stabilizing buffer containing 2% formaldehyde, 0.5% Triton-X 100, 1 mM taxol, 10 units/ml aprotinin and 50% deuterium oxide. Samples were washed three times in a blocking solution of PBS containing 2% BSA, 2% powdered milk, 2% NGS, 0.1 M glycine and 0.01% Triton X-100 and stored at 4°C in blocking solution until processing.

Drug Treatment of In Vitro Matured Oocytes- To determine the effect of taxol which lowers the critical concentration of tubulin polymerisation, pulse experiments were performed at the metaphase-anaphase transition of meiosis-I. Oocytes (n=63) were cultured for 6-8 hrs in IVM medium. Taxol (1mM) was applied to oocytes for 10 minutes and fixed for fluorescence microscopy. Secondly methylbenzimidazole carbamate (MBC) was tested that was previously reported to differentially act on meiotic centrosomes (8). MBC was dissolved in DMSO and 30mM were used to treat COCs during different stages of oocyte maturation. First group of COCs (n=74) was treated during initial stages of *in vitro* maturation for 7-8 hours between GV-stage and metaphase-I (M-I). Second group (n=51) was exposed to MBC during an 8-18 hour-interval between metaphase-I and metaphase-II (M-II).

Immunostaining- Double fluorescence labelling has been performed to evaluate the organisation of meiotic spindle microtubules and centrosomes. For visualisation of microtubules, optimal results were obtained using a 1:100 dilution of a mouse monoclonal antibody, specific for α-tubulin (Sigma Che Co. USA). After treatment with primary antibody, samples were incubated with fluorescein conjugated anti-mouse secondary antibodies. Primary and secondary antibodies were diluted in blocking buffer (see above) and applied for 90 min at 37°C in a humidified chamber. Centrosomal protein, pericentrin was localised by incubating samples for 90 min at 37°C with anti-pericentrin 4b antibody (kindly gifted by S. Doxsey) at a concentration of 1:100 in blocking buffer. Cy3 goat anti-rabbit were used as a secondary antibody. Then oocytes were mounted between glass coverslips and slides using spacers allowing a ~100 mm space in between which was filled with a 1:1 glycerol/PBS medium containing 25 mg/ml sodium azide as anti-fading reagent.

Confocal Microscopy-Labelled oocytes were examined and images were recorded using a Zeiss LSM-510 confocal laser scanning microscope (Germany) equipped with 488nm Argon ion and 543nm green He-Ne, and a 63x

Zeiss Plan-Apo objective. Single and z-axis optical sections were collected by LSM-510 Software running on a Siemens-Nixdorf PC.

Results

We have evidenced that in germinal vesicle (GV) stage, pericentrin is a single, compact mass which is adjacent to nucleus and performing a potent cytoplasmic microtubule polymerising activity (Figure 1). By the breakdown of germinal vesicule (GVBD) the expression of pericentrin is increased with multi-centre localization around the dissolving nuclear envelope (Figure 2). In this stage, partial microtubule polymerising activity is also confined to cell centre. At the early pro-metaphase stage the congression of pericentrin as a huge mass is tightly associated with monopolar spindle (Figure 3). The transfer and the lining-up of several pericentrin foci through the spindle poles is detected during pro-metaphase (Figure 4) and metaphase-I respectively (Figure 5a-b). In addition, during metaphase-I, pericentrin was distrubuted along microtubules as individual foci, and clusters of foci accumulated at the future spindle poles. As meiosis proceeded, the spindle acquired a bipolar barrel-shape with chromosomal bivalents tightly arrenged at the metaphase plate and condensed agregates of pericentrin appeared at the spindle poles. Pericentrin was specifically localized to the spindle poles during metaphase of meiosis-I as arcs or incomplete ring-shaped structures. After that, translocation of some foci to the lateral sides of spindle occurs and the quantity of pericentrin decrease gradually at anaphase (Figure 6). When it is reached to telophase there is a minimal pericentrin positivity, only confined to the oocyte-end of the polar body (Figure 7). Finally, pericentrin appears at the spindle poles at metaphase-II with lesser amount compared to metaphase-I (Figure 8).

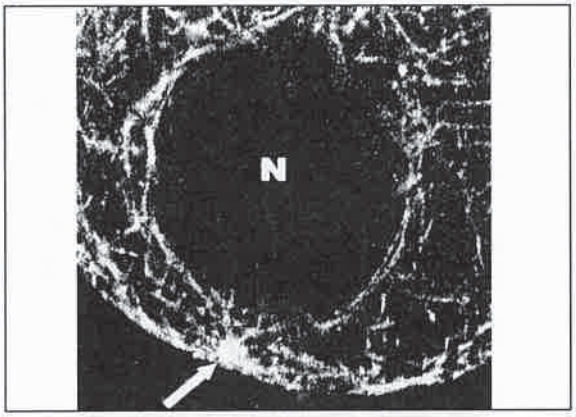

Figure 1. *Germinal Vesicle Stage: Pericentrin (arrow) is located close to the germinal vesicle (=nucleus of oocyte; N) where cytoplasmic microtubules (gray).*

Figure 2. *Germinal Vesicle Breakdown: Dramatically increased amount of pericentrin is localized adjacent to the nuclear envelope as 4-5 major foci (arrows) where groups of cytoplasmic microtubules (gray) emanate. N= nucleus.*

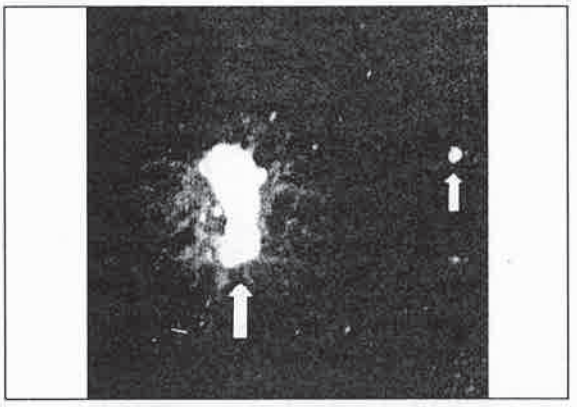

Figure 3. *Early Pro-Metaphase Stage: Pericentrin is seen as a huge aggregate (white) associated with the newly forming monopolar meiotic spindle (gray). Different from previous stage, pericentrin is also localized to the cytoplasmic centrosomes (small arrow).*

Taxol treatment resulted in enlargement and elongation of the spindle as evidenced by increased spindle length and width. Taxol causes

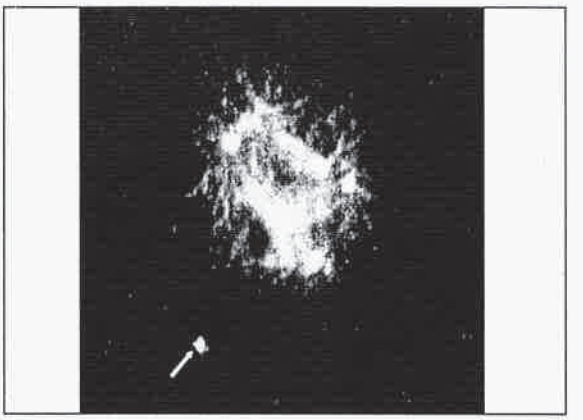

Figure 4. *Pro-Metaphase Stage: Pericentrin (white) moves towards the spindle poles to involve in bipolar meiotic spindle (gray). Compared to previous stage, pericentrin is seen as more condenced spots associated to both meiotic spindle and cytoplasmic centrosomes (arrow).*

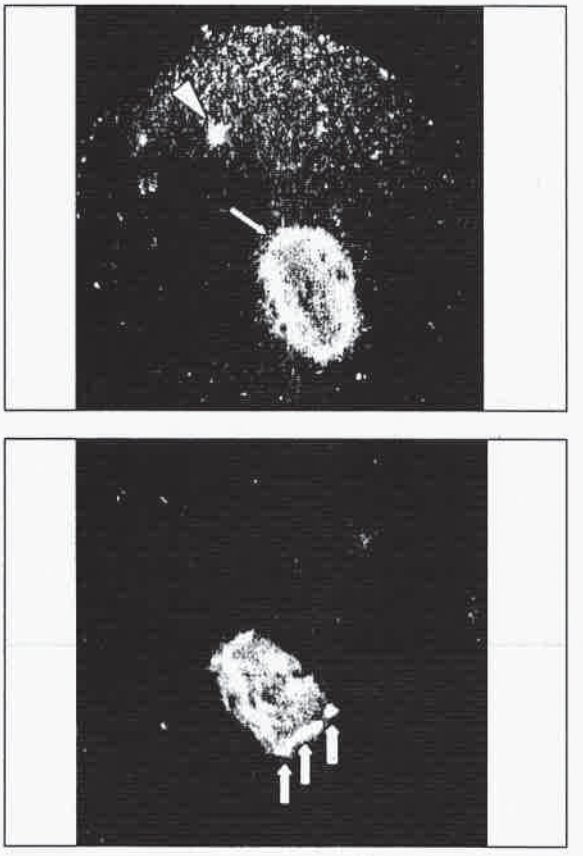

Figure 5 a-b. *Metafase-I Stage: Pericentrin foci (white) are lined up at spindle poles occasionally forming an arc or an incomplete ring-shape appearance (arrows). Cytoplasmic pericentrin persist in cytoplasmic centrosomes(arrowhead).*

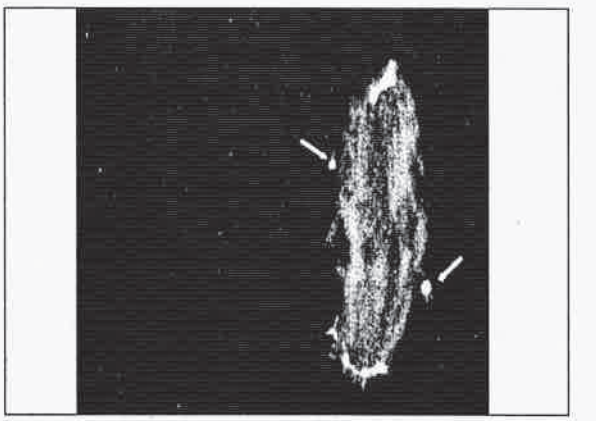

Figure 6. *Anaphase-I Stage: Bipolar pericentrin foci (white) begin to loosen up as evidenced by the loss of ring-shaped appearance and a decrease in staining intensity. Occasionally, pericentrin translocation to lateral margins of the spindle (arrows) is noted.*

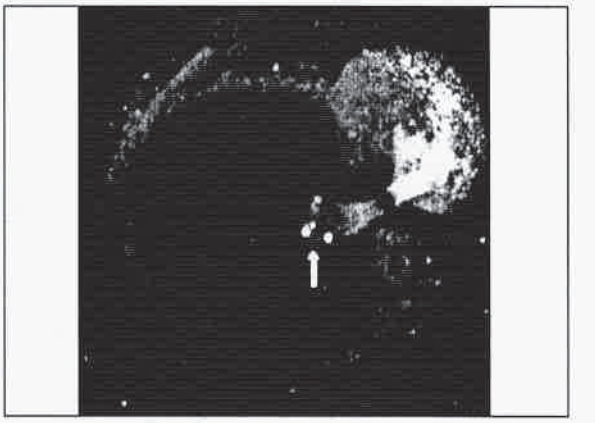

Figure 7. *Telophase-I Stage: Compared to previous stages pericentrin is dramatically decreased retaining only as a few condensed spots (white) at the oocyte-end of the mid-body, whereas a cloud of pericentrin positivity is noted in the polar body (asterisk).*

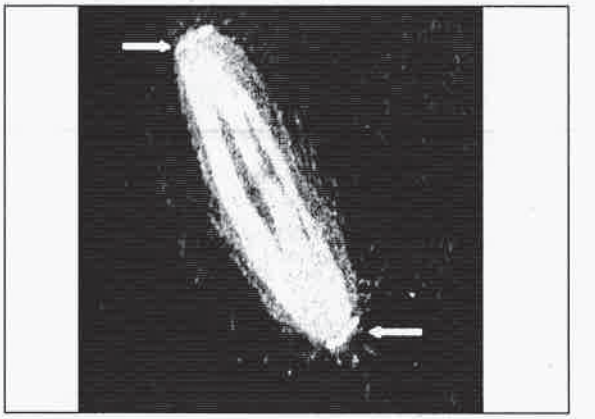

Figure 8. *Metaphase-II Stage: Pericentrin is relocated at the spindle poles (arrows) hence with a decreased quantity compared to metaphase-I.*

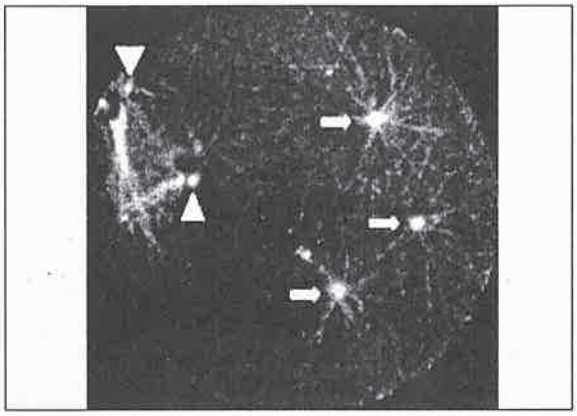

Figure 9. *Taxol (1 mM) treatment: Pericentrin incorporation (arrowheads) into both spindle poles and cytoplasmic centrosomes is incresed (arrows). Microtubule polymerisation (gray) is forced due to taxol treatment as seen in a pro-metaphase oocyte.*

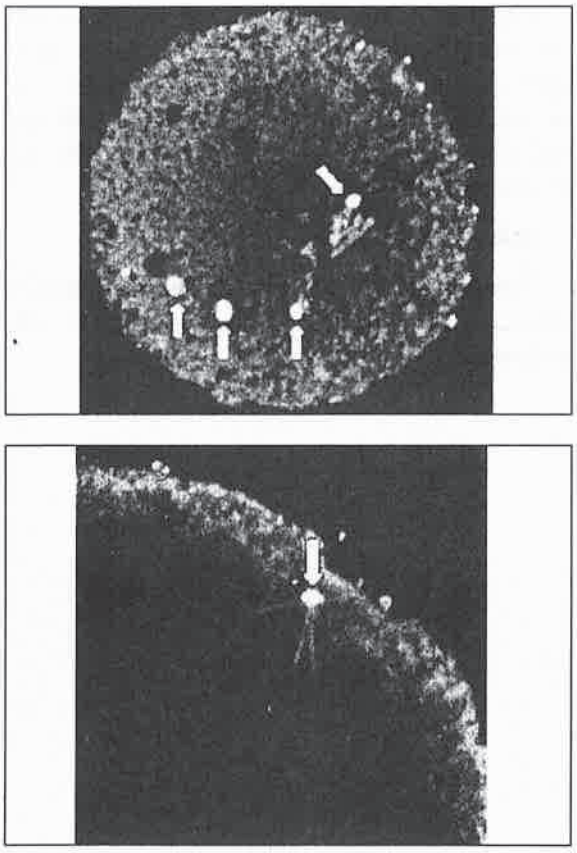

Figure 10 a-b. *MBC (methylbenzimidazole carbamate) (30 mM) treatment: Meiotic spindle is severely disrupted. Only few microtubules retained that are associated with clumps of pericentrin (arrowheads). No cytoplasmic centrosomes are detected.*

a rapid increase in the amount of both tubulin and pericentrin associated with the enlarged spindle (Figure 9). Large cortical microtubule asters with associated pericentrin were observed in response to taxol treatment. These data suggest that microtubule polymerization and assembly play a critical role in the organization of centrosomal material. Furthermore, the increased association of pericentrin to both cytoplasmic asters and the prometaphase spindle suggests the presence of a large soluble pool of pericentrin that is not utilized during normal spindle assembly or cytoplasmic centrosome formation. After MBC treatment in our study, a severe disruption has been detected in the meiotic spindle of oocytes. Only few microtubules retained that were associated with clumps of pericentrin; where no cytoplasmic centrosomes were seen (Figure 10a-b).

Discussion

Oocyte centrosomes may undergo changes in their MT nucleation capacity during meiotic cell cycle progression. Pericentrin displays a very dynamic pattern throughout the meiotic cell division. Variation in the amount of immunodetectable pericentrin during meiosis suggests concurrent expression levels. Pericentrin existance is proportionally related to microtubule polymerisation, the more microtubule is polymerised the more pericentrin is shown up (as also evidenced by taxol and MBC treatments).

Oocytes have an enormous pool of available α/β tubulin that is accessible for assembly in response to taxol (3). Moreover, we have evidenced that taxol readily recruits a substantial pool of pericentrin that is assembled into agregates not unlike those typically seen at meiotic spindle poles. Our findings have also shown that; taxol causes hyperpolimerisation of the tubulin, like other scientists mentioned before (9). After taxol exposure, pericentrin incorporation into both spindle poles and cytoplasmic centrosomes was increased. Contrast to this, MBC treatment resulted in disapperance of cytoplasmic centrosomes and decrease in microtubule formation (8).

Interesting enough, pericentrin localisation displays a asymmetric manner at the two spindle poles during M-I and M-II. The fact that multiple centrosomes exist in mouse oocytes, and that they are dynamically regulated with respect to location and cell cycle state, implies that as a whole, the oocyte centrosome complex serves to sort and coordinate the multiple activities of nuclear and cytoplasmic maturation.

Since the total MT nucleating activity of a cell may be influenced by MTOC number or availability of γ-tubulin /pericentrin stores, any spatial and temporal constrait on MT nucleation would requare strict sorting or sequestration of rate-limiting factors for MT assembly (10).

The displacement of pericentrin to lateral sides at anaphase may ensure the exclusion of the pericentrin from the polar body thus retained in the oocyte. As to possible consequences of varying cortical MT displays during meiosis, it is interesting to note that nucleation coincides with anaphase onset at a time when the asymmetry of cytokinesis is established. We propose that cortical centrosomes anchor organelles and the oocyte cortex during the asymmetric cleavage that results in polar body formation. The fact that these structures are absent in oocytes of other species suggest that different mechanisms exist to retain 'cytoplasmic components' or these structures are labile to available means for their preservation and detection. These data suggest that oocyte centrosomes may undergo changes in their MT nucleation capacity during meiotic cell cycle progression.

Disappearance of pericentrin in polar body (seen as a cloud) suggests that pericentrin assembly is regulated by cell division machinery as in oocyte. At present, little is known about how microtubule nucleating activity at the centrosome is controlled. Microtubule nucleation could be regulated by one ore more mechanisms including. The total microtubule nucleating activity may be affected by the number of MTOCs in the cell (10).

Although there is much information on constituent proteins of the centrosome and their roles in the regulation of duplication and of microtubule assembly, the above points indicate that there are many fascinating aspects to centrosome behaviour.

Acknowledgments

The authors thank to Drs. S. Doxsey, and D. Albertini for providing the pericentrin 4b antibody.

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ANTIBIOTIC SUSCEPTIBILITY OF STREPTOCOCCUS PYOGENES STRAINS ISOLATED FROM THROAT CULTURES OF CHILDREN WITH TONSILLOPHARYNGITIS

Ergin Çiftçi* ✣ Ülker Doğru* ✣ Haluk Güriz* ✣ Ahmet Derya Aysev* ✣ Erdal İnce*

SUMMARY

Streptococcus pyogenes is the most important causative agent of tonsillopharyngitis. Although penicillin is drug of choice, and macrolide antibiotics are recommended drugs in patients who have penicillin allergy, various antibiotics other than penicillin and macrolide antibiotics are also used in the treatment of streptococcal tonsillopharyngitis. In addition, resistance to macrolide antibiotics is an important problem in some regions of the world. For these reasons, we designed a study to determine the antibiotic susceptibility of S. pyogenes strains isolated from children with tonsillopharyngitis. Two hundred and sixty three S. pyogenes strains were examined for penicillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, erythromycin, clarithromycin and azithromycin, clindamycin, ofloxacin, and vancomycin susceptibility. Tolerance against penicillin was also investigated. All S. pyogenes strains were determined to be susceptible to penicillin, ampicillin, cefazolin, cefuroxime, ceftriaxone, ofloxacin, and vancomycin. Resistance to erythromycin, clarithromycin, azithromycin, and clindamycin were detected as 3.8%, 4.2%, 4.2%, and 3.0%, respectively. Penicillin tolerance wasn't determined. These data indicate that antibiotic resistance of S. pyogenes strains is not a clinically significant problem in Turkey.

Key Words: *Streptococcus Pyogenes, Tonsillopharyngitis, Antibiotic Susceptibility.*

ÖZET

Tonsillofarenjitli Çocukların Boğaz Kültürlerinden İzole Edilen Streptococcus Pyogenes Suşlarının Antibiyotik Duyarlılığı

Streptococcus pyogenes tonsillofarenjitin en önemli etkenidir. Tedavide birinci seçenek penisilin ve penisilin allerjisi olanlarda makrolid antibiyotikler önerilen ilaçlar olmasına karşın streptokoksik tonsillofarenjit tedavisinde penisilin ve makrolid antibiyotikler dışında antibiyotikler de kullanılmaktadır. Ayrıca dünyanın bazı bölgelerinde makrolid antibiyotiklere direnç önemli bir sorundur. Bu nedenle tonsillofarenjitli çocukların boğaz kültürlerinden izole edilen S. pyogenes suşlarında antibiyotik duyarlılığını saptamayı amaçlayan bir araştırma planladık. Toplam 263 S. pyogenes suşu penisilin, ampisilin, sefazolin, sefuroksim, seftriakson, eritromisin, klaritromisin, azitromisin, klindamisin, ofloksasin ve vankomisin duyarlılığı açısından araştırıldı. Penisiline karşı tolerans da araştırıldı. Bütün S. pyogenes suşları penisilin, ampisilin, sefazolin, sefuroksim, seftriakson, ofloksasin ve vankomisine karşı duyarlı bulundu. Eritromisin, klaritromisin, azitromisin, ve klindamisine karşı sırasıyla %3.8, %4.2, %4.2 ve %3.0 oranında direnç saptandı. Penisilin toleransı saptanmadı. Bu bulgular S. pyogenes suşlarında antibiyotik direncinin Türkiye'de klinik olarak önemli bir sorun olmadığını göstermektedir.

Anahtar Kelimeler: *Streptococcus Pyogenes, Tonsillofarenjit, Antibiyotik Duyarlılığı.*

Tonsillopharyngitis is one of the most common infections encountered in children. Most bacterial infections are caused by *Streptococcus pyogenes* (1). In addition, resurgence of severe forms of disease caused by *S. pyogenes* has been detected in various parts of the world (2, 3). Although all *S. pyogenes* strains remain exquisitely sensitive to penicillin, erythromycin has been the drug of choice for individuals who cannot take penicillin. However,

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Received: *March 12, 2003* Accepted: *May 23, 2003*

there is a concern that a significant incidence of erythromycin resistance of *S. pyogenes* has been reported from the various regions of the world (4-10). Because the nonsuppurative sequels of *S. pyogenes* infections are still an important problem in Turkey and invasive infections due to *S. pyogenes* have increased recently, the treatment of infections due to *S. pyogenes* is very important in our country (11). Because of these observations, it is important to determine the current status of antibiotic susceptibility of *S. pyogenes* strains.

Methods

Children with tonsillopharyngitis in Ankara University Faculty of Medicine, Department of Pediatrics between December 2000 and March 2001 were enrolled in the study. All children were examined by a pediatrician. Tonsillopharyngitis diagnosis was established based on symptoms such as fever, sore throat, headache and abdominal pain, and signs such as pharyngeal and tonsillar hyperemia, exudate and painful cervical lymphadenopathy.

Throat swabs were obtained from the children, and immediately cultured in Mueller-Hinton blood agar. After 24 hour incubation at 35ºC, colonies surrounded by beta hemolysis were selected for grouping and antimicrobial susceptibility procedures. Strains were grouped by Streptococcal Grouping Kit (Oxoid, Diagnostic Reagents, Hampshire, UK). Group A beta hemolytic streptococci were analysed with respect to ampicillin, cefazolin, cefuroxime, ceftriaxone, erythromycin, clarithromycin, azithromycin, clindamycin, ofloxacin, and vancomycin susceptibilities using the agar dilution method. Penicillin G susceptibility was determined by broth dilution method. The minimal inhibitory concentration (MIC) limits for selected were determined according to the values determined by National Committee for Clinical Laboratory Standards (12). For cefazolin and cefuroxime for which there are no established NCCLS break points for *Streptococcus pyogenes*, NCCLS break points established for *Streptococcus pneumoniae* were used (12). Resistance limits determined as: penicillin G ≥ 4.0 µg/ml, ampicillin ≥ 8.0 µg/ml, cefazolin ≥ 2.0 µg/ml, cefuroxime ≥ 2.0 µg/ml, ceftriaxone ≥ 2.0 µg/ml, erythromycin MIC≥1.0 µg/ml, clarithromycin MIC≥1.0 µg/ml, azithromycin MIC≥2.0 µg/ml, clindamycin ≥1.0 µg/ml, ofloxacin ≥8.0 µg/ml, and vancomycin ≥2.0 µg/ml. Minimal bactericidal concentrations (MBC) for penicillin G were also determined (13). Penicillin tolerance was defined as an MBC-MIC ratio of greater than or equal to 32 (13).

Results

During the study period, 3127 children were diagnosed as tonsillopharyngitis. *S. pyogenes* were isolated from 345 throat swabs (11.0%). Because of contamination or missing of isolated strains, 263 *S. pyogenes* strains were found eligible.

Penicillin G susceptibility. All *S. pyogenes* strains were found to be susceptible to penicillin G. MIC values of *S. pyogenes* strains for penicillin G were determined as 0.0004-0.03 µg/ml (Table 1). Tolerance to the penicillin G was not determined in any of the isolates (Table 2, and Figure 1).

Macrolide resistance in *S. pyogenes* strains. Out of 263 *S. pyogenes* strains, 10 (3.8%) were resistant to erythromycin, 11 (4.2%) were resistant to both clarithromycin and azithromycin (Table I).

Susceptibility to other antibiotics. All *S. pyogenes* strains were found to be susceptible to ampicillin, cefazolin, cefuroxime, ceftriaxone, ofloxacin and vancomycin. Eight of the 263 *S. pyogenes* strains (3%) were resistant to clindamycin (Table 1).

Discussion

Antimicrobial resistance is an important problem in the management of patients with infectious diseases. Interestingly, *Streptococcus pyogenes* remains susceptible to penicillin during the past 70 or 80 years. The reason for this unique lack of development of resistance to penicillin is unknown (14). On the other hand, numerous reports have demonstrated a significant prevalence of erythromycin resistant *S. pyogenes*

Table 1: Resistance to eleven antibiotics, MIC_{90} values, and MIC ranges of 263 S. pyogenes strains.

Antibiotic	Resistant strains (n/%)	MIC_{90} (µg/ml)	MIC ranges (µg/ml)
Penicillin G	0/0	0.0075	0.0004-0.03
Ampicillin	0/0	≤ 0.125	≤ 0.125-0.25
Cefazolin	0/0	≤ 0.125	≤ 0.125-1.00
Cefuroxime	0/0	≤ 0.125	≤ 0.125-0.50
Ceftriaxone	0/0	≤ 0.125	≤ 0.125-≤ 0.25
Ofloxacin	0/0	1.0	≤ 0.50-1.0
Vancomycin	0/0	≤ 0.25	≤ 0.25-0.50
Clindamycin	8/3.0	0.25	≤ 0.25->2.0
Erythromycin	10/3.8	≤ 0.125	≤ 0.125-2.0
Clarithromycin	11/4.2	0.25	≤ 0.125-2.0
Azithromycin	11/4.2	0.25	≤ 0.125->2.0

Table 2: Penicillin G MBC/MIC ratios of S. pyogenes strains.

MBC/MIC	Number of strains
1	246
2	15
4	2
8	0
16	0
32	0
Total	263

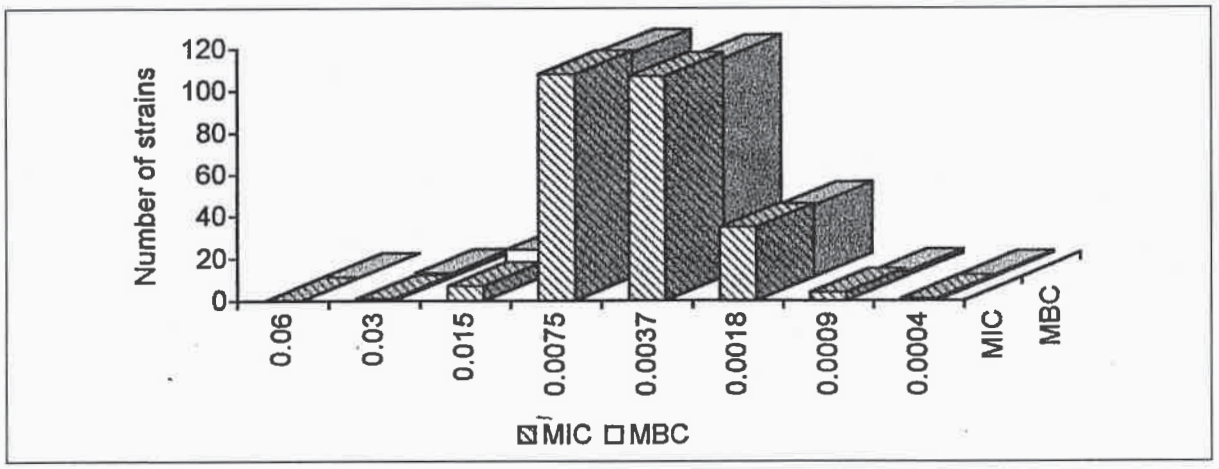

Figure 1: Penicillin G MIC and MBC values of S. pyogenes strains.

around the world during the past three decades (4-10). This resistance has been temporally related to increased or excessive use of macrolide antibiotics. Because of this relation, it is important to determine the geographic prevalence of resistant *S. pyogenes* to facilitate clinical care and to address public health concerns.

Our study shows that penicillin is active for *S. pyogenes* in low MIC values. This finding is

concordant with other studies from around the world (15-17). We also could not determine any *S. pyogenes* strain tolerant to penicillin G. Penicillin G MIC and MBC values of *S. pyogenes* were similar in our study. Penicillin failure in streptococcal tonsillopharyngitis reported as 10-25% (18, 19). Some authors blamed penicillin tolerance in patients with penicillin failure (20, 21). Although we could not determine clinical response of our patients, our results do not support penicillin tolerance theory for penicillin failure.

Like various parts of the world, invasive infections due to *S. pyogenes* have increased recently in Turkey (unpublished data). Causative agents sometimes cannot be determined, and various antibiotics are chosen in these patients. Thus, it is important to know the current status of antibiotic susceptibility in *S. pyogenes* strains. Our study shows that many antibiotics are active for *S. pyogenes* strains. Although these antibiotics are not first choice, they can be used in invasive streptococcal infections.

Resistance to erythromycin, clarithromycin, azithromycin, and clindamycin were detected as 3.8%, 4.2%, 4.2%, and 3.0%, respectively in this study. During the past three decades, numerous reports have demonstrated a significant prevalence of erythromycin resistant *S. pyogenes* around the world (4-10). Furthermore, several reports have demonstrated that the increase in the incidence of erythromycin resistant *S. pyogenes* strains is related to increased macrolide consumption in the community (22-26). Macrolide antibiotics, especially new ones such as clarithromycin and azithromycin, are widely selected for the treatment of upper respiratory tract infections such as sore throat in our country. In a recent study from Ankara, erythromycin resistant *S. pyogenes* strains were increased from 3.29% to 15.74% in a 7-year-period[26]. The authors emphasized that a substantial increase in erythromycin resistance was associated with the increase in the consumption of macrolide antibiotics.

Our results demonstrate that antibiotic resistance of *S. pyogenes* strains is not a clinically significant problem in Turkey. However, the susceptibility pattern of *S. pyogenes* strains must be monitored.

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MINIMUM EFFECTIVE DOSE OF DEXAMETHASONE FOR PREVENTING NAUSEA AND VOMITING AFTER ADENOTONSILLECTOMY

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SUMMARY

Background and objective: The minimum effective dose of dexamethasone in conjunction with 50 μg kg^{-1} ondansetron was evaluated in the treatment of vomiting after elective tonsillectomy or adenotonsillectomy.

Methods: 102 healthy children aged between 2-12 were participated in this prospective, randomized, double-blind study. A single intravenous (IV) dose of dexamethasone (50, 100, 150 μg kg^{-1}, maximum dose 8 mg) with ondansetron (50 μg kg^{-1}) was administered just before the end of surgery. Equal amounts of normal saline was given to the control group. General anesthesia was induced and maintained by inhalation of N_2O/O_2 and sevoflurane. All other preoperative and postoperative medications (including a supplementary dose of antiemetics if necessary), anesthesia and surgical techniques were standardised.

Results: No significant differences were observed between groups in postoperative vomiting on the day of surgery and the next day, or in the need for postoperative pain medication and supplementary doses of antiemetics ($p>0.05$).

Conclusions: These results indicate that surgical tecnique and anesthetic management used in this study could be the cause of lower incidence of nausea and vomiting. Assessment of nausea and vomiting in a prospective study with larger groups of patients may reflect different results.

Key Words: *Adenotonsillectomy, Dexamethasone, Ondansetron, Postoperative Vomiting*

ÖZET

Adenotonsillektomi Sonrası Bulantı ve Kusmanın Önlenmesinde Deksametazonun Minimum Efektif Dozu

Amaç: Elektif tonsillektomi yada adenotonsillektomi vakaları sonrası bulantı ve kusmanın önlenmesinde 50 μg kg^{-1} ondansetronla birlikte kullanılan deksametazonun minimum efektif dozunu belirlemektir.

Metod: Prospektif, randomize ve çift kör yapılan bu çalışmaya yaşları 2-12 arasında değişen 102 çocuk dahil edildi. Cerrahinin bitiminden hemen önce tek doz intravenöz ondansetron (50 μg kg^{-1}) ve deksametazon (50, 100, 150 μg kg^{-1}, maximum dose 8 mg) uygulandı. Kontrol grubuna da eşit miktarlarda normal salin verildi. Genel anestezi indüksiyonu ve idamesi N_2O/O_2 ve sevofluran ile sağlandı. Diğer bütün preoperatif ve postoperatif ilaçlar (Gerektiğinde uygulanan ek doz antiemetikler), anestezi ve cerrahi teknikler standardize edildi.

Sonuçlar: Cerrahi güne ve ertesi güne ait; postoperatif kusma, ağrı kesici ihtiyacı ve ek doz antiemetik ihtiyacı parametreleri açısından gruplar arasında anlamlı fark yoktu ($p>0.05$).

Bu sonuçlar ışığında, bulantı ve kusma insidansının düşük bulunma sebebi bizim uyguladığımız cerrahi teknik ve anestezik yöntem olabilir ancak daha geniş hasta gruplarıyla yapılacak prospektif çalışmalarda farklı sonuçlara varılabilir.

Anahtar Kelimeler: *Adenotonsillektomi, Deksametazon, Ondansetron, Postoperatif Kusma.*

Ondansetron and dexamethasone have been observed to decrease the incidence of vomiting in children after general anesthesia, and low dose ondansetron plus dexamethasone is a more effective prophylactic antiemetic combination than high dose ondansetron (150 μg kg^{-1}) in children, and it is known that each episode of in hospital vomiting prolongs discharge by 13 ± 2 min (1,2). Vomiting is a common unpleasant sequalea to surgery and anesthesia may result in

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Received: *May 20, 2003* Accepted: *May 28, 2003*

dehydration, important electrolyte disturbances, delayed discharge from hospital and unanticipated admission to hospital (2,3). As much as 40-73 % of children vomit after tonsillectomy, and anesthesiologists are searching for cost-effective techniques to minimize this problem (4).

Patients and Methods

With the Hospital Ethics Committee's approval and parental consent, 102 healthy children aged between 2-12 undergoing elective tonsillectomy or adenotonsillectomy were enrolled in this prospective, randomized and double-blind study. Patients were excluded from the study if they had an allergy to any of the drugs to be used or if they had a symptomatic medical illness or motion sickness, or required reversal before extubation.

As premedication, 0,5 mg kg^{-1} midazolam (maximum dose 15 mg) was given orally 20-30 min before surgery. When the patients arrived in the operating room, baseline hemodynamic data were recorded after routine monitorization. Anesthesia was induced with sevoflurane and N_2O/O_2. After induction, mivacurium (0,25 mg kg^{-1}) was administered and 20 µg kg^{-1} atropin was given to all patients. Endotracheal tube was inserted while patients were under anesthesia of appropriate depth. Anesthesia was maintained with 70 % N_2O and 2 % sevoflurane. The intraoperative intravenous fluids used was Ringer's lactate at standard rates, which were defined as one half of the deficit during the first hour plus maintainance fluids.

A combination of ondansetron and dexamethasone was administered intravenously in a double-blind manner just before the end of surgery. There were four groups.

Group I : 50 µg kg^{-1} (max 8 mg) ondansetron + 150 mg kg^{-1} (max 8 mg) dexamethasone

Group II : 50 µg kg^{-1} (max 8 mg) ondansetron + 100 µg kg^{-1} (max 8 mg) dexamethasone

Group III : 50 µg kg^{-1} (max 8 mg) ondansetron + 50 µg kg^{-1} (max 8 mg) dexamethasone

Group IV : Normal saline was given to this group.

Patients were allocated randomly to receive one of the 4 treatments. A randomization list was prepared by a random number function in a computer spread - sheet and identical syringes containing each drug and saline for control group were prepared by personnel not involved in the study.

For the purpose of this study, vomiting was defined as "the forceful expulsion of liquid or solid gastric contents". Retching and nausea were not considered vomiting. Postoperative vomiting was treated with 1 mg kg^{-1} dimenhydrinate given intravenously, if the patient had vomited twice or more. The incidence of vomiting in the hospital was recorded by the nursing staff. Postoperative pain was treated with 15 mg kg^{-1} metamizol.

Patients were discharged according to standardized criteria which included a minimum 4-hour stay in the day care surgical unit (DCSU). Standardized criteria included lack of repiratory distress, stable vital findings for 30-60 minutes, tolerance of clear oral fluids, capability of mobilisation and oral intake for pain management. Patients were observed for 24 hours after the surgery. 24-hour observation was divided into 4 different periods as follows; 0-30 minutes in postanesthesia care unit (PACU), 30 minutes-4 hours in day care surgical unit (DCSU), in postoperative 4-12 hours (surgery day) and in postoperative 12-24 hours (first day). Parents were interviewed on the day after surgery by the research assistant. The parents reported all episodes of vomiting and any other surgical or anesthesia related problems.

Data were compared by one-way analysis of variance, chi-square analysis, Fisher's exact tests or kappa test whichever was appropriate. Data are presented as mean ± SD.

Results

We enrolled 102 patients in the study. Group I (n = 26), group II (n = 27), group III (n = 24) and group IV (n = 25) were similar with respect to age, weight, and duration of anesthesia. Duration of surgery was significantly low in group I ($p<0.05$) (Table I). Vomiting was assessed at four different times, in PACU, in the DCSU, on surgery day and on postoperative first day as previously described. With respect to four different times and four different groups, the incidence of vomiting was similar ($p>0.05$) (Table 2). In group I, the incidence of vomiting in PACU was similiar with in DCSU ($p>0.05$), and on surgery day ($p>0.05$), also in DCSU and on surgery day ($p>0.05$). In group II, the incidence of vomiting in PACU was similar with in DCSU ($p>0.05$), and also between that in PACU and on surgery day ($p>0.05$) and in DCSU and on surgery day ($p>0.05$). In group III, the incidence of vomiting in PACU was similar with in DCSU ($p>0.05$), and also between that in PACU and on surgery day ($p>0.05$), also in DCSU and on surgery day ($p>0.05$). In group IV, the incidence of vomiting in PACU was similar with in DCSU ($p>0.05$), and also between that in PACU and on surgery day ($p>0.05$) and in DCSU and on surgery day ($p>0.05$) (Table 2).

In hospital vomiting, there was no requirement for treatment with dimenhydrinate. Non of the patients required reversal at the end of the surgery. Discharge rates from the hospital were similar in all groups.

Discussion

Morbidities like pain, inadequate oral intake, dehydration, fever, bleeding and vomiting can follow tonsillectomies in children. Postoperative nausea and vomiting is a common problem after general anesthesia (5). It has an incidence of 40 - 73 % following tonsillectomies (4). It may lead to some wound site complications and aspiration pneumonia syndromes (5-7). On the other hand it elongates stays in postanesthesia care units, it may cause delayed discharges from hospital and even unanticipated hospitalisations.

Table 1. Demographic data,*$p<0.05$

	Group I (n = 26)	Group II (n = 27)	Group III (n = 24)	Group IV (n = 25)
Age (yr)	5.32 ± 2.16	6.12 ± 2.23	5.89 ± 1.78	5.76 ± 1.96
Weight (kg)	21.07 ± 5.35	18.00 ± 5.28	20.75 ± 6.68	19.63 ± 6.04
Sex M/F	18/8	15/12	17/7	18/7
Operation time (min)	44.80 ± 13.30*	50.37 ± 8.65	52.50 ± 12.93	50.19 ± 9.24
Anesthesia time (min)	61.61 ± 16.47	63.81 ± 13.59	66.25 ± 16.50	62.94 ± 15.72

Table 2. Incidence of vomiting in groups.

	Group I (n = 26)	Group II (n = 27)	Group III (n = 24)	Group IV (n = 25)
PACU	3	3	3	3
DCSU	1	5	2	2
Surgery Day	2	2	2	2
Postoperative 1st Day	1	0	0	2

Administration of perioperative opioids is the most common cause of postoperative nausea and vomiting. On the other hand opioids are most commonly used drugs for pain control in children undergoing surgery. An alternative of opioids may be an antiinflamatory drug named ketorolac which is nearly as potent as morphin but does not cause respiratory depression (8). But use of ketorolac is limited particularly in children undergoing tonsillectomy because of its effects on platelet aggregation and adhesion (9). Among recently used antiemetics, 5-HT_3 receptor antagonists like ondansetron and granisetron have an increasing popularity. In the previous literature comparing ondansetron and placebo in tonsillectomy cases, incidence of postoperative nausea and vomiting was reported to be 32 % with ondansetron, while it was 61 % with placebo (5). In other series ondansetron was reported to be superior to placebo, too. In these series incidence of more than 2 episodes of postoperative nausea and vomiting was reported to be 7 % with ondansetron, while it was 57 % with placebo (10). Although 5-HT_3 receptor antagonists are very effective antiemetics, their respectively high costs limits their widespread usage. Other antiemetics like anticholinergics, dopamin receptor antagonists and antihistaminics have significant side effects. These reasons force anesthesiologists to investigate effective antiemetics with fewer side effects and low costs.

Dexamethasone is a corticosteroid with effective antiinflammatory and prolonged antiemetic efficacy. Dexamethasone has an elimination half life of about 3 hours and a duration of action of 48 hours. Among patients receiving chemotherapy, dexamethasone is superior in suppressing delayed nausea when compared with either ondansetron or granisetron (11,12). Perioperative use of, dexamethasone has been shown to decrease the incidence of postoperative vomiting (2,8,13,14). It is a safe and effective antiemetic in patients receiving cancer chemotherapy (15-17). IV administration of dexamethasone before electrocautery tonsilloadenectomy reduces the incidence of postoperative nausea and vomiting while increasing the quality of oral intake (18). Though it reduces the incidence of postoperative vomiting and surgery related side effects, such as delayed wound healing and increased incidence of wound infection, cautious use of dexamethasone in surgical patients is recommended (2,8,19-21). Dexamethasone doses used for antiemesis varies between 8-10 mg and 1mg kg^{-1} (22,23). To achieve the best antiemesis with the fewest side effects, Liu et al compared dexamethasone doses of 10 mg, 5 mg, 2,5 mg, and 1,25 mg with placebo in patients undergoing general anesthesia for major gynecological surgery, and they found 2,5 mg to be the minimum effective dose without discernible side effects (6). In another study including thyroidectomy cases, it is reported that a dose of 2,5 mg is partially effective and a minimum effective dose is 5 mg (24). Cost-effectivity is increasingly a focus in health care, and neither which combination of dexamethasone and ondansetron is most cost-effective, nor the best antiemetic dose of dexamethasone to be used in children is well established. A dexamethasone dose of about 150 mg kg^{-1} up to 8 mg is reported to be effective (1).

Splinter et al have found that 50 mg kg^{-1} ondansetron plus 150 mg kg^{-1} dexamethasone more effectively decreased the incidence and severity of vomiting in children after strabismus surgery than did 150 mg kg^{-1} ondansetron (1). Which combination of dexamethasone and ondansetron has the best cost-effectivity after adenotonsillectomy has not been established yet. We hypothesized that a lower dose of dexamethasone would be as effective as a larger dose in combination with 50 mg kg^{-1} ondansetron.

In this study, we compared 3 different doses of dexamethasone in children plus 50 mg kg^{-1} ondansetron and the control group. All four groups were not different in respect to postoperative nausea and vomiting.

In our study the incidence of vomiting was not as high as it had been reported in previous studies. Additionally there was no significant

difference between the control group and the antiemetic treatment groups. These results indicate that surgical tecnique and anesthetic management used in this study could be the cause of lower incidence of nausea and vomiting. Assessment of nausea and vomiting in a prospective study with larger groups of patients may reflect different results.

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COMPARATIVE ARRHYTMOGENIC EFFECTS OF LIGNOCAINE AND BUPIVACAINE

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SUMMARY

Background and objective: In this study we aimed to evaluate whether lignocaine and bupivacaine caused arrhythmias in ASA I status patients, during spinal anesthesia, by using Holter monitorization and QT dispersion parameters. Methods: Spinal anesthesia was performed at the L3-L4 level. Patients in Group I (n=16) and Group II (n=17) were given 2%, 3ml lignocaine and, 0.5%, 3ml plain bupivacaine respectively. Starting 45 minutes before the operation, 24h Holter ECGs were recorded. Preoperative and postoperative 12 lead ECGs were recorded for QT dispersion measurements which were obtained by a blinded cardiologist. Results: In our study there were no ST segment depressions as an indication of ischemia in Holter recordings and there were no significant differences in both groups (p>0.05). The mean preoperative QT interval dispersion was 52.87±14.24 ms and 44.7±10.67 ms in lignocaine and bupivacaine groups respectively. Postoperative QT interval dispersion was 43.75±14.54 ms in lignocaine and 47.05±8.48 ms in bupivacaine group. There were no significant differences between two groups and also in each group with regard to preoperative and postoperative QT dispersion (p>0.05). Conclusions: More prospective studies with larger groups of patients are needed to have a conclusion that bupivacaine can be more arrhythmogenic than lignocaine in these clinical doses that we use routinly.

Key Words: *Bupivacaine, Lignocaine QT Dispersion.*

ÖZET

Lidokain ve Bupivakain'in Aritmojenik Etkilerinin Karşılaştırılması

Amaç: *ASA-I grubu hastalarda, spinal anestezide kullanılan lidokain ve bupivakainin aritmiye neden olup olmadıklarını Holter Monitörizasyonu ve QT dispersiyonu parametrelerini kullanarak araştırmak.*

Metod: *Spinal anestezi L3-L4 aralığından yapıldı ve sırasıyla grup I'deki (n=16) hastalara 3mL %2'lik lidokain ve grup II'deki (n=17) hastalara %0.5'lik 3mL düz bupivakain verildi. Ameliyattan 45 dakika önce başlamak şartıyla, 24 saatlik Holter EKG'leri kaydedildi. Preoperatif ve postoperatif EKG'ler QT dispersiyonu ölçümleri için kaydedildi ve hastalar kör bir kardiyolog tarafından değerlendirildi.*

Sonuçlar: *Çalışmamızda Holter kayıtları incelendiğinde iskemi göstergesi sayılabilecek bir ST segment depresyonuna rastlanmazken, iki grup birbirinden farksızdı (p>0.05). Lidokain grubundaki preoperative QT interval dispersiyonu 52.87±14.24 ms iken bupivakain grubunda 44.7±10.67 ms'idi. Postoperative QT interval dispersiyonu lidokain grubunda 43.75±14.54 ms, bupivakain grubunda 47.05±8.48 ms'idi. Preoperatif ve postoperatif QT dispersiyonu karşılaştırıldığında gruplar arasında ve her bir grupta istatistiksel olarak anlamlı fark yoktu (p>0.05).*

Rutin olarak kullandığımız bu klinik dozlarda bupivakainin lidokainden daha aritmojenik olduğunu söyleyebilmek için daha geniş hasta grupları içeren prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Bupivakain, Lidokain, QT Dispersiyonu*

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Received: *May 20, 2003* Accepted: *May 28, 2003*

All local anesthetics have a direct depressant effect on the cardiovascular system in a dose related fashion (1).

Bupivacaine, which is highly lipid soluble, has a fast in, slow out kinetic pattern at the sodium channel, resulting in accumulation of bupivacaine in the conduction system that increases as the heart rate increases (2). When the primary conducting system is blocked, there is increased activity in reentrant pathways that predisposes the heart to ventricular arrhythmias (3). QT dispersion is of much more value in patients with less overt cardiac disease and more normal ECGs. Patients which were enrolled in our study had normal ECGs.

A further population based study involving over 3000 adult and children suggested that QT dispersion <= 50 ms indicated normality, age or gender having no impact on this population (4). In this study we evaluated whether lignocaine and bupivacaine caused arrhythmias in ASA I status patients, during spinal anesthesia, by using Holter monitorization and QT dispersion parameters after the standardization of other parameters.

Methods

Upon the approval of ethical committee, 33 patients (ASA I status), between the ages of 20 to 50 were included in this double blinded and randomized study. Before the lower extremity surgery they were informed about the regional anesthesia tecnique, and informed consents were obtained. Spinal anesthesia was performed via lumbar puncture at the L3-L4 level. Patients in Group I (n=16) and Group II (n=17) were given, 2%, 3ml lignocaine and, 0.5%, 3ml plain bupivacaine respectively with a 25 gauge needle, in sitting position.

Before the spinal anesthesia was performed, 16G IV catheter was inserted and 1000mL Lactated Ringer solution was given to the patients. Until the block levels were assessed patients were in supine position and continuous monitoring for electrocardiogram, pulse oximetry, and non invasive blood pressure were available throughout the surgery. Patients were oxygenated during the surgery (3 L min^{-1}).

Starting 45 minutes before the operation, 24h Holter ECGs were recorded. Preoperative and postoperative 12 lead ECGs were recorded for QT dispersion measurements which were obtained by a blinded cardiologist.

Patients were evaluated preoperatively for arrhythmias, rheumatic valvular heart disease, rheumatoid arthritis, coronary heart disease and fainting to predict any hidden cardiac pathology. All patients had preoperative chest x-ray, 12 lead ECGs, and complete blood count.

Following parameters were monitored during the preoperative, peroperative and postoperative periods:

After the regional anesthesia was performed, sensory and motor block segments and recovery time of the neural blockade (5, 10, 15, 30 minutes after the spinal anesthesia was performed) were recorded. Blood samples were collected for evaluation of the arterial blood gases and electrolyte levels (including Mg), in preoperative period, 15 minutes after the commencement of surgery and just after the surgery. Arterial blood gases were evaluated as the patients were sedated with midazolam and to exclude hidden hypoxia that can increase the local anesthetic toxicity. Pre and postoperative 12 lead ECGs were screened for QT dispersion and also the local anesthetic plasma levels were checked at the commencement of the surgical procedure.

Student's t test and Man-Whitney U test were used to compare the differences among the groups. Paired t test was used to compare the "before" and "after" values in each group. Chi-square test was used to compare the time dependent changes' increase ratios in both groups. To analyse the relationship between each group's variables Pearson χ^2 correlation analysis was used and Spearman Rank Correlation Analysis was used to detect the relationship between the difference portions.

Results

Thirty three patients were included in the study. As shown in Table 1, there were no

intergroup differences in regard to sex distribution, age, heart rate and type of surgery. During spinal anesthesia blood pressure and heart rate did not change more than 20 % of baseline values, and there was no need for ephedrine for any patient.

There were no significant intergroup diffrences in regard to preoperative (Before the spinal anesthesia was performed), peroperative and postoperative hemoglobin, hematocrit levels. All the electrolyte levels were in normal ranges.

All the arterial blood gase (ABG) levels were in normal ranges with regard to preoperative, peroperative and postoperative periods, in both groups.

Solid phase extraction method was used to determine the plasma lignocaine and bupivacaine concentrations, and the levels were determined as mg mL^{-1}. In this method plasma was stored at –4°C for later analysis. Plasma samples were extracted with "c" 18 solid phase extraction columns using lignocaine and bupivacaine as the internal standart for each group.

The columns were rinsed first with distilled water and then with methanol. 500 mg L^{-1} of plasma was added to the column under pressure and the column rinsed with 3mL distilled water and 1 mL methanol, at the end of these processes elutions of each plasma were obtained with the addition of 200 mg L^{-1} methanol to the columns for two times.

Elutions of lignocaine and bupivacaine were obtained with the same method for 0.3, 0.61, 0.91, 1.22, 1.464 mg mL^{-1} standart lignocaine and 0.5, 1, 1.5, 2, 2.5 mg mL^{-1} standart bupivacaine solutions.

These lignocaine and bupivacaine elutions were given to the Gas Chromotography/ Mass Spectrophotometry (GC-MS) device and the recoveries (Table 2) of each solution were obtained for three times and the mean values were used to obtain the linear calibration curves for lignocaine and bupivacaine groups.

Plasma elutions of each group were given to the GC-MS device and the concentrations were found on these calibration curves for each group in mg mL^{-1}. There were no significant differences between the plasma lignocaine and bupivacaine concentrations at the commencement of the surgery.

The time period between the spinal anesthesia and the commencement of the surgical procedure was 20.374 ± 99 min for lignocaine group and 19.64 ± 4.21 min for the bupivacaine group ($p>0.05$). The maximum dermatomal levels of spinal block was T6 and T5 in group I and group II respectively. Recovery time of sensorial block was 115.68 ± 43.56 min and 140.58 ± 53.41min in group I and group II respectively ($p>0.05$) and median range of motor blockade was 4 (According to the Bromage Scale) in both groups.

In our study there were no ST segment depressions as an indication of ischemia in Holter recordings. Holter recordings were examined

Table 1. The comparison of lignocaine and bupivacaine groups with regard to sex distribution, age, type of surgery, pre and postoperative heart rates. ᵞBimalleolar and tibia fractures. Data are Mean ± SD.

	Lignocaine	Bupivacaine
Age (years)	33.8 ± 8.06	29.5 ± 10.8
Bender	10 M / 6F	12 M / 5F
Type of surgery	11 arthroscopy 5 others^{ᵞ}	12 arthroscopy 5 others^{ᵞ}
Heart rate (preoperative) bpm	75.13 ± 10.03	79.53 ± 15.92
Heart rate (postoperative) bpm	82.62 ± 11.03	77.88 ± 12.43

Table 2. Lignocaine and bupivacaine elutions were given to the Gas Chromotograpy/Mass Spectrophotometry (GC/MS) device and the recoveries of each solution.

		Values obtained from the GC/MS in μg mL^{-1}	Recovery values %
Lignocaine solutions in μg mL^{-1}	0.3	0.24	80
	0.61	0.453	74.2
	0.91	0.701	77.03
	1.22	0.930	76.229
	1.464	1.214	82.92
Bupivacaine solutions in mg mL^{-1}.	0.5	0.43	86
	1	0.92	92
	1.5	1.31	87
	2	1.78	89
	2.5	2.075	83

according to the Lown Classification and there were no significant differences in both groups ($p>0.05$) (Figure 1). The mean preoperative QT interval dispersion was 52.87 ± 14.24 ms and 44.7 ± 10.67 ms in lignocaine and bupivacaine groups respectively. Postoperative QT interval dispersion was 43.75 ± 14.54 ms in lignocaine and 47.05 ± 8.48 ms in bupivacaine group. There were no significant differences between two groups and also in each group with regard to preoperative and postoperative QT dispersion ($p>0.05$). As shown in Figure 2., QT dispersion

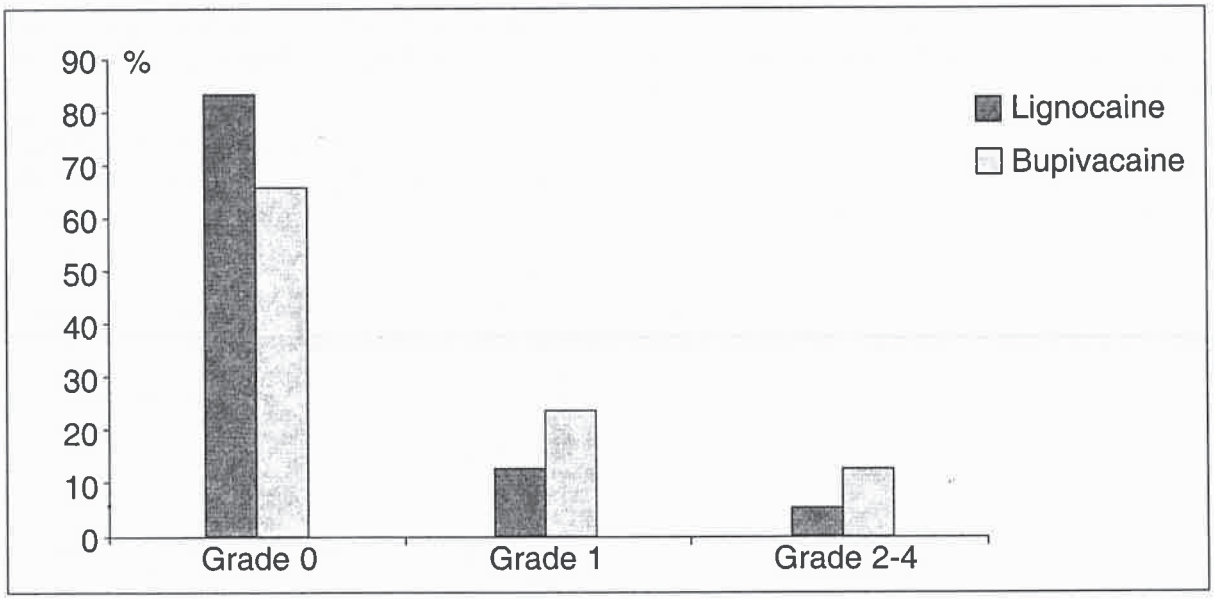

Figure 1. *Holter monitorization results of lignocaine and bupivacaine ($p>0.05$). According to the Lown Classification Grade 0: Premature ventricular conduction (PVC) 0/h Holter monitoring, Grade 1: PVCs 1/h Holter monitoring, Grade 2: Frequent PVCs > 10/h Holter monitoring, Grade 3: Multiform PVCs, Grade 4: Repeated PVCs.*

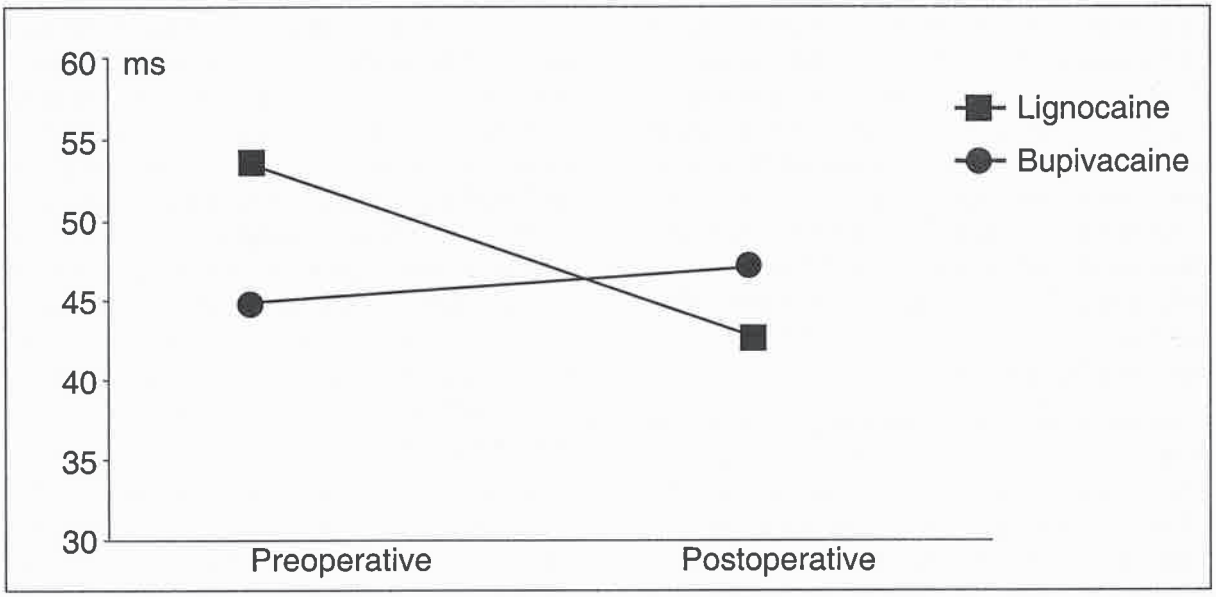

Figure 2. Preoperative QT dispersion values were 52.87 ± 14.24 ms and 44.7 ± 10.67 ms in lignocaine and bupivacaine groups respectively. Postoperative QT dispersion values were 43.75 ± 14.54 ms in lignocaine and 47.05 ± 8.48 ms in bupivacaine group. Data are in mean ± SD, p>0.05

in bupivacaine group tend to increase during the postoperative period, but this result is not significant.

With regard to preoperative (75.12 ± 10.02 bpm vs 79.52 ± 15.91 bpm) and postoperative heart rates (82.62 ± 11.03 bpm vs 77.88 ± 12.43 bpm), there were no significant differences between lignocaine and bupivacaine groups. There was no relationship between the plasma local anesthetic concentration, block level and also QT dispersion values.

Discussion

Bupivacaine and lignocaine may differ markedly in their effects on the heart when adminestered intravenously (5). Although the majority of toxic reactions occur as a result of high plasma levels of local anesthetic agent , a review of the literature demonstrates multiple case reports describing morbidity and mortality shortly after injection of even small doses of bupivacaine (6).

Several mechanisms are proposed to account for the malignant arrhythmias (re-entrant ventricular arrhythmias), conduction disturbance, and myocardial depression typical of this phenomenon. Bupivacaine inhibits sodium, calcium, and potassium ion channels. It is reported to interfere with beta adrenergic and lysophosphotidate signal transduction pathways and can activate the autonomic nervous system. At high concentrations bupivacaine also collapses the mitochondrial transmembrane potential and inhibits electron transport necessary for oxidative phosphorylation (7). Kasten (5) et al investigated the hemodynamic and electrophysiologic effects of bupivacaine and lignocaine and found that all two agents produced similar hemodynamic effects but effects on the ECG were different. Compared with the control period, lignocaine produced slight increases and bupivacaine much greater increase in the area under the curve of the T wave, lengthening of the QTU interval, and enhancement of the "slow wave" or U wave following the T wave. The result of this study suggests that bupivacaine can result in the "Torsades de Pointes like syndrome" (Polymorphic, undulating ventricular tachycardia). The effective refractory period (ERP) temporal dispersion which is evaluated in this study is related to ventricular arrhythmias (8).

Comparison of ERP temporal dispersion of bupivacaine and lignocaine may allow for greater understanding of local anesthetic cardiovascular toxicity. As a result of this study it was seen that bupivacaine increased ERP temporal dispersion more than lignocaine. In contrast, only lignocaine group sustained mild alterations in the relevant parameters and did lead to ventricular tachycardia. The results support the concept that lignocaine is safer to use in clinically equivalent doses than bupivacaine..

In our study Holter monitorization results were evaluated as a significant criteria to establish the arrhythmias and the value of QT interval dispersion was considered to be important to predicting the probable arrhythmias. There are genuine methodological difficulties in measuring QT intervals in ECGs which are frankly abnormal. For this reason, QT dispersion is of less value to cardiologists, whose patients really always have very abnormal ECGs (4).

The side effects of local anesthetic, indicating toxicity, include cardiac arrhythmias and grand mal seizures (9). Data from animals and humans indicate that bupivacaine induced convulsions are accompanied by hypoxia, hypercapnia and acidosis (10,11). The study of Rosen (12) et al. in hypoxic and acidotic sheep were given equivalent low and high intravenous doses of lignocaine and bupivacaine over ten seconds. The most common abnormality after bupivacaine administration was a wide QRS complex bradycardia regardless of dose. Although the mechanism of action is not known bupivacaine appears to be more cardiotoxic than lignocaine. This toxicity is enhanced by the presence of hypercarbia, acidosis, and hypoxia (13). The preoperative, peroperative and postoperative arterial blood gas values were evaluated in our study, and also the pulse oximeter was a standard monitorization for all groups. All arterial blood gas values and also the synchronous pulse oximeter values were in normal ranges.

Both atrial and ventricular arrhythmias have been associated with hypomagnesemia (14). In a review of arrhythmias associated with hypomagnesemia, Millane (15) et al. found that concurent hypokalemia was a consistent feature . The causes of potassium and magnesium depletion are similar. And there appears to be no evidence that isolated hypomagnesemia is proarrhythmic or that myocardial magnesium depletion precipitates arrhythmias but it may exacerbate potassium mediated arrhythmias by a complex interaction which modifies the action potential. In the treatment of arrhythmias related to hypomagnesemia and hypokalemia, it is recommended that both of them be administered at the same time.

Magnesium has been used successfully in the treatment of ventricular arrhytmias associated with long QT syndromes. Tzivoni (16) et al. reported the successful use of magnesium in patients with drug induced torsades de pointes. Despite normal serum potassium and magnesium concentrations, all patients responded to IV bolus of magnesium .

Parikka (17) et al. reported that magnesium decreases QT dispersion in acute myocardial infarction. The decreased arrhythmicity is related to enhancement of homogenicity in repolarization .

The importance of magnesium in atrial and ventricular arrhythmias is obvious. In this study we evaluated the preoperative , peroperative, and postoperative Mg levels in both groups. Magnesium levels were in normal ranges and it was concluded that magnesium did not effect the arrhythmia incidence in our study.

Hyperkalemia enhances the cardiotoxic effects of both lignocaine and bupivacaine, with this enhancement being more pronounced in the case of bupivacaine (18,19). Timour (20) et al. reported that the combinations of bupivacaine and hyponatremia, and bupivacaine and hyperkalemia tended to increase ERP more than did bupivacaine alone. The electrolyte levels were in normal ranges and we concluded that plasma concentrations of electrolytes did not alter the arrhythmogenic effects of these two local anesthetics.

In our study there were no ST segment

depressions as an indication of ischemia in Holter recordings and two groups were not different ($p>0.05$). There were no significant differences between two groups and also in each group with regard to preoperative and postoperative QT dispersion ($p>0.05$) and also preoperative and postoperative heart rates were not different between the groups.

More prospective studies with larger groups of patients are needed to have a conclusion that bupivacaine can be more arrhytmogenic than lignocaine in these clinical doses that we use routinly.

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MILIARY TUBERCULOSIS IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS WITH ABSCESS FORMATION IN THE UPPER EXTREMITIES

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SUMMARY

A 53-year-old man with arthritis and fever was admitted to hospital. He had been followed with systemic lupus erythematosus for the last seven years. He was on corticosteroid therapy. Laboratory work-up revealed tuberculous abscesses on both hands and the patient died of respiratory failure due to miliary tuberculosis on the fourth day of anti – tuberculous therapy. It should be kept in mind that tuberculosis is frequently encountered in the systemic lupus erythematosus patient population due to nature of the disease and the therapy given. It may be fatal unless treated aggressively.

Key Words: *Abscess, Systemic Lupus Erythematosus, Miliary Tuberculosis*

ÖZET

Sistemik Lupus Eritematozuslu Bir Hastada Her İki Elde Abse Oluşumu Sonrası Gelişen Miliyer Tüberküloz

Yedi yıldır sistemik lupus eritematozus tanısı ile takip edilmekte olan 53 yaşındaki erkek hasta artrit ve ateş şikayetleri ile servise kabul edildi. Kortikosteroid kullanmaktaydı. Yapılan tetkikler sonucunda her iki elde tüberküloza bağlı abse saptandı. Hasta antitüberküloz tedavinin dördüncü gününde solunum yetmezliği nedeni ile kaybedildi. Hastalığın seyri ve verilen tedaviler nedeni ile sistemik lupus eritematozuslu hastalarda tüberküloz ile sık karşılaşıldığı akılda tutulmaldır. Eğer uygun tedavi kısa sürede başlanmazsa ölümcül seyredebilir.

Anahtar Kelimeler: *Abse, Sistemik Lupus Eritematozus, Miliyer Tüberküloz*

Tuberculosis had been a long dreaded disease until development of antituberculosis drugs. The relief was not long lasting, since the number of immunocompromised patients infected with tuberculosis are increasing with the widespread use of immunosuppressants and increasing infection rate with acquired immunodeficiency syndrome AIDS (1). About one third of the world population is infected with tuberculosis at present, and about 90 million new cases are being reported every year. In Mexico, the incidence of tuberculosis in patients with systemic rheumatic diseases was %2.5 in 1994 (1). In Korea, in a recent study it was shown that tuberculosis incidence rate was 20/1000 patients - years of tuberculosis in the same patient group (2).

In Turkey, we know that tuberculosis is still an epidemic with an annual incidence of 39.4 cases per 100000 (as reported in 1993).

Patients with rheumatic diseases are more susceptible to infection with mycobacterium species because of the nature of the disease and

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Received: *Dec 06, 2001* Accepted: *May 20, 2002*

because of the immunosuppressive treatment regimens (1). Infection is a frequent problem in patients with systemic lupus erythematosus (SLE), especially in those hospitalized with complications of disease. Infections increase morbidity of disease and often are the cause of death. Most are due to gram positive or negative bacteria. However, there is increasing evidence that opportunistic infections contribute greatly to infectious mortality in SLE. However diagnosis of these infections is difficult and most are superimposed with SLE activation (3).

Here we present a male patient with SLE who developed miliary tuberculosis associated with severe abscess formation bilaterally in the forearms and hands and who died on the fourth day of anti – tuberculous treatment because of respiratory failure.

Case Report

A 53 - year - old farmer was admitted to our department with arthralgia and fever. He was diagnosed with SLE based on the ARA classification criteria of presence of arthritis, proteinuria, malar rash and anti-ds-DNA and ANA positivity, seven years ago. He was started on steroids and nonsteroidal anti-inflamatory drugs. He was being followed by the outpatient department on an irregular basis. He was incompliant to the follow-up plans for the last few years and was taking 10 mg of glucocorticoid daily.

His recent complaints had started about seven months previously, with cellulitis and abscess formation on the right forearm. The abscess was drained and a course of antibiotics was given. Six months later he was rehospitalized because of abscess formation on the left forearm. Abscess was drained and cultures of the material revealed Staph. aureus. He was treated with amoxicillin 1gr and clavulonic acid (Augmentin) tid for three weeks. He was admitted to the department of clinical immunology and rheumatology because of SLE activation. He had spiking fevers and arthritis of the hands despite antibiotic therapy and drainage of the abscess.

He had smoked 1 pack/day for 20 years. He quit smoking two months ago. His family history was insignificant.

He was an obese man showing his age. On physical examination, blood pressure was 130/90mmHg, pulse rate was 70/minute and body temperature was 36.2°C. There were no lymphadenopathies. Breath sounds were roughened and bilaterally there were basilar rales. Cardiovascular examination revealed a systolic murmur of the second degree. There was no hepatosplenomegaly, ascites, intraabdominal masses. Extremity examination revealed pretibial (+++) pitting edema bilaterally and instability of the right knee.

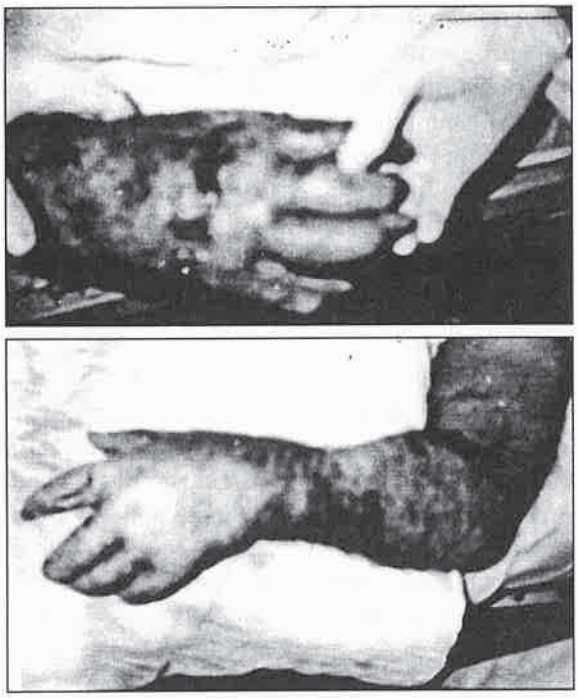
Laboratory examination revealed mild anemia, due to chronic illness. Serum Vit B12, folate and iron levels were within normal limits. Biochemistry of the blood showed altered renal functions. Urinalysis showed proteinuria (4.2 g/day) and microscopically erythrocytes, leukocytes and granular casts. Immunological parameters were as follows: ANA: ++++, homogenous pattern; anti-ds-DNA: 496 IU/ml (0 - 7 IU/ml); CRP: 21.9 IU/L (0 - 5 IU/L); ESR: 74 mm/hour; C3c: 0.642 g/L (0.9 - 2 g/L); C4: 0.0851 g/L (0.1 - 0.4 g/L); protein electrophoresis revealed hypergammaglobulinemia (26.1%).

His chest X-ray findings were insignificant. There were no signs of a past tuberculosis infection such as calcified lymph nodes, apical fibrosis or cavity formation.

Direct radiographs of the hands, wrists and elbows did not show any significant changes other than soft tissue swelling of the hands. Magnetic resonance imaging (MRI) of the right knee revealed rupture of posterior horn of medial meniscus and anterior horn of lateral meniscus; patella alta; erosion of cartilage and cortex of medial plato of tibia; a Baker's cyst and changes secondary to operation done for the knee trauma three years ago.

High resolution thoracic computed tomography showed pretracheal, precarinal, aorticopulmonary and axillary lymphadenopathies not reaching pathological

sizes; minimal pericardial effusion. Signs for diffuse interstitial pathology were not observed. There were fibrotic bands in the basal regions and a 1 cm subpleural nodule in the right middle lobe.



Figures 1 - 2: *On the day 75, abscess formation was observed in both hands. Spontaneous drainage of the right hand occurred.*

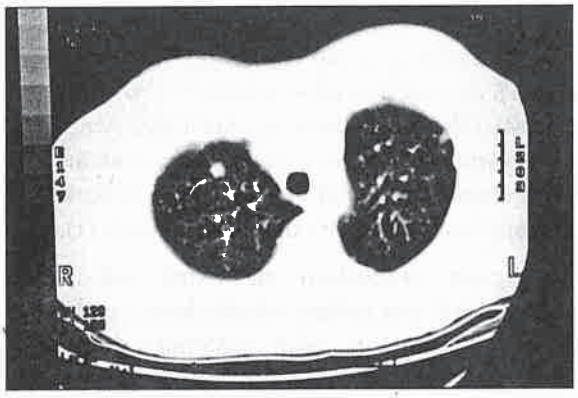


Figure 3: *A new thorax CT revealed axillary lymphadenopathies, largest being 1.5 cm in diameter. Parenchymal micronodules were present mainly on the right side. Multiple parenchymal and subpleural nodules were observed, largest being 1 cm in diameter. Findings were interpreted as compatible with miliary tuberculosis.*

On the third day of his admission gluococorticoid was increased to a dose of 40mg/day. 18 days later azathioprine (Imuran) 50 mg bid was added to the therapy. Steroid doses were slowly decreased. His clinical condition seemed to be improving with immunosuppressive treatment.

On the sixth week of admission, arthritis on second, third and fourth metacarpophalangeal (MCP) joints of the left hand and first MCP of the right hand was observed. Steroids had been decreased to a dose of 25mg/day. There was no demonstrable site of infection and because the involvement was bilateral and it occurred during steroid dose reduction, this was accepted as SLE flare–up. Steroid dose was increased to a dose of 30 mg/day and azathioprine to 50 mg tid. Amoxicilline – clavulonic acid was added to the treatment at a dose of 1 gr. bid PO in case there was an undetected infection.. However the condition of the arthritis worsened, extending to uninvolved joints of both hands, to include the wrists.

On day 59, auscultation revealed rales all over the right lung. Chest X-ray revealed right paracardiac pneumonic infiltration. Leukocyte count was 2100 /mm3. Imuran was stopped. Meropenem (Meronem) 500 mg qid I.V. was started after samples for culture were obtained. Sputum culture revealed Staph. aureus. Blood culture results were negative. Teicoplanin (Targocid) was added to therapy on a dose of 400 mg every 36 hours (dosage adjusted for renal failure) I.V. after a loading dose of 800mg. On the third day of the new antibiotic, there was no response, fever continued, steroid dosage had been decreased to 15 mg/day. On the day 75, abscess formation was observed in both hands. Spontaneous drainage of the right hand occurred (pictures 1 and 2). Microscopic examination of the material was reported to show many leukocytes. Culture specimens were taken.

On day 80, he was operated on as an emergency case for abscess drainage. Abscess material was sent again for culture and microscopic examination. This time microscopic examination revealed many acid fast bacteria.

Anti-tuberculosis treatment was started with isoniazid (INH) 300 mg/day, rifampicin (Rifcap) 600 mg/day, ethambutol (Embutol) 1250 mg/day and morphazinamide (Morfozid) 1000 mg tid PO. However, by this time his pulmonary functions were deteriorating. He was hypoxemic. Upon auscultation, there were rhonchi and rales over the lungs. However there were no new findings on the chest X-rays. A new thorax CT revealed axillary lymphadenopathies, largest being 1.5 cm in diameter. Parenchymal micronodules was present especially on the right side (picture 3). It was accepted as a sign for an inflammatory pathology, not SLE involvement. Multiple parenchymal and subpleural nodules were observed, largest being 1 cm in diameter. Findings were interpreted as compatible with miliary tuberculosis.

On day 81 melena was detected. Steroid and aspirin were discontinued. Anti-ulcer treatment with antacids and parenteral H1 blockers was started, two units of erythrocyte suspensions were transfused. Vit K replacement was given. Patient vital signs were stable, hemoglobin and hematocrit levels were stable. However melena continued. Fibrinogen levels were high, d-dimer levels and bilirubin levels were normal, excluding a diagnosis of disseminated intravascular coagulation.

On the fourth day of the anti-tuberculosis treatment, and on the 85th day of admission, massive gastrointestinal bleeding started and a short while after patient respiratory distress increased. Respiratory arrest occurred a few hours later and was not responsive to cardiopulmonary resuscitation.

Discussion

A similar case was reported from Malaysia: a 28 – year – old lady with SLE was on oral cyclophosphamide and prednisolone when presented with cellulitis of the left lower limb. It failed to respond to usual antibiotics and prompted reevaluation of the condition. The diagnosis was made on the presence of granulomas, multinucleated giant cells and acid fast bacilli on the skin biopsy (4).

As in the case presented, the clinical manifestations of the systemic rheumatic disease activation and tuberculosis infection can be quite confusing as fever, weight loss, asthenia are present under both conditions (1,3).

SLE patients are accepted as immunocompromised hosts although they are nonleukopenic (3). Host resistance to Mycobacterium tuberculosis is mediated by cellular immunity, a defense system that is deficient in these patients both due to the nature of their disease and due to the treatment (chronic high dose steroid and cyclophosphamide therapy) they are receiving. These factors cause the rheumatic disease patient to be prone to tuberculosis infection, and a delay in diagnosis.

In the evaluation of 33 patients with systemic rheumatic disease and tuberculosis by Hernandez – Cruz et al, it was shown that 10 patients had pulmonary tuberculosis and 20 had extra pulmonary disease (the three patients were excluded because they had tuberculosis before the diagnosis of rheumatic disease). Six of the seven patients with miliary tuberculosis had concomitant SLE (13 patients out of 30 had SLE). The commonest clinical manifestations were fever and weight loss. Only 16 patients had abnormal chest X – rays. Only 18 had positive cultures, of these six were with pulmonary tuberculosis and six had miliary tuberculosis. Two women with SLE and miliary tuberculosis died because of acute respiratory failure after 5 and 15 days of anti-tuberculosis therapy, like our patient . The period between the initial symptoms of tuberculosis and hospitalization was 46 and 78 days respectively, and the interval to initiation of therapy was 48 and 93 days respectively (1).

Higher proportion of extra pulmonary tuberculosis and miliary tuberculosis cases were found in patients with systemic rheumatic disease, 42% and 24% respectively. There was an association with miliary tuberculosis and SLE (1).

In a study reported from Slovakia in a group of 388 patients with SLE tuberculosis was diagnosed in 3.6%. The occurrence of septic fevers in SLE patients that did not respond to

glucocorticoid treatment indicated the possibility of complication with tuberculosis. SLE associated tuberculosis included miliary and far advanced pulmonary and extra pulmonary forms (5).

Düzgün et al reported a case of lupus vulgaris in a patient with systemic lupus erythematosus and corticosteroid induced hypogammaglobulinemia. This was the first case of lupus vulgaris in a patient with systemic lupus erythematosus reported (6).

Much tuberculosis cases in adult age classes groups be caused by reactivation of a latent infection, as opposed to reinfection (7). This is important in a country like Turkey where the incidence of latent infections is high. During rheumatic disease activation or due to treatment given, these latent infections may reactivate.

Mortality rates in SLE patients with tuberculosis were especially high. This could be related to delay in diagnosis, need for higher doses of immunosuppressive therapy, and concomitant disease exacerbation with infection (1). Besides, the screening test results were different in this patient group. PPD response >10 mm was found to correlate highly with tuberculosis activity, whereas milder responses did not rule out the disease. Furthermore, patients with extra pulmonary tuberculosis and miliary tuberculosis tended to have milder responses (1).

In the immunocompromised host without neutropenia any pathogen may produce a variety of clinical conditions and tuberculosis may be the cause of any clinical or radiological situation. It must be kept in mind that new extra pulmonary symptoms or signs with a rapid progression of fever, diffuse opacities or nodules on chest X - ray may sign tuberculosis. Sputum, blood samples should be obtained for microscopic evaluation and cultures. A CT scan of the thorax may be useful to characterize the lesions especially if there is concomitant pleural effusion. Where plausible, bronchoalveolar lavage (BAL) may be performed. Yet, BAL results may be negative occasionally (8).

Advisory council for the elimination of tuberculosis suggests, PPD reaction > 5 mm should be considered significant in patients with organ transplants and other immunosuppressed patients (receiving the equivalent of > 15 mg/d of prednisone for a month or more) (9).

In the case of miliary tuberculosis, early empiric therapy can be started if there is sufficient clinical suspicion based on the presenting signs and symptoms as well as the pattern of organ involvement. As with all infections, particularly of the immunosuppressed early implementation of treatment is essential and life saving (3,5).

In conclusion, in dealing with systemic rheumatic disease patients, one should always be aware of the possibility of concomitant tuberculosis infection. Keeping in mind that most patients will have extra pulmonary disease, any clinical finding that cannot be explained by rheumatic disease activity should raise the suspicion of tuberculosis infection. Also, any infection unresponsive to standard antibiotic regimens, when cultures are nondiagnostic, should prompt search for a specific infection. They should be evaluated promptly and treatment should be started immediately. Tuberculosis can be fatal in these patients.

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A CASE OF BRONCHIAL MUCOEPIDERMOID CARCINOMA WITH CUTANEOUS METASTAS: LOW-GRADE HISTOLOGY BUT AGGRESSIVE BEHAVIOUR

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SUMMARY

Mucoepidermoid carcinomas are malignant neoplasms that rarely arise in the tracheobronchial tree. Primary or metastatic cutaneous involvement is unusual. We describe a bronchial mucoepidermoid carcinoma that presented with cutaneous metastases and showed aggressive biological behavior. The microscopic and ultrastructural features of the cutaneous and bronchial tumors were compatible with low-grade mucoepidermoid carcinoma. However, there was widespread metastasis to the skin, subcutaneous and intraabdominal fat tissue, and several bony structures, and the patient died 5 months after the initial diagnosis. We emphasize that benign histological features of primary mucoepidermoid carcinomas are not always associated with low-grade behaviour.

Key Words: *Bronchial Carcinoma, Cutaneous Metastases, Mucoepidermoid Carcinoma*

ÖZET

Kütanöz Metastazlarla Tanı Alan Bronşiyal Mukoepidermoid Karsinoma Olgusu: Benign Histolojiye Rağmen Kötü Klinik Seyir

Mukoepidermoid karsinomalar trakeobronşiyal bölgeye nadiren yerleşen malign tümörlerdir. Deriye primer olarak ya da metastaz sonucunda yerleşmeleri de sık görülmemektedir. Burada, kütanöz metastazları ile tanı alan ve kötü bir klinik seyir izleyen bronşiyal kökenli mukoepidermoid karsinoma olgusu sunulmaktadır. Kütanöz ve bronşiyal tümörlerin mikroskopik ve ultrasütrüktüyel özellikleri histolojik olarak düşük evreli mukoepidermpid karsinoma ile uyumluydu. Buna rağmen, deri, subkutan doku, intraabdominal yağ dokusu ve birçok kemikde metastazlar saptandı, ve hasta tanı aldıkdan sonra 5 ay içinde öldü. Bu olguyla, benign histolojik özelliklere sahip primer mukoepidermoid karsinomaların herzaman iyi bir klinik seyir izlemeyebilecekleri vurgulanmak istenmiştir.

Anahtar Kelimeler: *Bronşiyal Karsinoma, Kütanöz Metastazlar, Mukoepidermoid Karsinoma*

Mucoepidermoid carcinomas (MECs) are malignant tumors that usually arise in the salivary glands(1), but occasionally develop in the bronchus(2), esophagus(3), lacrimal glands(4), pancreas(5), thymus(6), and thyroid gland(7). These tumors are composed of mucus-secreting, epidermoid, and intermediate cells arranged in sheets and glandular formations(8-10). The history of MECs has been the subject of much discussion in recent years. In particular, efforts have been made to correlate morphological characteristics with biological behavior. In the most widely accepted approach to predicting clinical aggressiveness and prognosis, MECs are morphologically classified as low-grade and high-grade according to gross, microscopic, and ultrastructural features(8-11).

We report a patient with bronchial MEC who presented with cutaneous metastases. Although the bronchial tumor and the cutaneous lesions exhibited low-grade histologic features, the patient died due to widespread metastases within months of the initial diagnosis.

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Received: *March 29, 2002* Accepted: *July 11, 2002*

Case Report

A 55-year-old man presented with asymptomatic nodules on his face and chest. The lesions had been present for 1 month, and were slowly enlarging. The patient was otherwise in good health, and coronary angioplasty was the only noteworthy item in his medical history. Dermatologic examination revealed a firm erythematous nodule inferior to the left nostril that was 1.3 cm in diameter and had a poorly defined, indurated border (Figure 1). Three other cutaneous nodules ranging from 0.5 cm to 1 cm in diameter were detected on the lateral aspect of the left lip commissure, in the right preauricular region, and on the presternum. Excisional biopsies were performed on one face lesion and the chest lesion. Histological examination of both specimens showed a dermal tumor composed of islands of mucus-secreting, intermediate, and epidermoid cells with no pleomorphism, mitotic figures, or cellular necrosis (Figure 2a). The biopsy tissues stained positive with mucicarmine (Figure 2b), alcian-blue, and periodic acid-Schiff, and also for cytokeratin on immunoperoxidase staining.

Electron-microscopic examination revealed that many of the tumor cells contained large numbers of mucous droplets in their cytoplasm. Other cells showed squamous differentiation and contained cytoplasmic tonofilaments. Scattered intermediate cells were also observed. Based on these findings, the morphologic diagnosis was low-grade MEC.

A chest radiograph was normal, but thoracic computed tomography (CT) revealed a lobulated

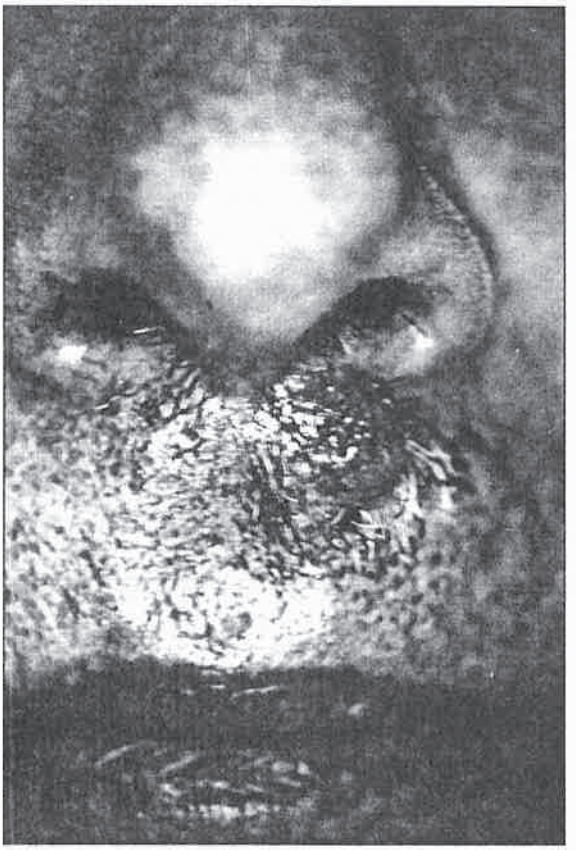

Figure 1. *Cutaneous metastatic MEC. An erythematous nodule inferior to the left nostril.*

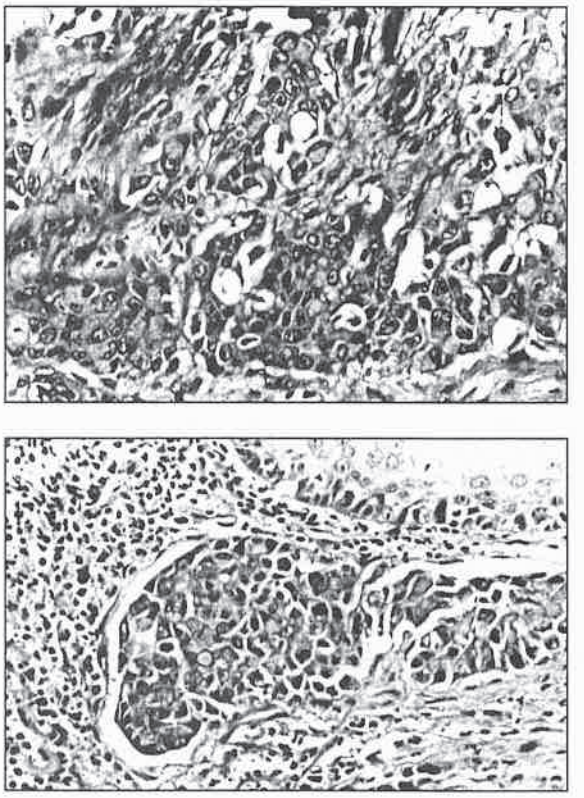

Figure 2. *(a) Histology of a cutaneous metastatic tumor indicating low-grade MEC: Squamoid cells (thin arrow) admixed with rare mucinous cells (thick arrow) (haematoxylin and eosin; original magnification x 230); (b) Intracytoplasmic mucin (arrows) (mucicarmine; original magnification x 230).*

soft-tissue mass in the right middle-lobe bronchus. Bronchoscopy showed stenosis of the same bronchus, but no apparent endobronchial tumor. A transbronchoscopic biopsy specimen of the stenotic bronchial wall exhibited similar microscopic features to those noted in the cutaneous lesions (Figure 3a and 3b). Further work-up with abdominal CT revealed multiple nodular lesions in the subcutaneous and intraabdominal fat tissue that were thought to be metastases. Lytic bone lesions in several of the patient's ribs, the vertebral column, and the right pelvis were also demonstrated on Tc-99m MDP total-body bone scanning. When the diagnosis of metastatic bronchial MEC was established, the patient was started on chemotherapy with cisplatin and gemcitabine. Two months later, the protocol had to be switched to a cisplatin-docetaxel combination due to the appearance of new cutaneous lesions. However, 3 weeks after this change, the patient developed hepatosplenic and cranial metastases, and palliative radiation therapy was applied to the cranium. Despite all treatments, the patient's condition continued to deteriorate, and he died 5 months after the initial diagnosis.

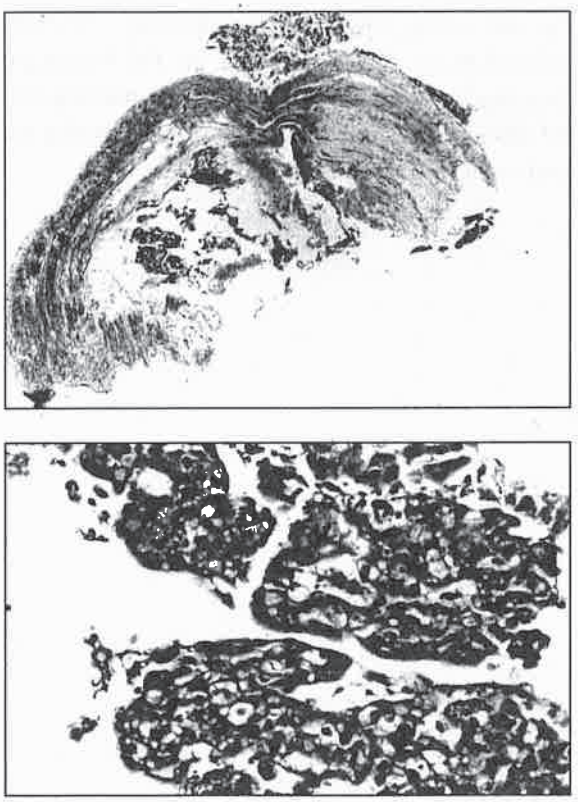

Figure 3. *(a) A group of tumor cells (arrow) in the bronchoscopic biopsy specimen (haematoxylin and eosin; original magnification x 45); (b) Higher magnification reveals mucinous (thick arrow) and intermediate cells (thin arrow) (haematoxylin and eosin; original magnification x 230).*

Discussion

MECs are malignant tumors that are composed of mucus-secreting, epidermoid, and intermediate cells(8-10). The history of these neoplasms is interesting. Initially, they were known to occur only in salivary glands, the site that has the highest frequency(12). However, with the first account of bronchial MEC by Smetana et al. in 1952(13) as well as other reports of bronchial involvement(14), it was recognized that these tumors occasionally arise in the tracheobronchial tree. Subsequently, various other sites, including the esophagus(3), thymus(6), and thyroid(7), have also been noted in rare cases. The skin has also been reported as a primary site of MEC(15,16) but this is extremely unusual. MECs presenting with cutaneous metastases are rare, with only three cases published to date (9,11,17). The first of these was reported by Metcalf et al(11). in 1986, and was a bronchial MEC that had metastasized to the skin. The other two cases presented with cutaneous metastases, originated from the sublingual gland(17) and parotid gland(9), respectively. Early reports of MECs indicated that these tumors were essentially benign neoplasms(14,18). However, later studies documented a malignant form that tended to produce widespread metastasis. As mentioned above, in attempt to predict malignant potential from histologic appearance, a classification system was proposed that divided MECs into low-grade and high-grade types according to their histological and ultrastructural characteristics(2,10). Low-grade MECs show minimal pleomorphism, rare mitoses, and minimal or no necrosis. The metastatic potential of this type is reported to be extremely

low, and death due to this form is very unusual. In contrast, the histologic features of high-grade MECs are marked nuclear pleomorphism, increased mitotic rate, and cellular necrosis. Widespread metastasis is common with this type(19), and the histology of the metastases may indicate even more aggressive malignant features than the primary tumor(8).

Although this classification system is accurate in the majority of MEC cases, a few reports have noted low-grade histologic features in association with fatal outcome. Barsky and colleagues(8) reported a case of bronchial MEC in which the primary tumor showed low-grade histologic features but exhibited aggressive biological behavior. The findings were similar in a case described by Metcalf et al(11). that detailed a bronchial MEC presenting with cutaneous metastases. The morphologic features of our patient's tumor on light- and electron microscopy were compatible with low-grade MEC. However, the clinical course, namely, death due to widespread metastases, was obviously that associated with high-grade tumors.

It is true that some high-grade MECs contain areas of low-grade growth, and that these areas may be missed if the tumor is not sufficiently sampled. In our case, total excision of the bronchial tumor was not performed due to widespread metastasis. Because of this, we were unable to investigate the primary tumor extensively. However, the features of the transbronchial biopsy specimen indicated low-grade MEC, as did the histologic examination of the two cutaneous (face and chest) lesions that were sectioned extensively. Furthermore, in cases of mixed low- and high-grade MEC, the metastases are expected to be less differentiated (higher grade) than the original tumor(8).

To the best of our knowledge, this is only the second reported case of a MEC diagnosed by cutaneous metastases that behaved aggressively despite having low-grade morphology. Although classification of MECs based on the histologic features has high prognostic value in the majority of cases, it does not always accurately predict the potential for metastases.

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JOURNAL OF ANKARA MEDICAL SCHOOL Vol 25, No 1, 2003 47-50

TRICUSPID INSUFFICIENCY AFTER BLUNT CHEST IN A PATIENT WHO PREVIOUSLY UNDERWENT CABG

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Hakkı Akalın****

SUMMARY

A 67-year-old man sustained traumatic rupture of the tricuspid valve in an automobile accident. Four years later, progressive fatigue and cardiac enlargement developed.He has undergone CABG 7 years ago. Angiography revealed the trombosis of the saphenous graft anastomosed to the RCA. For these reasons tricuspid valve replacement and re-do CABG was performed. The patient died of multiorgan failure on the second postoperative day.

Traumatic tricuspid regurgitation is relatively uncommon. In this article we report our experience with surgical treatment of traumatic tricuspid valve insufficiency accompanied by re-do CABG in a patient previously underwent CABG.

Key Words: *Trauma, Trcuspid Valve, Tricuspid Insuffuciency, Open Heart Surgery.*

ÖZET

Koroner Bypass Geçiren Hastada Künt Göğüs Travması Sonrası Triküspit Yetmezliği: Olgu Sunumu

67 yaşındaki erkek hasta otomobil kazası sonrası triküspit kapakta travmatik rüptür gelişti. Hastada 4 yıl sonra progresif yorgunluk ve kalp büyümesi tespit edildi. 7 yıl önce koroner bypass (CABG) ameliyatı yapılan hastanın anjiyografisinde sağ koroner arterdeki (RCA) safen anastomozunun tromboze olduğu gözlendi. Hastaya bu nedenle triküspit onarımı ve re-do CABG yapıldı. Postoperatif dördüncü günde multiorgan yetmezliği nedeniyle exitus oldu.

Travmatik triküspit yetmezliği rölatif olarak seyrek görülür. Biz bu çalışmada travmatik triküspit yetmezliğine re-do CABG'nin eşlik ettiği cerrahi tedavi tecrübemizi bildirdik.

Anahtar Kelimeler: *Travma, Triküspit Kapak, Triküspit Yetmezliği, Açık Kalp Cerrahisi.*

Traumatic tricuspid insufficiency following blunt chest trauma, although an uncommon entity, has been reported more frequently over the past 2 decades (1). The most frequently reported is chordal rupture, followed by rupture of the anterior papillary muscle and leaflet tear primarily of the anterior leaflet (2). Early surgical correction has become the prefemed treatment in most instances and may be influenced by clinical status and other associated comorbid conditions (2). A patient with a history of coronary artery bypass surgery and traumatic trikuspid insufficiency is presented.

Case Report

A 67 –year old man who underwent CABG 7 years ago and sustained blunt chest trauma in a car accident 4 years ago was admitted to hospital with peripheral edema, hepatic congestion and ascites. He was previously diagnosed as traumatic portal venous thrombosis. As he conducted repeating symptoms, he was admitted to our hospital.

On examination there was a prominent V wave in the jugular venous pulse and there was a Grade 3/6 murmur of tricuspid regurgitation.

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Received: *July 18, 2002* Accepted: *Sept 26, 2002*

Peripheral edema was present. A chest film showed enlargement of the right atrium, right ventricle, and vena cavae. An echocardiogram showed marked dilatation of the right atrium, right ventricle and inferior vena cava. A contrast echocardiographic study indicated severe tricuspid regurgitation and no evidence of a right-to-left shunt. A repeat angiogram revealed the the total stenosis of the RCA-saphen bypass, but the patency of the LIMA to LAD anastomosis performed 7 years ago.

Surgery was performed with cardiopulmonary bypass using aortic and bicaval cannulation. After cardioplegic arrest, distal anastomosis of saphen venous graft to RCA was performed first, and after, a right atriotomy was performed to visualize the tricuspid valve. The septal leaflet was retracted and adherent to the ventricular septum. Tricuspid annuloplasty was performed with Carpentier-Edwards ring (Baxter Healthcare Corp., Edwards Div., Irvine, Calif). The valve was then competent with saline distending the ventricle. IABP was used to wean from CPB. The patient died of multiorgan failure on the 1st postoperative day.

Discussion

Valve rupture is a widely recognised result of nonpenetrating trauma to the heart (1) Traumatic tricuspid incompetence may be well tolerated for a long time (1)or may cause symptoms necessitating early surgical treatment. Rupture of the papillary muscle typically becomes symptomatic rapidly, whereas ruptured chordae or torn leaflets may have a more insidious onset of symptoms. Exertional dyspnea and fatigue are the most common early symptoms.

The most common mechanisms involved associate an antero-posterior compression of the chest with a sudden increase in the right ventricular presure during the end diastolic phase, when the main pulmonary vessels are compressed. This generates a marked traction on both the valvular and subvalvular apparatus (2). Sub-valvular lesions are responsible for the incompetence in 75% 0f the cases, the leading cause being the rupture of one of the two papillar muscles, most often the anterior one (2).

Conversely, although it is much less frequent, the leaflets themselves can be damaged either by laceration (2) or by an abrupt rupture near the annulus. Indeed, in the mid 1980s, it was common practice to postpone the intervention until the patient became really symptomatic. Delays could sometimes be very long, with an avarage of 16 years according to Van Son et al (3), causing deterioration of the valve, necrosis of the papillary muscles and retraction of the chordae, making valvuloplasty an illusive treatment option. Also when operative intervention is unduly delayed irreversible right ventricular myocardial dysfunction may develop, as in our case. Long term results will likely be better if operation is performed before right ventricular function deteriorates, rather than the onset of progressive right heart failure. Although the literature contains litle information concerning the late results of tricuspid valve repair, we believe results should be better with repair than with valve replacement because the geometry and function of the right ventricle are better preserved and complications inherent in prosthetic heart valves are avoided. The operative technique will be dictated primarily by the specific injury encountered at the time of operation. If the injury is limited to the chordae tendinae,papillary muscle, or a leaflet, repair can usually effected. The recent use of artificial chordae may facilitate salvage of some valves(4). This case supports our thesis that early repair would limit right heart failure and lead to a better prognosis in the postoperative period, because even obtaining the patency of the graft to the right coronary artery again was not enough to survive the patient.

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MECONIUM THORAX: A CASE OF BOCHDALEK HERNIA AND CECAL PERFORATION WITH CYSTIC PERIVENTRICULAR LEUKOMALAISIA IN A NEONATE

Meral Barlas* ✣ Aydın Yağmurlu**

SUMMARY

A 35 week pre-term male neonate with a prenatal history of polyhydroamnios and intrauterine growth retardation was delivered from a 25 year old mother. Chest radiograph and CT showed pleural effusion, and mediastinal shift to the right. The patient undervent an exploratory laparotomy and a posterolateral left diaphragmatic hernia was identified as well as 3mm perforation of a normally positioned cecum. The left pleural space was cleared of debris, then the diaphragmatic defect was closed. After appendectomy and colonic biopsy cecostomy was performed. His postoperative course was uneventfull. However, the infant presented a spastic posture, opistotonic movement and tonic-clonic seizures. Cystic encephalomalasic areas in both hemispheres, loss of volume in white matter and cortical atrophy were detected by MRI. Performing colostomy closure he was discharged to the pediatric neurology department. At 8 months and 3 years follow up, the child has no problems due to CDH, but he has very severe neurologic deficit and is mentally retarded.

Key Words: *Congenital Diaphragmatic Hernia, Cecal Perforation, Cystic Periventricular Leukomalaisia.*

ÖZET

Mekonyum Toraks; Bochdalek Hernisi Olan Bir Yenidoğanda Çekal Perforasyon ve Kistik Periventriküler lökomalazi

Gelişme geriliği ve polihidroamniyos nedeniyle 25 yaşındaki anneden normal vajinal yolla doğan 2500 gr ağırlığındaki 35 haftalık prematür erkek yenidoğan, sol Bochdalek herni öntanısıyla yatırıldı.Radyolojik görüntüleme yöntemlerini takiben laparatomi yapıldı. Sol hemitoraksta ve karın içindeki mekonyum bulaşısının, normal yerleşimli çekumdaki 3 mm perforasyondan kaynaklandığı diğer barsakların normal çap ve görünümde olduğu saptandı. Karın ve toraks yıkanıp temizlendi, diyafrağma defekti dikilerek onarıldı. Apendektomi, Kolon biyopsisi ve çekostomi yapıldı, cerrahi girişim sonrası 7. gün şifa ile taburcu edildi. Hasta 4 aylık iken spastik kasılmaları nedeniyle MRI yapıldı. Tüm beyinde kistik oluşumlar, beyaz cevherde hacim kaybı ve kortikal atrofi saptandı. Çekostomi kapatılarak, çocuk nörolojisi kliniğine yollandı. Gelişme geriliği olmayan 3 yaşındaki hastada KDH nedeniyle ilgili bir komplikasyon yoktur, ancak ileri derecede nörolojik defisit ve mental retardasyonla yaşamını özel eğitimle sürdürmektedir.

Anahtar Kelimeler: *Bochdalek Hernisi, Çekal Perforasyon, Kistik Ensefalomalazi.*

The incidence of associated malformations in infants with congenital diaphragmatic hernia (CDH) is approximately 30-40 percent. The predominance during these associated anomalies is in neural tube defects including anencephaly, myelomeningocele, hydrocephalus and encephaloceles. Cardiac defects are the second most common group (1-3). Periventricular leukoencephalopathy is a pathologic process that has attracted little attention in neurodiagnosis. However its association with extremely low birth weight infants, hypocarbia and mechanical ventilation is well demonstrated (4). We present herein as a case of CDH and cecal perforation and cystic periventricular leukomalasia.

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Received: *May 20, 2002* Accepted: *Sept 30, 2002*

Case Report

A 35-week-preterm male neonate with a prenatal history of polyhydroamnios and intrauterine growth retardation was delivered from a 25 year old mother via spontaneous vaginal route. The baby weighed 2500 g. APGAR scores were 5 and 8 at 5 and 10 minutes respectively.

Cyanosis and respiratory distress required as rush to the neonatal intensive care unit. He received oxygen in the hood. On physical examination the respiratory sounds were diminished in the left side and the heart sounds were displaced to the right. With the suspect of CDH a radiocontrast enema was performed and the colonic segments under the diaphragma was observed. A normal sized and placed cecum, contrast leaked into an ill-defined collection in the right lower quadrant. Also the upper gastrointestinal series with radiocontrast material revealed no abnormality. Chest radiograph and CT showed pleural effusion, and mediastinal shift to the right. The patient undervent an exploratory laparotomy on day 2 of life. A posterolateral left diaphragmatic hernia was identified as well as 3mm diameter perforation of a normally positioned cecum (Figure 1). A significant degree of meconium staining was seen throughout the peritoneal cavity and thorax. The left pleural space was cleared of debris then the diaphragmatic defect was closed, after which appendectomy and colonic biopsy cecostomy was performed. Pathologic examination showed a congenital deficiency of the muscularis propria in the perforated area and normal ganglion cells. The postoperative period was uneventful. No mechanical ventilation was required, and he was discharged from the hospital in the 10th postoperative day. Cecostomy closure was planned. The child presented four months later with a spastic posture, opistotonic movement and tonic-clonic seizures. Magnetic resonance imaging revealed cysticencephalomalasic areas in both hemispheres, loss of volume in white matter, and cortical atrophy (Figure 2). The patient's screening for inborn errors of metabolism did not reveal any abnormality.

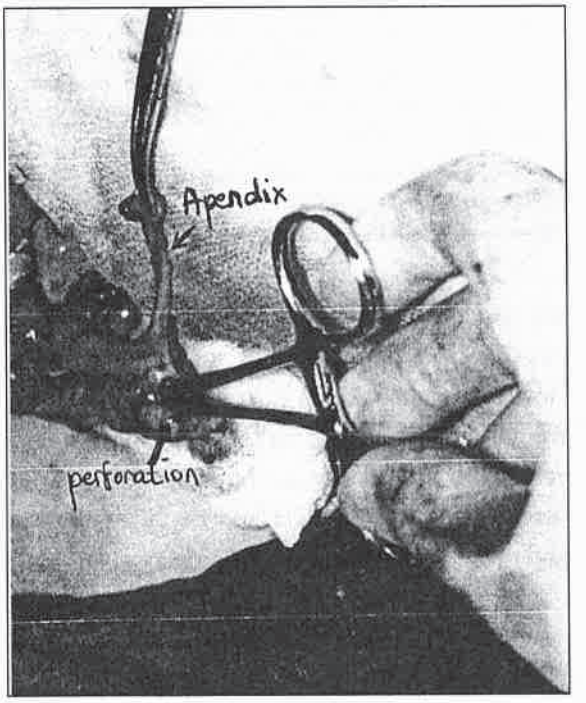

Figure 1: Tip of Mosquito clamp directs to the cecal perforation. Please note the rest of the bowel in normal appearance.Operative photograph on day 2.

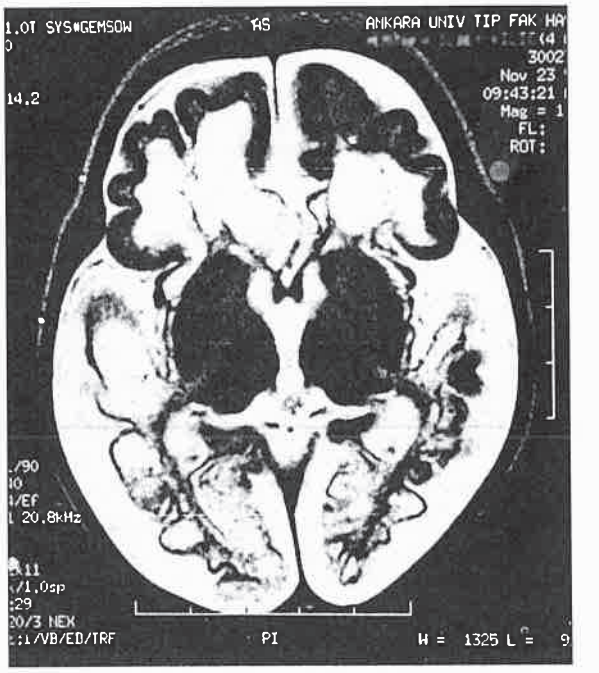

Figure 2: Cystic periventricular leukomalasia in both hemispheres ,loss of volume in white matter, and cortical atrophy on T2 images in MRI at 4 months postoperatively

Performing colostomy closure he was discharged to the Pediatric Neurology Department for this rare neurological entity. At 8 months and 3 years follow up, the child has no problems due to CDH, but he has a very severe neurologic deficit and is mentally retarded.

Discussion

Although neonatal care has improved over the past 20 years, congenital diaphragmatic hernia remains as an anomaly with a high mortality rate (3). This is not only due to the defect itself but also a combination of associated anomalies. Cardiovascular malformations and neural tube defects including anencephaly, myelomeningocele, hydrocephalus, and encephaloceles have a predominance among these anomalies (1,2,5). The rate of gastrointestinal disorders remains low. Patole et al, have presented a case in which extension of meconium peritonitis through muscular defect in the diaphragm lead to intrathoracic calcifications diagnosed ultrasonographically at 23 weeks of gestation (6). Butterworth et al. reported third meconium torax with Job's syndrome (3). The case we present here is the second one in the English literature with CDH and gastrointestinal perforation presented as fecaloid material in the thorax. The reason of cecal perforation has not been clearly defined. Except the perforation site, rest of the intestines were macroscopically normal both vascularisation and diameter. The histopatologic examination excluded Hirschsprung's Disease.

The association of neurological defects seems to be high with CDH but this is the first case of congenital leukoencephalopathy. It was reported by Wisewell et al. that mechanically ventilated premature infants are at increased risk for cystic periventricular leukomalasia, particularly if hypocapnia occurs (4). The presented case had no need for mechanical ventilation because of the small diaphragmatic defect and lung hypoplasia was not severe. Though it is hard to differentiate the congenital form from the acquired one, we believe that this pathologic entitiy is a congenital form which was previously demonstrated in three Turkish children by Oliver et al. (7). The neurological findings were noted in the first months of life and include spasticity and impairment of motor and mental retardation, just like the present case with spastic posture and opistotonic movements and tonic-clonic seizures. Magnetic resonance imaging of the brain showed extensive cysts within the cerebral hemispheres, ventricular enlargement and white matter disease similar to the previously reported three cases.

To conclude; meconium Thorax in CDH with cecal perforation is a rare case especially when accompanied with cystic periventricular leukomalacia.

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