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BLOOD SELENIUM, ZINC AND COPPER LEVELS IN PATIENTS WITH BLADDER CANCER

Kadirhan Sunguroğlu* • Cumhur Kılınç • Ahmet Fuat Peker*****

SUMMARY

Serum levels of selenium, zinc and copper were measured in 51 patients with bladder cancer (15 patients in Grade I, 19 patients in Grade II and 17 patients in Grade III) and 22 healthy controls. Decreased serum levels of selenium was found in cancer patients in Grade III while zinc levels decreased in Grade II and III when compared with control group. Serum copper levels were found statistically higher in patients in every stages when compared to control group.

These results suggest that, serum selenium, zinc, and copper levels may be important in evaluation of bladder cancer.

INTRODUCTION

The biological role of selenium, zinc, and copper, as well as fluctuations in their concentrations in various physiological and pathological conditions, has been intensely investigated in recent years (1-3).

The human essentiality for selenium is based on its incorporation into the enzyme glutathione peroxidase (2, 3). Selenium has no other confirmed human function but may be important for the activity of other human enzymes, such as thyroxine-5'-deiodinase (3). Low blood selenium concentrations have been observed in patients with cancer (3-5).

Decreased serum zinc levels and increased serum copper levels have been consistently reported in patients with lymphoproliferative disorders (6, 7), lung and gastrointestinal cancers (8-10) and gynecologic malignancies (11-13).

These changes in the concentrations of trace metals in serum prompted us to investigate whether there are also such changes in urological (specifically, bladder) malignant tumors, and whether this relationship between the stages of disease and trace element concentrations in serum can be used for diagnostic purposes.

MATERIALS AND METHODS

Serum concentrations of selenium, zinc, and copper were measured in 38 male and 13 female patients with various types of bladder cancer (15 patients in Grade I, 19 patients in Grade II and 17 patients in Grade III) and 22 healthy controls within the same ages (15 men, 7 women). Patient and control groups were in the same socioeconomic class.

Overnight-fasting blood samples were collected by venipuncture, the serum was separated within 2 hours after blood withdrawal and divided into aliquots and stored at -20 °C until analyzed. All plastic and glassware used in experiments were treated with deionized water and then dried.

Selenium in serum was determined by the spectrofluorometric method described by Lalonde et al (14) and reported as µg/L.

Serum samples were diluted with deionized water (1:5 v/v) for determination of zinc and copper by atomic absorption spectrophotometry (Varian Techtron Model 1200). The concentrations of zinc and copper in serum were reported as µg/dl.

Mean values of the parameters and their standard deviations were calculated and compared by Student's t Test.

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Table 1. Serum selenium, zinc, and copper levels in control group and bladder cancer groups in Grade I, II, and III. (Mean value ± standard deviation)

Groups / Parameters	Healthy Controls (n=22)	Bladder Cancer Grade I (n=15)	Grade II (n=19)	Grade III (n=17)
Selenium (µg/L)	102,17±15,09	96,26±15,82	93,86±14,85	85,12±12,55
Zinc (µg/dl)	105,26±17,33	95,90±16,71	91,45±14,40	73,11±13,50
Copper (µg/dl)	124,76±21,14	135,14±18,05	147,15±12,16	162,57±17,24

RESULTS

The levels of serum selenium, zinc, and copper in control group and in bladder cancer groups in grade I, II, III are shown in Table 1.

Significances of differences of trace element levels between control group and patient groups are shown in Table 2.

DISCUSSION

Bladder cancer is the most common urological cancer and approximately one-third of these tumors are found to be invasive at the time of diagnosis. The other two-thirds are initially localized and noninvasive but are responsible for considerable discomfort, disability, and expense, especially since they have rates of recurrence reported to be as high as 80%, and may become invasive (15-17).

A number of environmental risk factors for bladder cancer have been identified (18). Most studies of the preventive factors for bladder cancer have focused on nutrients such as selenium, zinc, and vitamins (18).

The support for a possible role for selenium in protecting against bladder cancer comes from a study of glutathione-related enzymes in the transitional epithelium of the urinary bladder in rabbits (19). The authors postulated that the vulnerability of bladder transitional epithelium to chemical carcinogens might be a result of the low levels of these selenium-dependent enzymes in bladder tissue. Selenium is believed to operate as a biological antioxidant primarily as a component of glutathione peroxidase (2). Low blood selenium concentrations have been observed in patients with cancer (3-5). However, only the difference of selenium levels between control group and cancer patients in Grade III was statistically significant in the present study.

Many authors have reported that serum zinc levels are decreased in cancer patients (5,8,10,11,13). Zinc levels were significantly lower in patients in Grade II and Grade III when compared with the control group in the present study. Zinc deficiencies in patients with neoplastic diseases have been attributed to anorexia, starvation, and loss of zinc from catabolized tissue, and increased urinary excretion of zinc subsequent to its mobilization by interleukin-1 (3).

Abnormally high concentrations of copper have been observed in serum from patients with various malignancies (7,11,13). It has been suggested that an increase in serum copper is secondary to elevated levels of the copper-containing oxidase ceruloplasmin. Increased production of ceruloplasmin has been shown to occur as an acute phase reactant protein response to fever, infection, and malignancy (20). Serum

Tablo 2. Significances of differences of trace element levels between the control and patient groups.

	Control–Grade I	Control–Grade II	Control–Grade III	Grade I–II	Grade II–II	Grade I–III
Selenium	N.S.	N.S.	p<0,001	N.S.	N.S.	p<0,05
Zinc	N.S.	p<0,01	p<0,001	N.S.	p<0,001	p<0,001
Copper	N.S.	p<0,001	p<0,001	p<0,05	p<0,01	p<0,001

N.S.: not significant

copper levels have been found to be a nonspecific indicator of disease activity in many malignant and nonmalignant diseases (7). In the present study, copper levels were increasing by the progression of stages of bladder cancer. Serum copper concentrations were significantly different between the patient groups in different stages.

Different sera levels of these trace elements in bladder cancer patients might be the outcome of illness. But taking into account the references concerning of low selenium and zinc levels for cancer development, we can also attribute to our data showing that serum levels of selenium, zinc and of copper might have an important role in bladder cancer.

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SERIAL D-DIMER CONCENTRATIONS AND ITS RELATION TO THROMBOLYSIS

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Ender Semiz**** • Filiz Ersel***** • Necmi Değer*****

SUMMARY

This study asseses the correlation of serially measured plasma D-dimer concentrations and the status of reperfusion in patients with acute myocardial infarction who were treated with streptokinase. Thirty-six patients were enrolled and divided into two groups in respect to the patency of the culprit coronary artery. Thrombolytic therapy was considered as successful in group A (31 patients) and as unsuccessful in group B (5 patients). In group A, D-dimer values 2 hours after the streptokinase had a peak and were significantly higher than those obtained before streptokinase ($p < 0.0001$). In group B, D-dimer values 2 hours after streptokinase were non-significantly higher than those obtained before streptokinase ($p = 0.068$). When the corresponding D-dimer values were compared in both groups, 2 hours and 6 hours after streptokinase, group A had a significantly higher D-dimer value ($p = 0.0001$ and $p = 0.0002$, respectively), 24 hours after streptokinase, there was not any significant difference between the two groups ($p = 0.16$). This study demonstrates that serially measured D-dimer values could serve as a useful laboratory tool to support reperfusion or to suspect failed thrombolysis.

Key Words: *acute myocardial infarction, D-dimer, streptokinase, thrombolysis.*

Studies about the pathogenesis of acute myocardial infarction (MI) have concluded that thrombosis of the coronary arteries is the main cause of MI(1,2). Accordingly, thrombolytic therapy given in the first 4 hours of MI, significantly lowered mortality in large scale trials(3). However, there is not a very sensitive test to confirm successful thrombolysis after thrombolytic therapy, apart from coronary angiography. Complete resolution of ST segment elevation and/or chest pain was found to be highly associated with reperfusion (very specific) but was rarely observed (very insensitive)(4).

Fibrin formation occurs in the thrombus as a result of hemostatic activation(5). Thrombolytic therapy increases the fibrinolytic activity resulting in formation of fibrinogen degradation products through lysis of fibrinogen and in formation of crosslinked fibrin polymers through lysis of fibrin clot at the site of thrombosis(6). D-dimer is a derivative of crosslinked fibrin polymer and its increased levels indicate a fibrinolytic state lysing the fibrin clot(6,7). In a study, during fibrinolytic therapy of pulmonary embolus with streptokinase, D-dimer was found to be useful as an early prognostic parameter of successful thrombolysis(8). We therefore sought to test whether elevations of baseline D-dimer concentration among patients with acute myocardial infarction receiving thrombolytic therapy might serve as a marker of successful thrombolysis.

METHODS

Thirty-six patients (30 men, % 83.3) were enrolled in the study with a mean age of 54.75 ± 9.88 years. Patients with a prior myocardial infarction, with contraindications to coronary angiography and/or thrombolysis, those who presented later than 180 minutes after the onset of chest pain and those with an equivocal infarct-related artery in the coronary angiogram were excluded. All patients had at least 30 minutes of chest pain accompanied by ST segment elevations of more than 2 mm (0.2 mV) in two or more contiguous

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Table 1. Clinical characteristics of groups A and B.

	Total number	Age (years)	Men (%)	Anterior MI	Inferior MI	Inferolat. MI
Group A	31	56 ± 9.6	80.6	17 (% 54.8)	10 (% 32.3)	4 (% 12.9)
Group B	5	47 ± 8.1	100	2 (% 40)	2 (% 40)	1 (% 20)

Inferolat.:Inferolateral, MI:Myocardial infarction

EKG leads. Of the patients, 19 (% 52.8) had anterior infarction, 12 (% 33.3) had inferior infarction and 5 (% 13.9) had inferolateral infarction. After confirming the absence of contraindications for thrombolytic therapy, all patients gave an informed consent and 1.5 million units streptokinase (Streptase, Hoechst) was administered in 60 minutes in the emergency room intravenously. The mean time between the onset of chest pain and the start of streptokinase infusion was 130 ± 23 minutes. All patients were put on oral 100 mg aspirin, intravenous (iv) 10 mg/min nitroglycerine infusion for 2 days, iv 30000 units/d heparin infusion starting 4 hours after streptokinase for 5 days. Blood samples were collected according to the instructions of the vendor (D-Di Test, Diagnostica Stago, France) before, 2 hours, 6 hours and 24 hours after streptokinase infusion and were centrifuged immediately for 10 minutes at 2500 g. Plasmas were collected and studied immediately. Plasma D-dimer values were determined qualitatively and semi-quantitatively by a latex agglutination slide test (D-Di Test, Diagnostica Stago, France). All patients but one, underwent cardiac catheterization and coronary angiography 24 hours after streptokinase and the angiograms were reviewed by five experienced cardiologists. One patient was taken to the cardiac catheterization laboratory at sixth hour after streptokinase because of ongoing chest pain, this particular patient (Group B patient number 4 in table-II) had no increase in serially measured D-dimer titers and his coronary angiography revealed that the culprit coronary artery was totally occluded. Rescue PTCA and intracoronary stenting were performed. Patients were divided into two groups in respect to the patency of the culprit coronary artery. Patients in group A had a TIMI grade 2 or 3 flow in the culprit coronary artery whereas patients in group B had a TIMI grade 0 or 1 flow in the culprit coronary artery. Thrombolytic therapy was considered as successful in group A and as unsuccessful in group B.

STATISTICS

For continious variables, independent student's t tests were used. For discrete variables, chi-square tests were used. In both groups, all semi-quantitative D-dimer values were compared with the subsequent one by Wilcoxon matched-pairs signed-ranks test. Then both groups were compared by their corresponding D-dimer values in pairs by Mann-Whitney U test.

RESULTS

Clinical characteristics of groups A and B are listed in Table 1. There were 31 patients in group A and 5 patients in group B.

Age, gender and localization of myocardial infarction were statistically non-significant between the two groups ($p > 0.05$). The time elapsed between the onset of chest pain and the start of streptokinase infusion was 132 ± 24 minutes for group A and 124 ± 13 minutes for group B ($p > 0.05$).

In group A, D-dimer values 2 hours after the streptokinase had a peak and were significantly higher than those obtained before streptokinase ($p < 0.0001$). D-dimer values at the sixth and twentyfourth hours were gradually decreased. In group B, D-dimer values 2 hours after the streptokinase were non-significantly hig-

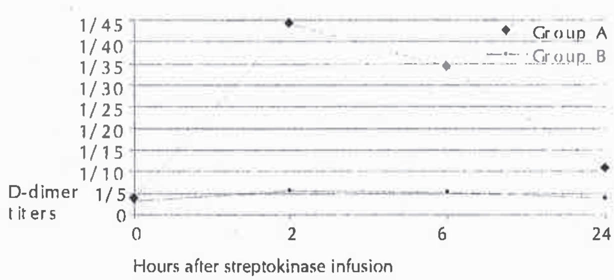

Figure 1. Mean D-dimer titers of groups A and B before and after thrombolytic therapy (Note that D-dimer values are expressed as titers and the range of parametric equivalents are as follows: 1/2 titer ≥ 1 and < 2 mgm/ml, 1/4 titer ≥ 2 and < 4 mgm/ml, 1/8 titer ≥ 4 and < 8 mgm/ml, 1/16 titer ≥ 8 mgm/ml, in fibrinogen equivalent units)

her than those obtained before streptokinase (p = 0.068), and the subsequent values did not show any significant changes. When the corresponding D-dimer values were compared in groups A and B, there was not any significant difference before the streptokinase therapy between the two groups (p = 0.94), 2 hours after the streptokinase, group A had a significantly higher D-dimer value (p = 0.0001), 6 hours after the streptokinase, still group A had a significantly higher D-dimer value (p = 0.0002), 24 hours after the streptokinase, there was not any significant difference in D-dimer values between the two groups (p = 0.16). D-dimer titers in both groups are listed in Table 2 and mean D-dimer titers are shown in Figure 1.

DISCUSSION

The purpose of the current study was to examine whether serially measured serum D-dimer concentrations could serve as a marker of successful thrombolysis in patients with acute myocardial infarction rece-

Table 2. Serially measured D-dimer titers in groups A and B.

	Before Streptokinase	2 hours after Streptokinase	6 hours after Streptokinase	24 hours after Strep Streptokinase
Group A patient 1	1/4	1/32	1/32	1/16
Group A patient 2	1/1	1/32	1/32	1/2
Group A patient 3	1/4	1/32	1/32	1/8
Group A patient 4	1/2	1/32	1/32	1/2
Group A patient 5	1/2	1/16	1/16	1/16
Group A patient 6	1/2	1/64	1/32	1/32
Group A patient 7	0	1/64	1/32	1/8
Group A patient 8	1/1	1/32	1/32	1/1
Group A patient 9	1/2	1/64	1/32	1/2
Group A patient 10	0	1/16	1/16	0
Group A patient 11	1/8	1/64	1/64	1/16
Group A patient 12	0	1/32	1/8	0
Group A patient 13	1/4	1/64	1/64	1/8
Group A patient 14	1/8	1/64	1/32	1/8
Group A patient 15	1/2	1/32	1/32	1/4
Group A patient 16	1/2	1/32	1/16	1/2
Group A patient 17	1/4	1/64	1/64	1/8
Group A patient 18	1/4	1/32	1/16	1/8
Group A patient 19	1/8	1/64	1/32	1/8
Group A patient 20	1/4	1/32	1/64	1/32
Group A patient 21	1/8	1/64	1/64	1/16
Group A patient 22	1/2	1/32	1/32	1/8
Group A patient 23	1/4	1/32	1/16	1/2
Group A patient 24	1/2	1/64	1/32	1/8
Group A patient 25	1/2	1/32	1/32	1/16
Group A patient 26	1/8	1/64	1/32	1/32
Group A patient 27	1/2	1/32	1/16	1/4
Group A patient 28	1/4	1/32	1/64	1/16
Group A patient 29	1/2	1/32	1/16	1/2
Group A patient 30	1/4	1/64	1/16	1/16
Group A patient 31	1/16	1/64	1/64	1/32
Group B patient 1	1/1	1/4	1/2	1/2
Group B patient 2	1/2	1/4	1/4	1/4
Group B patient 3	1/4	1/8	1/4	1/4
Group B patient 4	1/4	1/4	1/8	1/2
Group B patient 5	1/4	1/8	1/8	1/8

iving streptokinase. Our results suggest that serial D-dimer measurements could serve as an indicator of coronary artery patency after thrombolytic therapy. There are other investigators' studies with different protocols and/or end-points. Gulba et al. did not demonstrate any significant differences in D-dimer levels before and at 15, 60 and 120 minutes after two different regimens of thrombolytic therapy in patients with successful thrombolysis compared to the ones with nonsuccessful thrombolysis. However, they have demonstrated a significant increase in thrombin-antithrombin III complexes in patients with nonsuccessful thrombolysis and in those with early reocclusion(9). The study undertaken by Knecht et al. supports the results of our study, however their study population was composed of patients with deep venous thrombosis or pulmonary embolism who received streptokinase(8). Simoons et al. have demonstrated an increase in D-dimer values during the first hours after thrombolytic therapy with rt-PA and few hours before reocclusion(10). The latter investigators have considered D-dimer as an indicator of coagulation system activation. However, their consideration seems controversial if D-dimer values increase both after thrombolytic therapy, where thrombolysis should dominate and before reocclusion where thrombosis dominates.

Other investigators consider D-dimer as a direct marker of ongoing fibrinolysis(11) and it is the primary crosslinked plasmic degradation product of covalently crosslinked fibrin polymers(5). Alexopoulos et al. could not find any difference in D-dimer values of patients with unstable angina and stable angina nor could they find any difference in D-dimer levels in the coronary sinus and peripheral blood(12). Likewise, Lew et al. reported that plasma D-dimer values were infrequently elevated in patients with acute myocardial infarction who were treated conventionally(13). In light of these latter two studies and the current study, we speculate that thrombus already formed in the coronary artery itself does not result in increased levels of plasma D-dimer unless it is degraded by the thrombolytic agents and we think that current study also supports that thought as the baseline plasma D-dimer values were slightly elevated in our patients with acute MI. Nevertheless, others have found consistently increased levels of D-dimer in patients with unstable angina or acute myocardial infarction(14). Arnout et al. could not demonstrate any correlation between patency and plasma D-dimer values in patients with acute myocardial infarction treated with rt-PA but they reported increased levels of D-dimer during and after thrombolysis(15). In our study, although performed with a relatively small number of patients, streptokinase was used and a significant increase in serially determined D-dimer titers was strongly correlated with reperfusion.

In conclusion, this study demonstrates that serially measured D-dimer values could serve as a useful laboratory tool to support reperfusion or to suspect failed thrombolysis.

STUDY LIMITATIONS

A larger group of patients is needed to further support the results of the current study. A quantitative D-dimer assay would surely give more accurate results and parametric statistical analysis could be performed. The timing of coronary angiography could be criticized, it could give more information if serial angiograms were taken, nevertheless even if the timing of culprit coronary artery reperfusion did not coincide with the D-dimer peak, according to our results, a significant increase in D-dimer values can predict coronary artery reperfusion 24 hours after thrombolytic therapy and likewise non-significant increases or no increase can predict a TIMI grade 0 or 1 flow 24 hours after thrombolytic therapy. Although it is concluded that D-dimer could serve as a useful tool to support successful thrombolysis or to suspect failed thrombolysis, it is not the single most sensitive test and as serial angiograms were not taken to fully prove it, we recommend that clinical findings, ECG s and other laboratory data should be interpreted altogether.

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THE CLINICAL AND METABOLIC EFFECTS OF FASTING ON 41 NIDDM PATIENTS DURING THE RAMADAN

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SUMMARY

Objective of the study was to observe the effects of Islamic Ramadan fast in patients with NIDDM. 41 NIDDM cases on a suitable diabetic diet with or without oral hypoglycaemic agents (OHA) were evaluated with respect to the criteria mentioned below two weeks before, during the last week of, and three weeks after the lunar month of Ramadan.

No significant changes occurred in BMI and total cholesterol values. The mean HDL-cholesterol level which was 39±7.7 mg/dl increased to a significantly higher value 43±7.7 mg/dl; p=0.04) after three weeks of fast. It was still significantly higher three weeks after Ramadan (42±7.7 mg/dl; p=0.03). The mean triglyceride level decreased only slightly in Ramadan, but it was significantly lower (p=0.02) three weeks after Ramadan the values, in mg/dl, before, in the last week of, and three weeks after Ramadan being 244±212, 240±204, and 205±158 respectively. The mean haemoglobin A1c increased slightly but significantly during Ramadan (from 7.30±1.6 % to 7.55±1.7 %; p=0.006), but returned to initial levels (7.32±1.7 %) soon after. Ramadan fast can have both favourable and unfavourable effects in NIDDM cases on a suitable diabetic diet with or without OHA.

Key Words; *Ramadan Fast, NIDDM.*

Every year, millions of Muslims fast from dawn until dusk during the lunar month of Ramadan. A Muslim is required to abstain from any oral intake for an average time of 13 hours daily during this month. A considerable number of these people are Type II diabetics and ask their physicians if they can fulfil their holy duties. In the lack of the adequate literature on the subject, the practicing physician could hardly answer this question (1,2,3,6,9). We, therefore, conducted the current study on 41 NIDDM patients during the Ramadan of 1997 to observe the clinical and metabolic effects of fasting.

MATERIALS AND METHODS

Forty-one NIDDM patients who were willing to fast, contrary to our classical general suggestion not to fast during the holy month of Ramadan, were included in the study. Inclusion criteria were being an NIDDM patient on diet alone or diet plus oral hypoglycaemic agents (OHA), experiencing less than one hypoglycaemic episode weekly before the study, and having normal renal and hepatic functions. All the patients gave their informed consent to the study. Altogether 41 patients (30 females, 11 males) were taken into the study. The ages of the patients were 38-70, the mean age being 55. Nine of the patients were on appropriate diabetic diet only. Ten of the patients were on sulfonylureas (SU), one on metformin (MF), and one on acarbose (AC) along with diabetic diet. Twenty of the patients were on combined OHA regimens.

Patients were recruited to the study during the two weeks before Ramadan. Their medical histories were taken with special attention on hypoglycaemic episodes and drug history. The patients were asked to take self notes of any episodes which indicate hypoglycaemia. The patient's body weights and heights were measured, and their body mass index (BMI) were cal-

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culated. Morning blood samples were obtained following a 12-hour fast for blood lipid and haemoglobin A1c (HbA1c) determinations. The daily OHA doses and the caloric intakes of the patients were not changed, but the ones on OHA were advised to take their drugs in two equally split doses with the meals just before dawn and at dusk in Ramadan. Likewise the usual daily caloric intake of each patient was distributed equally to the two customary meals eaten just before dawn and at dusk in Ramadan. This consummation of only two meals lead to daily fasting periods which extended to 13 hours in the Ramadan of 1997. The patients were re evaluated in a similar fashion in the last week of Ramadan following the above related ritualistic feeding regimen, and they were re evaluated again three weeks after the end of Ramadan fast. HbA1c measurements were repeated two months after Ramadan. During the second evaluation in the fourth week of Ramadan, patients interrupted their ritualistic fast for one day so that their plasma lipid levels could be measured following a 12-hour overnight fast to give results comparable with before Ramadan values. The hypoglycaemic episodes noted by each patient were reviewed by an experienced physician in the presence of the patient. The episodes were not biochemically verified.

Total, LDL, and HDL-cholesterol level and triglycerides were measured using a ' Beckman Synchron Clinical System CX-3' autoanalyzer. Haemoglobin A1c levels were measured by agar gel electrophoresis.

t-tests were used to compare paired samples of before, during and after Ramadan data.

RESULTS

Twenty-seven of the patients (66%) had considerably good metabolic control (HbA1c ≤ 7.5%), seven (17%) had moderate (7.5 < HbA1c ≤ 8.5), and seven (17%) had poor metabolic control (HbA1c >8.5) at the beginning of the study.

Number of the symptomatic hypoglycaemic periods, which were not biochemically verified and described as headaches, dizziness, sweating and tremor increased in 8 of the patients (% 19.5) during Ramadan. However, none of the patients experienced severe hypoglycaemia or neuroglycopenic symptoms. Only one of the patients had to break her fast due to one of these episodes. The HbA1c levels of these eight patients are given in table 1 along with the treatment regimes used. One was on diet alone, three were on SU, two were on SU+MF, and two were on a SU+MF+AC combination. Six of these patients were under strict metabolic control with HbA1c levels below 7.7 % (table 1).

No statistically significant change was observed in the mean body weight, BMI, total cholesterol level, and LDL-cholesterol level in the last week of Ramadan and three weeks after Ramadan over the respective means before Ramadan as shown in table 2.The mean HDL-cholesterol level increased significantly during Ramadan and it was still significantly higher three weeks after Ramadan than the before-Ramadan level (Table2). The mean triglyceride level was significantly lower during the fourth week of Ramadan than it was before Ramadan as indicated in table2. The mean

Table 1. Haemoglobin A1c levels and treatment used in eight patients who experienced a higher rate of hypogly caemic episodes Ramadan fast.

Patient	Weekly hypo. Episodes before Rama	Weekly hypo. Episodes During Rama	Treatment received	HbA1c before Ramadan %	HbA1c three Weeks after Ramadan %	HbA1c eight Weeks after Ramadan %
1	1	2	Diet Only	6.6	6.7	6.6
2	1	4	gliclazide	7.5	7.3	7.2
3	1	4	gliclazide	7.6	7.2	7.4
4	1	3	glyburniride	7.6	7.3	7.3
5	1	3	gliclazide, MF*	5.6	5.8	5.9
6	1	9	glyburniride, MF	7.5	7.6	7.5
7	1	3	glyburide, MF, AC†	8.2	8.6	8.7
8	1	8	glipizide, MF, AC	9.5	9.6	9.2

* MF- Metformin - †AC- Acarbose.

Table 2. Body Mass Index(BMI) , Metabolic control and lipid profiles of the patients before, during, and after Ramadan of 1997.

	Weight (kg) BMI (kg/m²)	HbA1c %±s.d.	Total Choles. mg/dl	HDL Choles. mg/dl	LDL Choles. mg/dl	Triglycerides. mg/dl
Before*	74.7±11 30.4±3	7.30±1.6	207±47	39±7.7	115±33	244±212
During†	74.6±11 30.4±4	7.55±1.7 p=0.006 [a]	203±50 p=0.65	43±7.7 p=0.004 [b]	119±36 p=0.40	240±204 p=0.86
After 3w‡	74.9±11 30.5±4	7.32±1.7 p=0.84	204±49 p=0.67	42±7.7 p=0.030 [c]	119±39 p=0.41	205±158 p= 0.02[d]
After 8w§	–	7.27±1.6 p=0.71	–	–	–	–

p values are the results of the comparisons between before and during-after Ramadan data. *-Before Ramadan, †-In the last week of Ramadan, ‡-Three weeks after Ramadan, §-Eight weeks after Ramadan. a and b - comparison between before and during Ramadan values. c and d- comparison between before and after Ramadan values.

HbA1c rose slightly but significantly during Ramadan. Then returned to its initial level three weeks after Ramadan, and stayed more or less the same as the mean value determined two months after Ramadan fast indicates.

DISCUSSION

Fasting in Ramadan can be considered a controlled partial type of fasting, which extends from dawn to sunset. The exact period of time during which a Muslim is supposed to fast differs from 12 to 15 hours, depending on 10 day yearly shifts of the lunar month (Calender of Hijra) and the geographical location of the country. Details about islamic fasting were reported by Sakr (4). The common practice is to eat two meals, one before dawn and one after sunset instead of three. Thus, food and fluid intakes become exclusively nocturnal. A decrease in sleep duration (5) and a reduction in physical activity during the day (6) occurs in Ramadan, as reported. Generally, one would expect limitation of total food intake that may lead to weight loss during the holy month. However, this is not always the case because a greater variety of foods which are rich in refined sugars, proteins, and saturated and unsaturated fats are consumed in large amount in dinners eaten at dusk in most of the Islamic countries. Limited number of studies that investigated the effect of Ramadan fasting on healthy people show that body weight and/or composition do not change when the food consumed is not restricted (7). Weight loss was a result when a hypocaloric diet was planned and strictly supervised by the investigator (8). Its our common experience to see people, in Turkey, several kilograms heavier by the end of every Ramadan. In agreement with the literature (3,9), our 41 NIDDM patients, on a fixed caloric intake did not gain or loose weight during the Ramadan of 1997.

Glycemic control is another important concern of the physician following a NIDDM case during Ramadan fast. Common belief is that Ramadan fasting might precipitate hypoglycaemia in diabetics treated with OHA, and would obviously do so in insulin treated patients. One could hardly argue not to let an insulin treated patient fast in Ramadan. We do not even think that it would be ethical to study this issue. However, we are aware, in our daily practice, that there are insulin treated patients who fast. Severe hypoglycemia or neuroglycopenia is not reported in NIDDM patients on OHA, mostly short acting sulfonylureas (1,2,3,6,9) during, Ramadan. Adjustment in SU doses were done in some of these studies (1). Belkhadir reversed the pattern of glibenclamide doses so that patients took their usual morning dose at sunset and their usual evening dose at dawn (1). We analyzed our patients for hypoglycaemic episodes retrospectively using their self notes. Eight of our patients had increased weekly incidence of symptoms attributable to low blood glucose. Only one of those had to brake her fast. The frequency of hypoglycaemia decreased again in those patients after Ramadan. Six of them were under relatively strict metabolic control with HbA1c levels below 7.7 %. Five of those six were on average doses of different short acting SU and one on diet only. The other two patients were under poor metabolic control and on triple combination (SU+MF+AC) regimens. Metabolic control levels of these patients did not seem to be affected by hypoglycaemic episodes. We believe that it is safe practice not to let patients under strict metabolic control with a SU to fast.

The available data about the effect of Ramadan on lipid profile are inconclusive and contradictory. A favourable lipid profile has been reported in some of the studies done on healthy people (8,10) and NIDDM patients on partial fasting (11,12). Several studies have reported improvement in diabetic dyslipidemia in obese NIDDM cases subjected to supplemented fasting with reduction in triglycerides and VLDL-cholesterol and increase in HDL-cholesterol (11,12). This improvement is mainly explained by a reduction in weight and metabolic control. Laajam reported a significant increase in total cholesterol and no change in triglycerides in a study in which he found no significant change in body weight and glycemic control over the month of Ramadan (9).The three important factors, important for both diabetics and none diabetics, that would determine the final lipid profile during the month of Ramadan could be exogenous dietetic factors, meal frequency, and postprandial lipemia (PPL) in close relation to the first two factors. As stated above, the food consumed during Ramadan is usually of higher fat and carbohydrate content than that consumed during the rest of the year, and alcohol was not consumed.

The common practice is to eat one large meal after sunset and an optional lighter meal before dawn. However, we split the calorie intake equally in the current study. Maislos showed a marked increase in HDL-cholesterol and its main apolipoprotein, apolipoprotein A-1, in Bedouin people in Ramadan (10). We also found a significant increase in HDL-cholesterol's of NIDDM patients eating twice a day which disappeared after this gorging of food ceased after Ramadan.

PPL is an important risk for atherosclerosis that is accentuated with insulin resistance and the presence of NIDDM. It is also known to be an important factor in ethiopatogenesis of diabetic dyslipidemia. Large fatty meals would increase PPL which, inturn, increases the atherogenic small dense HDL and LDL cholesterol particles measurable by some assays.

Combination of the above factors may explain the heterogenous lipid profile reported during Ramadan fasting. We found a desirable lipid profile, despite a slight deterioration in metabolic control, in our diabetics with increased HDL-Cholesterol, slightly decreased triglycerides and unchanged total and LDL-cholesterol levels which we believe is the result of a favourable combination of the above factors.

We found a slight deterioration in HbA1c which returned to the initial values levels early after Ramadan. Laajam reported insignificant increase in the HbA1c levels of his type II diabetics over the month of Ramadan (9). Others reported significant decreases in fructosamine and HbA1c levels (2,3).

The results of this study, suggesting that Ramadan fast can have both favourable and unfavourable effects in NIDDM cases, lead us to conclude that if patients are not on treatment with insulin and if they do not have major complications expected to be critically affected by a slight deterioration of glycemic regulation, NIDDM can only be a relative contraindication to fasting in Ramadan.

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THE EFFECTS OF NEOSTIGMINE ON PULMONARY VASCULAR TONE

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Kürşat Karadayı* • Melek Tulunay******

SUMMARY

The pulmonary vascular responses and changes in haemodynamics upon the administration of neostigmine were studied in patients undergoing elective abdominal tumour surgery. 0.03 mg/kg neostigmine was given at the end of the surgical procedure when the patients started to breathe spontaneously. Haemodynamic parameters and pulmonary vascular responses were measured before and after neostigmine. The results of this study indicate that neostigmine lowers mean arterial blood pressure and prevents the increase of mean pulmonary arterial pressure and pulmonary vascular resistance. We suggest that neostigmine may exert its dilator effect in this pilot study directly or via a complex interaction with muscarinic receptors and/or increasing VİP secretion, or via enhancing NO production. However, the present data is inadequate to support one of the above hypotheses. Therefore, further clinical and experimental studies are required for exact mechanism.

***Key Words**: Neostigmine – pulmonary circulation – drug effects; pulmonary - vascular – resistance – mus carinic-receptors*

A reduction in pulmonary artery pressure (PAP) was observed incidentally in some patients inserted pulmonary artery catheter when neostigmine was given at the end of major abdominal operations to reverse muscle relaxation. It has been established that human pulmonary arteries are provided with a rich cholinergic innervation and muscarinic acetylcholine (Ach) receptors are present in pulmonary vascular bed[1]. However, the functional roles and the distribution of muscarinic receptors in pulmonary vascular bed are not yet clear and to our knowledge, neostigmine has no direct effect on pulmonary arterial pressure and pulmonary vascular resistance. Therefore, we planned this study to confirm our findings by evaluating pulmonary vascular response to neostigmine given intravenously under clinical conditions.

METERIALS AND METHODS

Twenty three patients ASA class II or III scheduled for elective abdominal tumour surgery were studied after institutional review board and informed consent. Patients with chronic obstructive pulmonary disease or symptomatic cardiovascular disease were excluded. No premedication was given.

In addition to standard noninvasive monitorisation (three lead electrocardiograph, pulse oximetry and automatic blood pressure device), all patients were monitored with radial artery and pulmonary artery catheter (Thermodilution catheter, 7F, Abbott Critical Care systems, Abbott Laboratories/Hospital Products Division, North Chicago, Illinois 60064, USA).

All patients received a standardised general anaesthetic technique consisting of intravenous (iv) sodium thiopental (5-7 mg/kg), iv fentanyl (1mg/kg) and atracurium besylate (0.7 mg/kg) for induction. Anaesthesia was then maintained with isoflurane (1-1.5 %) and nitrous oxide (50%).

The patients were allowed to breathe spontaneously after fascia was sutured at the end of the surgical procedure.As soon as they started to breathe, patients were randomly allocated into two groups. First group (n=14) received iv 0.03 mg/kg neostigmine and the second group (n=9) received iv 3 ml saline.

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Table 1. Patients characteristics, duration of anaesthesia and surgery. Values are expressed as mean±SEM. Abbreviations: F: female; M: male.

	GROUP I (Neostigmine)	GROUP II (Saline)
Age (year)	56.1 ± 3.6	50.5 ± 2.6
Weight (kg)	65.4 ± 2.7	63.1 ± 4.2
Sex (F/M)	7/7	5/4
Duration of anesthesia (min)	202.8 ± 25.5	175.6 ± 14.0
Duration of surgery (min)	166.5 ± 25.5	138.0 ± 14.0

The investigators were blinded as to whether neostigmine or normal saline was being administered. The respiration of the patients were supported manually provided that normal haemoglobin saturation (SaO_2) was achieved. Haemodynamic measurements were obtained before induction of anaesthesia (baseline: B), 15 minutes after endotracheal intubation (EI 15), just after spontaneous breathing (SB) has started, and 2, 5, 10, 15, 20 and 30 minutes after study agents were given (SA2, SA5, SA10, SA15, SA20 and SA30). Haemodynamic measurements included heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was measured with thermodilution technique (COM II, Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine CA 92714 - 5686 USA), using 5 successive injections of cold (<10 C°) saline and a closed system (Model 93-600 Baxter co-set closed injectate delivery system, Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine CA 92714 - 5696 USA). Systemic (SVR) and pulmonary vascular resistance (PVR) were calculated by using standard formulas (Appendix).

Data were expressed as mean ± SEM. Statistical analysis of the data was carried out using Kruskal - Wallis one way variance analysis, Friedman two way variance analysis, Mann Whitney U test and Wilcoxon signed rank test where appropriate. $P<0.05$ was considered as significant.

RESULTS

The patients in both groups were similar with respect to age, sex, weight, the duration of anaesthesia and surgery (Table1). Baseline values for all haemodynamic measurements were not different between the groups, and there were no significant changes in HR, CVP, PCWP and CO at all measurement time intervals (Table 2).

Mean arterial pressure values were found significantly lower in neostigmine group in comparison to control group at 5, 10, 15, 20 and 30 minutes after study agents were given (Figure 1). MAP values were decreased significantly from 5 to 30 minutes after administration of study agent in neostigmine group ($p<0.05$) whereas no alteration was detected in the control group simultaneously.

Mean PAP and PVR values were significantly higher in control group at 5, 10, 15 and 20 minutes after study agents were given compared to neostigmine group (Figure 2). While MPAP and PVR values were increased from 5 minutes to 20 minutes after administration of study agent in the control group, no significant change was detected in neostigmine group.

DISCUSSION

In this clinical pilot study, the use of neostigmine produced a decrease in MAP and prevented the increase of MPAP and PVR seen in the control group after spontaneous breathing has resumed.

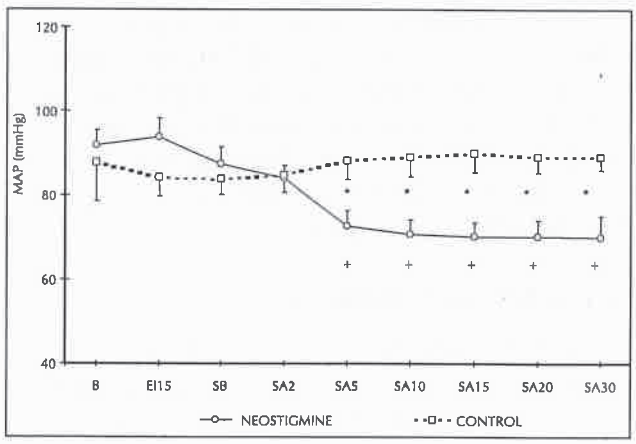

Figure 1: Mean arterial pressures. *: $p<0.001$ vs control group. +: $p<0.001$ vs SB in neostigmine group. Abbreviations: MAP: mean arterial pressure; B: baseline; EI15: 15 minutes after endotracheal intubation; SB: spontaneous breathing; SA2, SA5, SA10, SA15, SA20, SA30: 2, 5, 10, 15, 20 and 30 minutes after study agents were given.

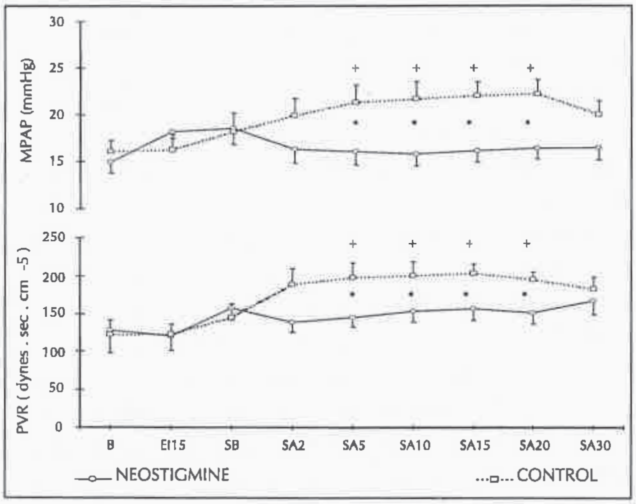

Figure 2: Mean pulmonary artery pressure and pulmonary vascular resistance. * : p<0.05 vs control group; + : p<0.05 vs SB in control group. Abbreviations: B: baseline; EI15: 15 minutes after endotracheal intubation; SB: spontaneous breathing; SA2, SA5, SA10, SA15, SA20, SA30: 2, 5, 10, 15, 20 and 30 minutes after study agents were given; MPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance.

Though it has no effect on HR, CO and SVR, a decrease in MAP was observed in neostigmine group. The decrease in MAP after neostigmine probably results from the combination of the non-significant changes in HR, CO and SVR. The reason that the changes in SVR and HR did not reach statistical significance might be low doses and slow rate of administration of neostigmine.

The cardiovascular actions of neostigmine are complex, since they reflect both ganglionic and post-ganglionic effects of accumulated Ach on the heart and blood vessels. The predominant effect of neostigmine is bradycardia and vasodilatation. It also decreases blood pressure at higher doses with its effects on medullary vasomotor center of the CNS[2].

The pulmonary circulation is known to differ widely from the systemic circulation in its response to anticholinesterase agents[2]. As concerns the dilator effect of neostigmine in the pulmonary vascular bed in the present study, different mechanisms might be responsible. The first hypothesis is that its effects are mediated by muscarinic receptors. However, there are conflicting reports about the functions of muscarinic receptors on the regulation of pulmonary vascular tone and which receptor subtypes mediate Ach's pulmonary vasoactive effects have not yet been determined extensively[3,4,5]. Besides, earlier investigations have established that the level of tone in the pulmonary vasculature is a critical factor in determining the response to Ach[6,7]. Therefore, we suggest that muscarinic receptors mediating vasodilatation in the pulmonary artery is not the only explanation of neostigmine's dilator effect.

The second hypothesis that the mechanism of action by which neostigmine exerts its pulmonary vascular effect is its direct effect on pulmonary vasculature or via activation of other mediators. It is reported that neostigmine increases the secretion of endogenous vasoactive intestinal peptide (VIP) and acetylcholine[8]. VIP exerts its function via receptor mediated systems activating signal transduction pathway including cAMP[9,10,11] and dilates the vessel smooth muscle. It can be hypothesised that the depressor effect of neostigmine in pulmonary vascular bed is due to its indirect mechanism of action.

Table 2. Measured and calculated haemodynamic parameters for both groups. Values are expressed as mean±SEM. Abbreviations: N: group I (neostigmine group); C: group II (control group); B: baseline; EI15: 15 minutes after endotracheal intubation; SB: spontaneous breathing; SA2, SA5, SA10, SA15, SA20, SA30: 2, 5, 10, 15, 20 and 30 minutes after study agents were given; CO: cardiac output; HR: heart rate; SVR: systemic vascular resistance; PCWP: pulmonary capillary wedge pressure.

	GROUPS		B	EI15	SB	SA2	SA5
CO	N	4,6±1,5	4,8±1,7	4,8±1,3	4,6±1,5	4,4±1,4	4,3±1,4
(L/min)	C	5,0±0,9	4,7±1,0	5,0±1,1	4,8±0,8	5,1±1,0	5,2±1,1
HR	N	90,7±5,7	90,4±4,5	80,8±4,7	90,4±5,4	85,4±5,9	84,9±5,6
(beat/min)	C	82,3±10,0	86,3±7,7	80,6±5,7	84,8±5,8	86,1±5,5	88,6±5,1
SVR	N	1696,8±188,3	1635,3±184,1	1411,9±88,1	1482,1±141,1	1324,5±127,8	1365,3±149,1
(dynes.sec. cm^{-5})	C	1347,9±194,0	1373,8±89,5	1274,4±85,8	1317,2±70,4	1308,8±79,0	1310,4±71,0
PCWP	N	8,7±1,5	11,6±1,3	9,57±1,2	8,6±1,1	8,4±1,1	8,1±1,0
(dynes.sec. cm^{-5})	C	8,8±0,6	9,0±1,1	9,11±1,0	8,6±0,8	8,8±0,9	8,8±0,8

Most investigations have indicated that Ach decreases PAP, pulmonary arterial resistance, total PVR or all three in the human pulmonary circulation. This effect can be potentiated by neostigmine, which inhibits the breakage of Ach[2]. Endothelium-derived nitric oxide (NO) may also be an important mediator of pulmonary vascular resistance. In healthy conscious adults, local NO production is responsive to receptor-mediated stimulation leading to further pulmonary vasodilatation and NO production can be stimulated with Ach[3,12,13]. As a result, neostigmine may potentiate the vasodilator effect of NO by enhancing the level of Ach.

There are conflicting reports indicating a pressor or a depressor effect of Ach in the pulmonary circulation of laboratory animals in a wide range of doses. Its actions on pulmonary circulation appear to be species specific. For example, acetylcholine causes pulmonary vasoconstriction in the rabbit[14], dog[15] and pig[16] but induces pulmonary vasodilatation in the calves[17] and cats[7]. The variability in the results of these studies might be due to experimental preparation, dose of acetylcholine, and initial level of tone in pulmonary vascular bed. Hyman et al.[6] reported that vasodilator response to Ach under high tone conditions are mediated by muscarinic receptors that are neither M_1 nor M_2 low affinity muscarinic type receptor in feline pulmonary vascular bed. The mechanism by which elevated tone changed the response to acetylcholine is not certain and is probably too complex to mechanistically describe by using only physiological means. The clinical significance of vascular status may take an important place in evaluating the pulmonary vasculature. Unfortunately, this phenomenon was not undertaken into consideration in the present investigation.

Although the present findings are inadequate to support one of the above hypotheses, it is important to recognise that the overall effects of neostigmine in the pulmonary circulation must be evaluated in association with those effects in the systemic circulation. Carefully controlled investigations including study groups with atropine to block muscarinic receptors, with VIP antiserum[11] (or VIP receptor binding inhibitor) to block the effects of VIP and with a specific inhibitor of NO NG-Monomethyl-L-arginine (L-NMMA)[12] to block the production of NO should be planned to explain the mechanism of action by which neostigmine exerts its pulmonary vascular effect. Additionally, arterial blood gases and end-tidal CO_2 should be monitorized to exclude the other possible causes such as hypercapnia and acidosis that can alter the response to neostigmine in pulmonary vascular bed. Tidal volume and airway pressure should also be standardised to minimize the limitations in the present study.

Regardless of its mechanism of action, it can be concluded from the present data that neostigmine decreases MAP and prevents the increase of MPAP and PVR. Neostigmine exerts its pulmonary vascular effects via a complex interaction with muscarinic receptors and/or increasing VIP secretion, or via enhancing NO production by increasing Ach concentration. However, we believe that further clinical and experimental studies are required to demonstrate the precise effects of neostigmine in pulmonary vascular bed.

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APPENDIX

MAP = DAP + ((SAP-DAP)/3)

MPAP= DPAP + ((SPAP-DPAP)/3)

SVR= ((MAP-CVP)*80)/CO

PVR= ((MPAP-PCWP)*80)/CO

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THE RANDOMIZED COMPARISON OF CEFOPERAZONE-SULBACTAM WITH IMIPENEM-CILASTATIN IN THE TREATMENT OF INTRAABDOMINAL INFECTIONS*

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Mustafa Kerek***

SUMMARY

Peritonitis is a polimicrobial disease. Both aerobes and anaerobes can be cultured from the infected site. Therefore, the antibiotic agent should be carefully selected. Nowadays monotherapeutic agents are safely and effectively used in the treatment of intra-abdominal infections. The present study was carried out on the patients who were surgically treated for intra-abdominal infections. The patients who died within the postoperative 24 hours, who were younger than 18 years, who received immunosupressive treatment and who had allergic reactions during antibiotherapy were excluded from the study. A total of 50 patient were studied and two equally numbered patient groups were formed. One group (Group A) received intravenous 2 g/24 hours imipenem-cilastatin and the other group (Group B) received intravenous 2 g/24 hours cefoperazone-sulbactam. The mean ages of patients were 46.1 and 50.8 years for groups A and B, respectively. The patients were evaluated for APACHE II scores at the admission and after the antibiotherapy diagnoses cultures from the secondary peritonitis sites were peroperatively obtained. The culture results mean antibiotic usage durations and treatment results were evaluated. Mean APACHE II score at the admission were 14.3 and 12.7 for groups A and B respectively. Mean intensive care unit stay was 6 days for group A and 8 days for group B. In group A 17 patients (68%) had recovery and 6 patients (24%) had resistance to antibiotic treatment. In group B, 14 patients (56%) had recovery and 8 patients (32%) had resistance to antibiotics. Staphylococcus aureus and Escherichia coli were the most frequently isolated microorganisms. The mean APACHE II scores after the treatment were 9.6 and 8.5 for groups A and B respectively. Two patients (8%) in group A and 3 patients (12%) in group B had postoperative intra-abdominal abscess and all the patients underwent percutaneus drainage in the guidance of computerized tomography. Five patients (20%) in each group had wound infections. Two patients in group A died of myocardial infarction and septic shock in the early postoperative period. As a result of this study, for the patients with high APACHE II scores, imipenem-cilastatin and cefoperazone-sulbactam can be used as effectively and therapeutic agents in the treatment of intra-abdominal infections. We could not demonstrate any superiority of one combination over the other. However, treatment costs can be a factor for the selection of antibiotics.

Key Words: *Antibiotherapy, Intra-abdominal infections.*

Intra-abdominal infections are caused by endogenous gastrointestinal micro-organisms after their leakage to the peritoneal cavity. These infections may appear as clinical forms of septicemia and intra-abdominal abscess formation secondary to peritonitis. Intra-abdominal infections are still one of the most controversial issues of general surgery intensive care units (1). At the beginning of the 20th century, the mortality rate of the intra-abdominal infections was 90% and it was decreased to 70% within the first years of antibiotic therapy era. Despite all the technological advances, today mortality rate is still between 0% and 60%. Systemic antibiotic therapy aims are to eradicate the residuals of intra-abdominal infection and to prevent the systemic extension of bacteria. Therefore, antibiotic therapy was started in all patients suspected of intra-abdominal infection (2). However, choosing antibiotics by the isolation of causative organisms in culture studies is the ideal way of treatment. If bacteriological study is not possible or patients general conditions are not suitable to wait for the results, empirical antibiotic therapy has to be started (1). Because these infections often have polymicrobial nature and the coliform and anaerobes are causative microorganisms, broad-spectrum antibiotics are the treatment of cohice. Monotherapy or combination therapy may be given (1,3). But it is reported that there is no differences between monotherapy and combination therapies (4,5). A regimen effective against endogenous anaerobe Bacteroides and coliform organisms may be satisfactory. For this purpose different combinations have been applied. There are many studies comparing the efficacy and advantages of these combinations. We compared the monotherapy regimens of Imipenem-Cilastatin and Cefoperazone-Sulbactam in the treatment of intra-abdominal infections.

* This study was orally presented in the 7th European Congress of Surgery in Athens on June 3-7,1997
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Table 1. Characteristics of patients

	Group A	Group B
Female/male	5/20	3/22
Mean age	46.1	50.8
Total no. of patients	25	25

MATERIALS AND METHOD

This prospective study was planned for patients undergoing surgical treatment because of the intra-abdominal infection. No difference was present between the two groups in sense of conditions of the patients. It was conducted in General Surgery Department of Erciyes University Medical School. The study had been approved by the appropriate committees of the surgical department. The patients were randomized into two treatment groups of 25 on imipenem/cilastatin (group A) and 25 on cefoperazone-sulbactam (group B). Imipenem/cilastatin was intravenously administered at 500 mg every six hours and cefoperazone/sulbactam was intravenously administered at 1 gevery twelve hours.

Antibiotic therapy was before the determination of the causative organism. Cultures were taken from the cavity during the surgical intervention. Bacteriological work up and antibiograms were performed. The patients on whom the treatment switched after antibiogram results were excluded from the study. Additionally, the patients who died during the first 24 hours, who were younger than 18 years, who had immunosupressive therapy or who were allergic to the antibiotics used in the study were excluded. The following parameters were evaluated in the groups; effect of antibiotics, cure or eradication, resistance, insufficiency, and success.

The majority of the patients were monitored in the Instensive Care Unit (ICU). The two groups were compared in respect of APACHE II scores, number of days in the ICU and hospitalization, ICU support, complications, ratios of wound infection, criteria of antibiotic therapy cessation, response to treatment, mortality rate and the cost of the treatment during the admission and at the end of the study. Student t-test was used for the comparison of the groups.

RESULTS

There were 25 patients in each group. The mean ages were 46.1 in the imipenem/cilastatin group and 50.8 in cefoperazone/sulbactam group (Table 1). In both groups the reasons for the secondary peritonitis were ulcer perforation and perforated appendicitis (Table 2). The APACHE II scores during the admission were 14.3 in group A and 12.7 in group B. The secondary peritonitis due to ulcer perforation and acute appendicitis was the main reason in the majority of cases. The mean ICU stays were 6 days in group A and 8 in days in group B. Seventeen patients (68%) in group A were cured and 6 patients (24%) showed resistance whereas in group B 14 patients (56 %) were cured and 8 patients (32%) showed resistance. Among the growing micro-organisms, Staphylococcus aureus and Escherichia coli were the most frequently seen. The mean APACHAE II scores of the patients were 9.6 in group A and 8.5 in group B. Two patients (8%) in group A and 3 patients (12%) in group B developed intra-abdominal abscess post-operatively. All of the abscesses were drained in the presence of Computerized Tomogarphy (CT). Wound infection was seen in only 5 patients (20%) in both groups. Two patients in group A were died because of Myocard Infarctus (MI) and septic shock in the early post-operative period. The mean ICU stays were 6 days for group A and 8 days for group B. In group A, 17 out of 25 patients were cured, 6 out of 25 developed resistance, 2 out of 25 developed intra-abdominal abscess. These abscesses were drained percutaneously in the presence of CT. Wound infection developed in only 5 patients (20%) in both groups and open wound treatment was done. Two patients were died in group A; one because of MI, one because of septic shock. This group was included in "success group" in sense of treatment. No patient was present in insufficiency group.

Table 2. Factors causing intra-abdominal infection in the patients

Diagnosis	Group A		Group B	
	n	%	n	%
Ulcer perforation	7	28	9	36
Perforated appendicitis	11	44	8	32
Anastomosis leakage	2	8	2	8
Gallbladder empyema	1	4	2	8
Acute suppurative cholangitis	1	4	1	4
Pancreas abscess	1	4	1	4
Acute pancreatitis	2	8	1	4
Liver abscess	–	–	1	4
Total	25	100	25	100

DISCUSSION

Secondary bacterial peritonitis is one of the most important problems of general surgery. One of every three

Table 3. Isolated micro-organisms and therapy results

Organism	Eradicated		Resistance		Failure	
	Group A(n)	Group B(n)	Group A(n)	Group B(n)	Group A(n)	Group B(n)
Escherichia coli	6/10	5/7	3/10	1/7	1/10	1/7
Staphylococcus aureus	1/3	2/7	1/3	3/7	1/3	2/7
Pseudomonas aeruginosa	2/2	1/1	–	–	–	–
Bacteroides fragilis	2/2	1/1	–	–	–	–
Nonhemolytic streptococcus	2/2	1/1	–	–	–	–

Table 4. Therapy results according to APACHE II scores

	>10						<10					
	Success		Resistance		Not satisfactory		Success		Resistance		Not satisfactory	
	n	%	n	%	n	%	n	%	n	%	n	%
Group A(n=25)	2/6	33.3	2/6	33.3	2/6	33.3	15/19	78.9	3/19	15.8	1/19	5.3
Group B(n=25)	2/8	25	3/8	37.5	2/8	25	12/17	70.5	5/17	29.4	1/17	5.8
p	>0.05		>0.05		>0.05		>0.05		<0.05		>0.05	

patients with severe secondary peritonitis dies despite advanced diagnostically tools, effective antibiotics, modern ICU and aggressive surgical treatment. It is claimed that the factors related to sepsis and the lack of effective sepsis management may play a role in mortality. Intra-abdominal infections are caused by endogenous gastrointestinal microorganisms after their leakage to the peritoneal cavity either due to spontaneous gastrointestinal perforation or as a result of complicated abdominal surgery. Perforated appendicitis and ulcer perforations are the main reasons in our series (Table 2). In many other studies, perforated acute appendicitis and peptic ulcer perforations are also the main reasons for intra-abdominal infections (6).

Today, there are three principles in the treatment of intra-abdominal infections: The eradication of septic focus, antibiotic therapy and intensive care support (6). It should be remembered that none of these methods are satisfactory for an effective treatment. Three methods have to be combined for a successful treatment. Antibiotics have a secondary but indispensable role in the treatment of intra-abdominal infections. Secondary peritonitis is a polymicrobial disease. Both aerobic and anaerobic organisms may grow in bacteriological cultures (6,7). Therefore, it is essential to choose an appropriate antibiotic. However, in relaparotomies performed due to diffuse peritonitis, it has been shown that there may be no bacteria growth during the initial period (7). This fact may be a factor that supports to initiate the therapy on an empirical basis. In addition, in our study, there were no bacterial growth in both groups of 25 patients each. E coli was the most frequent organism in both groups (10 cultures in group A and 7 cultures in group B). The most often encountered anaerobic organism, Bacteroides fragilis was identified in 2 cultures in group A and in one culture in group B.

In the treatment of intra-abdominal infections, mono therapy is safe and effective (2, 8). Although triple regimens were preferred in 1970s, today dual or monotherapies are current treatment (3). The identification and type of the pathogenic organism become important for mono therapy. Numerous single-agent and combination-drug regimens have been efficacious in clinical trials, based on coverage of Escherichia coli and Bacteroides species, the predominant pathogens isolated (9). Care should be taken of monotherapy if there are other pathogens besides anaerobes and enterococci present in the peritoneal cavity. Beta-lactam antibiotics may not be satisfactory in mono therapy if there is obligatory anaerobes in peritoneal cavity (6, 10, 11). Combination with metronidazol is recommended in such cases (6). Broad spectrum antibiotics and antibiotics with low resistance potential are preferred options in monotherapy. Carbapenem and third generation cephalosporins are in this category (11).

The multifactorial abdominal surgical infections, their severity and response to therapy are difficult to assess. The patients' physiological parameters and the changes in these parameters during therapy may be helpful. Some scoring systems may be used for this purpose. One of these scoring systems is APACHE II scoring system (6, 12, 13). We used APACHE II scoring systems during the assessments on admission and during the response to therapy. The number of patients with APACHE II scores<10 on admission in group A and B were 19 and 17, respectively. The number of patients with APACHE II scores>10 on admission was 6 and 8 in group A and B, respectively. Response to therapy was higher in patients with APACHE II scores<10. There was a reduction of APACHE II scores at the end of treatment in both groups (group A 9.6 and group B 8.5). There were no differences between APACHE II scores in respect of effectiveness in both groups.

There are different opinions concerning the duration of antibiotic therapy in intra-abdominal infections. Although certain parameters have to be considered in determining the duration, generally accepted duration of therapy is 5-7 days (14). If evidence of intra-abdominal infection in peritoneal cavity is found during operation, the reported duration of antibiotic therapy is 5 days (15). If it is decided to start empirical therapy, an antibiotic effective against facultative aerobic and anaerobic bacteria should be given. The cessation criteria are absence of fever, normalization of WBC count, and normal GI motility. However, there are controversies about these criteria. For instance, it is found that the fever has been normalized in patients after the antibiotic has been stopped despite fever (16). The same opinion is true for leucocystosis. In our study, the number of patients with fever is 10 in group A and 8 in group B. The antibiotic was also stopped in 3 patients in group A and in 5 patient in group B although their WBC counts were not normal.

Both Cefoperazone-Sulbactam and Imipenem-Cilastatin can be used as an effective regimen in severe intra-abdominal infections (17). However, with these monotherapies, one has to be cautious against nosocomial infections

Table 5. Cessation criteria, complications, ICU and hospital stays

Finding	Group A		Group B	
	n.	%	n	%
Antibiotic cessation criteria				
No fever during monitorization	15/25	60	17/25	68
Normal WBC count	22/25	88	20/25	80
Normal gastrointestinal functions				
No. of patients	22/25	88	23/25	92
Duration (mean days)	3.8		3.3	
Complication	8/25	32	7/25	28
Wound infection	5	62..5	5	71.4
Intra-abdominal abscess	3	37..5	2	28.6
ICU stays				
No. of patients	18/25	72	11/25	44
Duration (mean days)	6		8	
Hospital stays (mean days)	14		11	

and resistance (18). If nosocomial infection and resistance develop during follow up period, monotherapy should be combined with another antibiotic and the regimen should be changed accordingly. In our study period, resistance was developed in a total of 14 patients (in 6 patients in group A and in 8 patients in group B). There was no significant difference between two groups in resistance ($p>0.05$).

In secondary bacterial peritonitis, it is necessary to give intensive care support (19). Total parenteral nutritional support was given to 28 patients in our series (15 patients in group A and 13 patients in group B). Seventeen patients (68%) in group A were cured and 6 patients (24%) showed resistance whereas in group B 14 patients (56%) were cured and 8 patients (32%) showed resistance. Superinfection developed in two patients in each group. Two of these patients had diabetes mellitus and two had hemotological disorders.

Table 6. ICU supports to the patients

Support	Group A		Group B	
	n	%	n	%
Central venous catheter	18/25	72	17/25	68
Total parenteral nutrition	15/25	60	13/25	50
Ventilator support	3/25	12	1/25	4
Heparin	11/25	44	7/25	28

In conclusion, antibiotics play an important role in the treatment of surgical infections. The ideal method in the management of secondary peritonitis is to perform bacteriological work up from peritoneal cavity and to give apporpriate antibiotic accordingly. However, this ideal treatment may not be possible in every patient. Imipenem/cilastatin or cefoperazone/sulbactam is safe monotherapies for patients with high APACHE II scores in intra-abdominal infections. The cilinical efficacy and safety of both antibiotics in secondary peritonitis were compared in our study. Imipenem/cilastatin was as efficacious as cefoperazone/sulbactam in this setting and both drugs were safe. Therapy costs and the lack of allergic sensitivity may be determining factors in predilection.

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TYMPANOPLASTY, VENTILATION TUBES AND MASTOIDECTOMY IN THE TREATMENT OF ADHESIVE OTITIS

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SUMMARY

Adhesive otitis is a relative common sequela of chronic otitis media with effusion. Mastoidectomy for the treatment of adhesive otitis (AO) is controversial. This study includes 22 ears from 20 patients who were treated with mastoidectomy and tympanoplasty with tympanostomy tube insertions. Ears with cholesteatoma and purulent drainage were excluded. All the patients were accepted as Grade 4 according to the classification of Sade. Postoperative air-bone gap levels revealed no difference between patients in our study in comparison to patients from other studies who underwent only tympanoplasty and placement of ventilation tubes without mastoidectomy. Mastoidectomy is needed only when retraction pockets can not be approached by external auditory canal.

Key Words: *Adhesive otitis, Mastoidectomy, Tympanostomy tubes*

Adhesive otitis (AO) is a non-purulent form of chronic otitis which usually develops as a sequela of otitis media with effusion or recurrent acute otitis media. Eustachian tube dysfunction is also an other important factor, which may result in adhesive otitis (1). Lysis of the fibrous part of the tympanic membrane because of the continuous negative pressure and infections forms the basis of the pathology(2). The elasticity of the tympanic membrane is disturbed with lysis of the fibrous part, which results in adhesion to the adjacent structures because of retraction towards the middle ear.

The terms of retraction pocket (RP), atelectasis and adhesive otitis are used to illustrate the state of retraction of the tympanic membrane (TM). RP is the collapse of the pars flaccida or pars tensa parts of the TM forming a narrow or wide opening towards the attic or middle ear structures(3). Atelectasis is the displacement of the drum towards the promontorium(4). However, AO is the advanced stage in which TM adheres to the middle ear structures. Since there is a conductive type hearing loss and potential risk of development of cholesteatoma, AO should be treated without delay.

Up to now, a consensus has not been achieved in the treatment of AO.For the early atelectatic stages myringotomy with long lasting ventilation tube (VT) insertion are preferred. Mastoidectomy, excision of RP, repairing the defect in ossicular chain, grafting and VT placement are the treatment choices in advanced cases.

The aim of this study is to discuss the results of mastoidectomy, tympanoplasty and VT insertion which had been performed simultaneously to the 22 ears with AO.

MATERIALS AND METHODS

The present study included 22 ears from 20 patients who underwent mastoidectomy, tympanoplasty and tympanostomy tube insertions, between January 1993- June 1996. Of the 20 patients, 6 (30 %) were female and 14 (70 %) were male with a mean of 15.3 years of age (range 7-39). The history revealed recurrent acute otitis media in 12 of the patients (60 %), previous VT application in 9 (45 %) and tonsillectomy with adenoidectomy in 5 cases (25 %). Most of the patients (75%) complained of hearing loss. In all patients physical examination revealed adhesion of drum to the middle ear structures. Ears with cholesteatoma and purulent drainage were excluded. All of the patients were accepted as Grade 4 according to the classifica-

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tion of Sade(5). After postauricular incision was made and a piece of temporalis fascia was harvested, an intact canal wall mastoidectomy was performed. Atrophic parts of the drum as well as the parts which made adhesions to the ossicular chain and promontory were taken out with the pathological tissues of the middle ear. If a defect in the ossicular chain was present conduction was established by incus interposition. In five ears it was difficult to separate the adhesive membrane from middle ear mucosa. In those cases removal of the mucosa had to be performed and a thin silastic sheet was placed. Gelfoam was placed into the middle ear up to the level of annulus. VT was inserted to the anterosuperior quadrant of previously harvested temporalis fascia (Figure 1). Grafting was performed by using underlay technique (Figure 2). Modified Goode T-tubes with a length of 4.75 mm and inner diameter of 1.32 mm were used. Patients were followed-up for a mean period of 20.8 months (6-45 months).

The graft and VTs were inspected and audiologic examinations were performed at 3-months intervals.

RESULTS

Of the 22 ears in this study, in the frequencies of 500-1000-2000 Hz, the mean air-bone gap was 26 dB preoperatively. Tympanometric examinations revealed middle ear pressures with a mean of -314 mm H_2O (140-400). Preoperative radiodiagnostic evaluations revealed decrease in mastoid pneumatization in different degrees in all of patients. RP was detected during operation in 10 of 22 ears (45.5 %). Findings at surgery for adhesive otitis are presented in Table 1. In four patients mucoid type secretion was aspirated from antrum. Incus interposition between the stapes and the malleus was performed in 7 ears with erosion of long process of the incus in order to provide conduction. In two of these ears erosion of the head and crura of the stapes was also present.

The malleus handle was cut off in 3 ears in which the malleus had been in contact with the promontory. In five ears silastic was applied to the promontory because of formation of a defect in the middle ear mucosa. Cartilage harvested from the tragus was used to support the external ear canal in 3 ears. One of the 22 ears underwent only mastoidectomy and VT insertion as a result of drum elevation because of nitrous oxide.

Table 1. Pathology found in surgery for adhesive ears

Pathology	No. of ears	% of Total
Erosion of long process of the incus	7	31.8
Erosion of the stapes	2	9.0
Obstruction of the aditus	5	22.7
Thickened mucosa of mastoid air cells	3	13.6
Thickened middle ear mucosa	3	13.6

Figure 1. Modified Goode T-tubes were used for the ventilation of middle ear.

Audiologic examinations performed postoperatively revealed the mean air-bone gap to be 11 dB. Average bone conduction threshold was found to be 15.8 dB in 4000 Hz frequency. The comparison of preoperative and postoperative air-bone gap is shown in Table 2.

Postoperative air-bone gap examinations revealed a gain of 31-40 dB in 2 (9.1%), 21-30 dB in 4 (18.3 %), 11-20 dB in 8 (36.3 %) and 0-10 dB in 8 (36.3 %) ears.

One ear with no change in air-bone gap, underwent revision surgery. The incus which had been interpositioned was seen to be displaced and after replacement of the incus, 18 months postoperatively, the graft was found to be normal, tube was open and a gain of 15 dB was obtained. Postoperatively air-bone gap levels of 22 ears were evaluated and were detected to be under 20 dB in 17 (Table 3). The comparison of preoperative and postoperative air conduction thresholds are presented in Figure 3.

Of the 22 ears, ventilation tubes in 4 were extruded late after the operation. Ventilation tubes were reinserted to ears in which the tubes had been extruded in fourth and fifth months respectively because of the tendency of the drums towards retraction. VTs were not reinserted to 2 ears in which the tubes were extruded in late postoperative period (24^{th} and 30^{th} months). During the follow-up no retraction as well as no change in gain of hearing was observed.

Table 2. Preoperative and postoperative comparison of airbone gap levels

Air-bone gap	Preoperative Number of ears	%	Postoperative Number of ears	%
0-10 dB	3	13.6	11	50.0
11-20 dB	5	22.7	6	27.2
21-30 dB	5	22.7	4	18.1
31-40 dB	6	27.2	1	4.5
41-50 dB	2	9.0	0	0
50 + dB	1	4.5	0	0

DISCUSSION

The treatment of AO is surgery. However, the surgical method is debatable.

AO is usually seen in children and young adults. In the development of the disease improper treatment of the acute and secretory otitis media is the most important etiological factor, accepted by most of the authors(1,2,6,7). In our series the rate is calculated to be 54.5% (12 ears). Prevention of the disease may be achieved by treating the acute and secretory otitis media without delay. Eustachian tube dysfunction is also another important factor in the development of AO(8).

There is no agreement in the classification of the disease(4,9,10,11). There are different classifications suggested by Sirala(11), Sade and Berco(5), Akyildiz et al(9), and Charachon et al(10). Sade and Berco(5), in 1976, classified atelectasis into 5 grades.

Grade 1-Slight retraction of the tympanic membrane.

Grade 2-The TM is touching the incus or stapes.

Figure 2. Grafting was performed by using underlay technique.

Grade 3-The TM is inclined on the promontory.

Grade 4-The TM adheres to the promontory.

Grade 5-The TM is adherent to the promontory and is also perforated.

According to this classification, of our cases 21 ears were Grade 4 and 1 ear was Grade 3.

Sirala(11), is one of those who first performed tympanoplasty and mastoidectomy together in adhesive otitis. In 43 ears with AO which underwent surgery he reported a 50% success rate. Özgirgin et al(2), reported a rate of 58 % success in improvement of hearing in 143 atelectatic ears which had undergone 8 different surgical operations related with the degree of atelectasis.

Improvement in healing and prevention of the retraction of the fascia graft was obtained in the operated ears. In 17 of these 22 ears (77.2 %) air bone gap was found to be under 20 dB. This result is consistent with the studies of Tos(1) and Paparella(6) in which they reported a success rate of 61 % and 80 % under 15 dB and 20 dB respectively. Both of the authors performed tympanoplasty without mastoidectomy(1,6).

In AO the most common localization of ossicular chain destruction is the long process of the incus. Sade and Berco(5) has published this rate to be 58 %. In our study it is 31.8 %. In these situations, conduction was established by the interposition of incus between the stapes and the malleus. In two of the ears in which there had been a defect in head and crura of stapes, the incus was placed between the malleus and the footplate.

In AO, a frequent cause of revision surgery is the redevelopment of retraction and extrusion of the VT(6). Conductive type hearing loss, perforation in the graft and cholesteatoma formation are among the other reasons. A second operation was needed in 4 of 22 ears

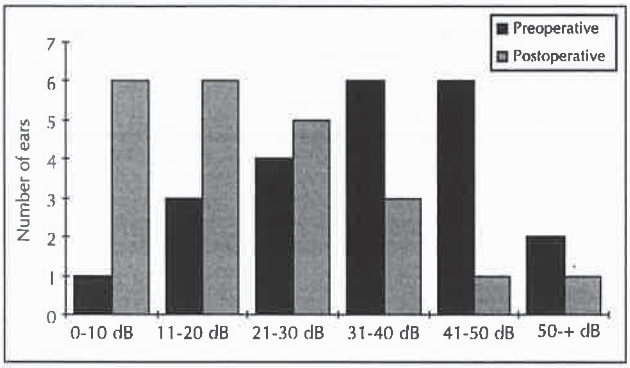

Figure 3-Preoperative and postoperative air conduction thresholds.

(18.2 %) in our study. Since VT extrusion was the reason in 2 of these, VT's are reinserted. In order to restore the conductive type hearing loss as a result of dislocation of the incus, revision surgery was performed to one ear. Perforation was repaired in the fourth ear.

Postoperatively at 4000 Hz frequency, an average of 7 dB decrease was observed in bone conduction. This is consistent with the 10 dB decrease reported in a study by Dommerby(12).

There is a debate about the need of mastoidectomy in AO. In some studies, good results were obtained without mastoidectomy(1,7). However, some authors say that the results of mastoidectomy are worse(13).

All of our patients underwent mastoidectomy. No significant difference was detected between the results of our study and the two studies (1,6) mentioned above in which tympanoplasty and VT insertion were performed without mastoidectomy. It is our opinion that instead of routine use in, mastoidectomy should be taken into consideration in the advanced cases AO in which RP's can not be approached by way of the external auditory canal.

In order to determine whether self aeration had been achieved in atelectatic ears previously fitted with ventilating tubes, Luntz et al (3) sealed the tubes. Thirtythree of the 37 ears tested showed that sealing of the VT was followed by the reappearance of an atelectasis. The first signs of atelectasis were detected on average 1-2 hours after sealing. This study confirms that the basic principle in AO is to provide the ventilation of the middle ear. This is achieved most often by VT. In the studies by Tos (1) and Paparella (6) it was also found that the results were more successful in cases with VT insertion. We used Modified Goode T-tube because its extrusion is difficult. Although insertion of the tube is difficult during the operation, it is preferred because it does not require a second operation and there is limited risk in escape of the tube into the middle ear.

Table 3. Postoperative air-bone gap levels

Air-bone gap	Number of ears	%
10 dB ↓	11	50.0
20 dB ↓	17	77.2
30 dB ↓	21	95.4

CONCLUSION

In the development of the disease improper treatment of the acute and secretory otitis media, and eustachian tube dysfunction are the most important etiological factors.

Appropriate treatment of these etiological factors which are the underlying causes of AO, without delay is important to prevent development of the disease. VT insertion alone may be enough for the early atelectatic stages whereas in advanced cases, in our opinion, tympanoplasty with the insertion of long-lasting VT is the most appropriate surgical treatment. We found no difference between patients in our study who underwent simultaneous mastoidectomy, tympanoplasty and placement of VT in comparison to patients from other studies who underwent only tympanoplasty and placement of VT without mastoidectomy.

These results have shown that mastoidectomy is needed only when there is severe RP which cannot be approached by external auditory canal.

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EXTRAPULMONARY INTRATHORACIC HYDATID CYSTS

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Mehmet Dakak* • Alpay Sarper*

SUMMARY

Extrapulmonary locations of hydatid cyst disease in the thorax is a rare condition. Sixteen patients with intrathoracic extrapulmonary hydatid cysts were reviewed retrospectively. Pleural cavity, diaphragm, mediastinum and pulmonary fissure were the locations of these hydatid cysts.

All of the patients underwent to thoracotomy and total resections of the cyst were applied. The follow-up period was 2 years and there were no mortality and morbidity. When an operation planning, it must be remembered that hydatid cyst may be located in many different sites, including extrapulmonary in the thorax.

***Key Words:** Hydatid cysts, Extrapulmonary intrathoracic hydatidosis*

Pulmonary hydatidosis is frequently encountered in the ship and cattle raising regions of the world as well as Turkey. In humans, hydatid disease effects the liver in 55% to 70 % of cases and the lung in 18% to 35%. Although, the liver and lung are the most common sites of the disease, it can also be seen elsewhere in the body (1).

Extrapulmonary location of the disease in the thorax is very rare, and surgical procedures can be considered that differ from those used for pulmonary cysts. We report 16 cases of hydatid cyst with thoracic but extrapulmonary location for which surgical procedures were performed.

MATERIAL AND METHODS

We reviewed retrospectively 16 cases of cysts located in the thorax without involving the lung between 1994-1998. Twelve patients were male and 4 were female. Their ages ranged from 22 to 64 years, with an average of 27.1 years.

We did not routinely use Casoni's intradermal test, the Weinberg complement fixation test, and the eosinophil count for diagnosis because their diagnostic value is minimal.

Preoperative diagnosis was based primarily on chest roentgenograms in 16 cases (100%), abdominal ultrasound to asses liver involvement in 7 cases (43.7%) and magnetic resonance imaging or computed tomography for detection of cyst's location in 10 cases (62.4%).

Pleural cysts were the most frequent types among extrapulmonary intrathoracic hydatid cysts (9, 50.6%). Among these, the cyst was in the fissure in 2 (12.4%) and in the pleural space in 7 (43.8%) (Fig.1 and Fig.2). The preoperative radiodiagnostic findings revealed that these cysts were located in the right hemithorax in 3 cases and in the left in 2 cases. Other locations of cases included the chest wall in 4 (3 cysts in right hemithorax and 1 cyst in the left), the diaphragm in 6 and the mediastinum in 1 (Fig.3).

Fifteen of cases underwent to right (10) or left (5) posterolateral thoracotomy. Before excision of the cysts, a small amount of cystic fluid was aspirated and inactivation was achieved with injection of 10% NaCl into the cystic cavity. Application of sponges with hipertonic saline solution around the incision and in the thoracic cavity was performed routinely.

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Table.1. Spesifications of Cases

Cyst	Total	Side		Operative
Location	**Number**	**Right**	**Left**	**Technique**
Pleural Cyst	7	4	3	Thoracotomy +
Fissure	2	2		Total Excision
Diaphragm	6	4	2	Total excision + Diaphragmatic repair
Mediastinal	1			Right thoracotomy + Total excision

RESULTS

Total excision of the cyst through a thoracotomy was carried out in 16 (100%) of the cases. Operative management is summarized in Table 1. The follow-up period was 2 year. There were no complications or deaths.

DISCUSSION

Hydatid cysts can be located in various tissues, although they are mostly seen in the liver and the lung. A statistical study among the Turkish population showed that 54 % of cases of hydatid disease involved the liver and 35 % affected the lung (2). Radiodiagnostic techniques, dermal tests, complement fixation test, and indirect hemagglutination test can be used for diagnostic purposes (3). Clinical findings and serological tests have limited value for the ultimate diagnosis of hydatid cysts. Clinical findings are nonspesific, with the exception of the laminated membrane fragments (4,5). Diagnosis of pulmonary cyst is generally based on radiological findings. Abdominal ultrasound or computed tomography can be used to asses the liver involvement and thoracic computed tomography is useful to determine the intrathoracic location of the cyst (3,6).

We found that it is possible to establish a satisfactory and reliable diagnosis when conventional roentgenogram is supported with CT scan, MRI or ultrasonography.

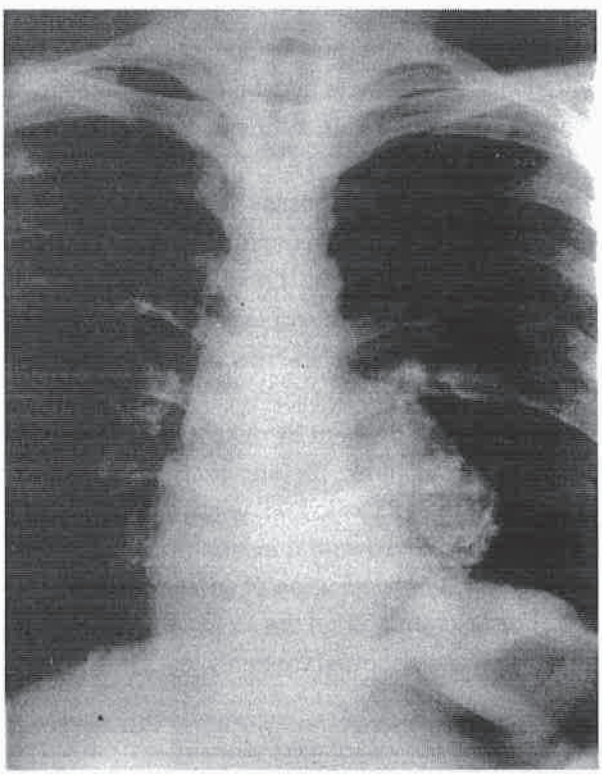

Figure 1. Chest radiograph of a pleural hydatid cyst

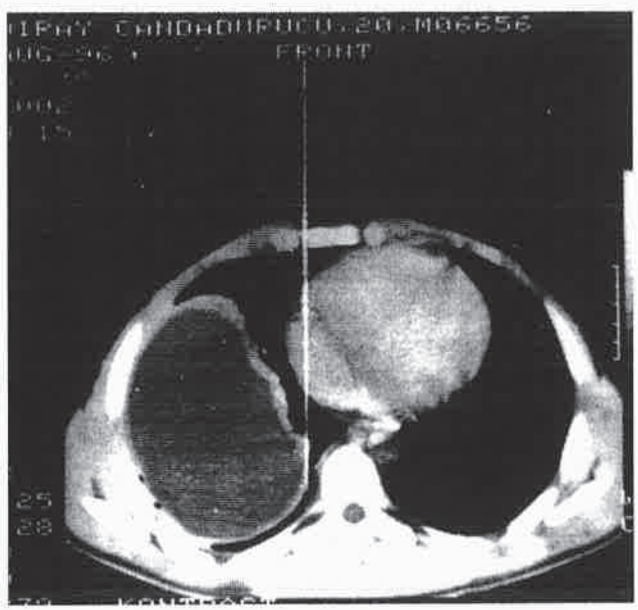

Figure 2. Thorax CT of a pleural hydatid cyst

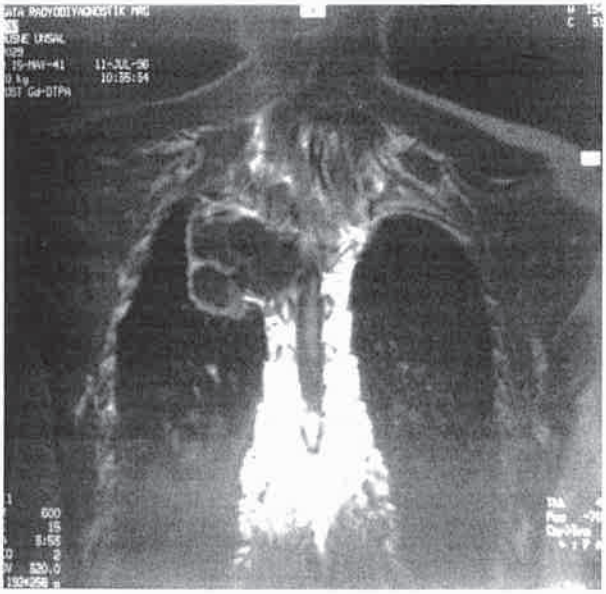

Figure 3. Thorax MRI of a mediastinal hydatid cyst

The intrathoracic location is the most common for hydatid cysts whereas the chest wall, mediastinal, pericardial,myocardial, fissure and pleural locations have been reported in the literature as extrapulmonary intrathoracic cyst (1,7). In our cases pleura (2 in fissure) and diaphragm were the most common sites among extrapulmonary cysts. A partial defect in the visceral pleura and undamaged pulmonary parenchymal unity after excision were features that differed from peripherally located hydatid cyst of the lung.

Location of cysts in chest wall is rare (8). In 1 of our cases with vertebral hydatid cyst, the cyst enlarged into T3 vertebra and destroyed the vertebral margin (Fig.3).

Mediastinal hydatid disease has been reported rarely in the literature (1,9,10). Mediastinal cysts are came into sight by pressure symptoms. In our case , the cyst was located in the mediastinum near the esophagus, a mild dysphagia was seen and after removal of the cyst there was no defect on esophagus and it wasnot needed a repair. After resection, the mediastinal pleura was repaired. Cyst located extrapulmonary in our series were removed surgically. There were no mortality and morbidity in 2 years follow-up period.

Hydatid cyst may be located in many different sites, including extrapulmonarily in the thorax. In this situation, surgical procedures give good results.

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THE RELATION BETWEEN HEPATITIS B VIRUS INFECTION AND PRIMARY LIVER MALIGNANCIES

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SUMMARY

Hepatocellular carcinoma (HCC) is the predominant primary malignancy of the liver, accounting for over 80% of the total. There is a varied presentation of HCC in different geografhic regions of the globe. There is a striking correspondance between areas where HCC is common and where hepatitis B virus (HBV) is hyperendemic.

Intrahepatic cholangiocarcinomas account for between 7% and 25% of primary hepatic malignancies. Most cases of intrahepatic cholangiocarcinoma demonstrate no particular underlying factor, but there is a possibility that in chronic HBV carriers HBV may be the etiological agent responsible for intrahepatic cholangiocarcinoma as well as HCC.

The exact pathogenesis leading to chronic HBV infection and HCC is only partially understood. Most of the studies imply that hepatitis B x antigen (HBxAg) plays one or more important roles in hepatocarcinogenesis.

The finding of HBxAg staining in several bile duct cell-derived tumors raise the possibility that HBV may be the etiological agent responsible for these other liver neoplasms in chronic HBV carriers.

Key Words: *Hepatocellular carcinoma, intrahepatic cholangiocarcinoma, hepatitis B virus, hepatitis B x antigen*

Hepatocellular carcinoma (HCC) is the predominant primary malignancy of the liver, accounting for over 80% of the total, and it ranks among the most common neoplasms in the world (1,2,3). There is a varied presentation of HCC in different geographic regions of the globe (1,2,4-6,7). In China, Taiwan, Korea and sub-Saharan Africa, HCC ranks as one of the top four malignant tumors in adults. In contrast, HCC ranks as the 22nd commonest form of the cancer in the United States (4,7).

The geographical variation in the prevalence of the carcinoma actually provides some of the most convincing evidence linking the disease and chronic hepatitis B virus (HBV) infection (3,4,8,9). There is a striking correspondence between areas where HCC is common and where HBV is hyperendemic (3,4,8). In China and most of Southeast Asia, virtually 100% of adults have serologic evidence of HBV infection and 10% to 15% are chronic hepatitis B surface antigen (HBsAg) carriers (4). In China and Korea, 85% to 95% of patients with HCC; inTaiwan, 80% to 88% of patients with HCC are HBsAg positive and the remainder usually have antibody to HBsAg or antibody to hepatitis B core antigen in serum (4,10). In these areas, HCC is also common and occurs at a rate of 20 to 150% per 100 000 a year. In the United States and Western Europe, only 5% to 15% of adults have serologic evidence of HBV infection and less than 1% are carriers. In these areas the carrier rate among patients with HCC is less, between 10% and26%. In Western nations, the rate of HCC is also less, ranging from 1 to 5 per 100000 a year (4).

Intrahepatic cholangiocarcinomas account for between 7% and 25% of primary hepatic malignencies (1). Its incidence is lower than that of HCC (11,12). In England and Wales, the frequency of cholangiocarcinoma is not easily extracted from mortality figures, but most reports emanating from Britain suggest a rate approximately 1/8 of that for HCC (11). Most cases of intrahepatic cholangiocarcinoma demonstrate no particular underlying factor, but there is a possibility that in chronic HBV carriers HBV may be the etiological agent responsible for intrahepatic cholangiocarcinoma as well as HCC (11,13).

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HBV is classified as a hepadnavirus. The viral genome consists of partially double-stranded circular DNA (14). HBV has four known viral genes coding for its proteins. These genes include gene "S" for HBsAg, gene "C" for hepatitis B core antigen (HBcAg), the large gene "P" for HBV particle-associated DNA polimerase, and the gene X whose protein, hepatitis B x antigen (HBxAg), and function have not yet been identified (4).

The S gene has three in-frame initiation codons and encodes the major HBsAg as well as polypeptides containing in addition pre-S2 or pre-S1 and pre-S2 sequences.

The C gene has two in-frame initiation codons and encodes HBcAg plus the hepatitis B e protein which is processed to produce soluble hepatitis B e antigen (HBeAg).

The P gene is associated with a large polymerase (P) protein that includes DNA polymerase, reverse transcriptase, and Rnase H activities (14).

The X gene product, HBxAg, has transcriptional transactivator properties (13, 14).

HBV appear to have a unique replicating cycle in that they replicate through an RNA intermediate and therefore require a reverse transcriptase activity for replication (4). The infectious virion attaches to cells and becomes uncoated. In the nucleus, the partially double-stranded viral genome is converted to covalently closed circular double-stranded DNA. The circular double-stranded DNA serves as template for all viral transcripts, including a 3.5-kb pregenome RNA.The pregenome RNA becomes encapsidated with newly synthesized HBcAg. Within the cores, the viral polymerase synthesizes by reverse transcription a negative strand DNA copy.The polymerase starts to synthesize the positive DNA strand, but the process is not completed. Cores may bud from the cell, acquiring HBsAg-containing envelopes. Alternatively, cores may be reimported into the nucleus and initiate another round of replication in the same cell (14).

Integration of HBV-DNA into hepatocytes occurs during the course of persistent HBV infection and precedes development of HCC (15-18). The integration site of HBV-DNA is variable, and although a specific hepatocyte oncogene has not been identified, the direct role of HBV in carcinogenesis is supported both from animal models and human studies (6). Several studies have demonstrated the presence of viral DNA,RNA, and occasionally viral proteins such as HBsAg and HBcAg within the tumor cells (1).

The exact pathogenesis leading to chronic HBV infection and HCC is only partially understood. Different molecular mechanisms contributing to hepatocarcinogenesis have been proposed, including: 1) HBV-DNA integration into genome of hepatocytes cause genomic instability or interfere with cell cycle regulation through HBV-DNA integration into the cyclin A gene. 2) Integration of HBV mediates chromosome aberrations, both deletions and translocations. 3) Accumulation of HBV envelope proteins in hepatocytes lead to hepatocellular injury, inflammation, regenerative hyperplasia and progression to HCC, as shown in a transgenic mice model. 4) In woodchucks a cellular protooncogene (N and c-myc) is frequently activated by woodchuck hepatovirus integration (6,19).The hepadnavirus X gene (in HBV, woodchuck hepatitis virus and ground squirrel hepatitis virus) acts as a transcription factor and transactivates viral and cellular promoters (6,19,20). 6) The protein of HBV-X gene(HBxAg) has transforming activity in transgenic mice and in conjunction with another oncogene (6,19).

The finding of HbxAg staining in the nucleus of hepatocytes from primary HCC patients with dysplasia, combined with the known trans-activating properties of HbxAg, implies that HbxAg plays one or more important roles in hepatocarcinogenesis. The finding of HBxAg in bile duct cells from HBV carriers suggests that liver cells other than hepatocytes infect with HBV. Infection of bile duct cells may be important because HBxAg staining was also observed in the several bile duct cell-derived tumors, namely hepatocholangiocarcinoma and cholangiocarcinoma. These results raise the possibility that HBV may be the etiological agent responsible for these other liver neoplasms in chronic HBV carriers (13).

Further support for this possibility derives from the recent finding that the related duck HBV was detected by immunohistochemical staining in bile duct epithelial cells and that bile duct proliferation is a feature of duck HBV infection (21).

These observations are consistent with the conclusion that hepadnaviruses may infect bile duct epithelial cells and that such infections could result in proliferation which may be an important step in the pathogenesis of cholangiocarcinoma(13).

In our study (22), to evaluate the role of HBV in patients with HCC and intrahepatic cholangiocarcinoma, paraffin sections of livers from 40 cases of HCC and 8 cases of intrahepatic cholangiocarcinoma were stained for HBsAg by Shikáta's orcein method. It was found that one patient with HCC and HBs antigenemia had the antigen demonstrable in liver and tumor tissue. One patient with HCC and uninformed serum HBsAg status had the antigen demonstrable in nontumorous liver parenchyma. It was observed that HBsAg was negative in liver and tumor tissue in patients with intrahepatic cholangiocarcinoma.

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ACHALASIA OF ESOPHAGUS WITH MULTISYSTEMIC MANIFESTATIONS

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SUMMARY

Achalasia of the esophagus is a relatively rare problem in children of unknown etiology. As it usually presents in adult life, the diagnosis is often delayed in childhood. Achalasia is known to be associated with various disorders, triple-A syndrome (Achalasia, alacrima, adrenal insufficiency) being the most known. We describe a child with esophageal achalasia who presented with various multisystemic manifestations.

Key words: *Achalasia, Childhood, Failure to thrive*

Esophageal achalasia is a rare disease of unknown etiology characterized by a functional obstruction of the lower esophagus due to failure of relaxation of the lower esophageal sphincter and altered motility of the body and distal esophagus. It is an uncommon disease, usually presenting in adult life, and because of its rarity in childhood, the diagnosis may be delayed (1). A wide variety of syndromes associated with achalasia has been reported (2). In this paper we report a boy with achalasia who presented with multisystemic manifestations.

CASE REPORT

A $3^{6/12}$ year old boy presented with complaints of vomiting ad failure to thrive. He had been regurgitating at night which caused nocturnal cough. His medical history included motor and mental developmental delay. His parents were consanguineous. He has a healthy 5 year-old sister. His physical examination revealed physical developmental delay (weight 7500 gr., SDs -4.5, height 88 cm, SDs -2.45), microcephaly (head circumference 45 cm), absence of tears (alacrima), a long philtrum, a narrow upper lip, a down-turned mouth, a nasal voice, scoliosis and camptodactily. He had also motor developmental delay and impaired intellect. Among his laboratory tests, complete blood count, urine examination, and serum biochemistry including BUN, creatinine, glucose, ALT, AST, Ca, P and serum electrolytes were normal. Abdominal ultrasonography was within normal limits. Arterial blood gas, blood and urine aminoacids and organic acids were normal, urine oligosaccharides and mucopolysaccharides were normal. EEG, MRI and BAER (Brainstem auditory-evoked response) were also within normal limits. A barium swallow was performed which disclosed esophageal dilatation with distal narrowing (Figure). Delayed films demonstrated minimal filling of stomach. Upper GI endoscopy revealed normal esophageal mucosa and easy negotiating of the stenosis. Manometric evaluation of esophagus demonstrated that the LES pressure was 80 mmHg; LES relaxation and peristalsis were absent. Achalasia of esophagus was diagnosed based on these findings. As there was also alacrima, 3-A syndrome was suspected, but laboratory investigations showed normal adrenal function (basal cortisol as well as ACTH stimulation test were within normal limits). Pneumatic dilatation was performed without any complication and his symptoms resolved. Control manometric study showed that LES pressure

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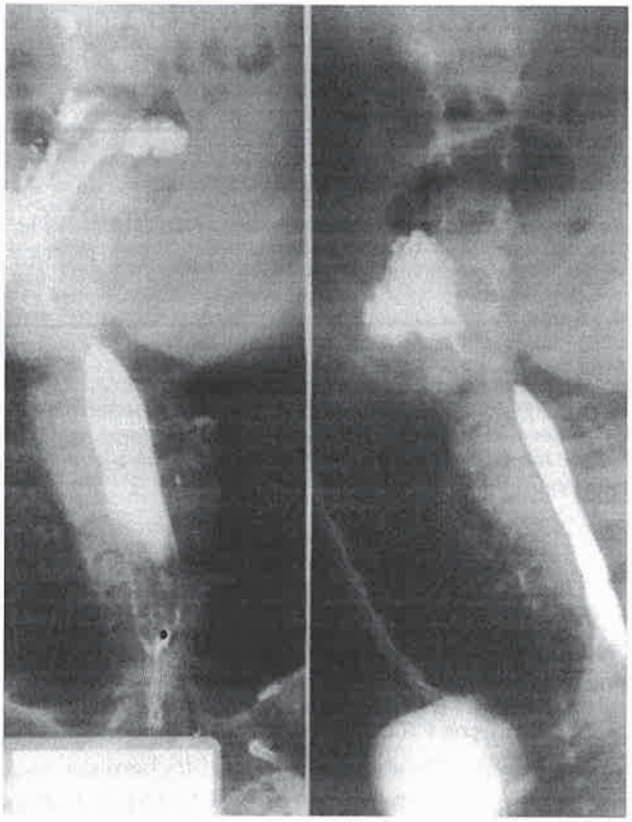

Figure 1. Barium swallow of the case showing esophageal dilatation with distal narrowing.

was within normal limits (24 mmHg).

DISCUSSION

Achalasia is a rare, primary esophageal motor disorder caused by the neuronal degeneration of the inhibitory nerves of the esophageal smooth muscle. This degeneration results in incomplete relaxation of the lower esophageal sphincter (LES) and the absence of peristalsis in the esophageal body. Its etiology is still unknown but the defect in intrinsic innervation is well established. It usually presents in adult life, and its occurrence in childhood is mainly vomiting. Delay in the diagnosis is reported in many pediatric series, and may be very long (3); this delay accounts for failure to thrive as in our case, and respiratory infections. Manometric evaluation is mandatory to confirm the diagnosis which was found diagnostic in our case.

Achalasia is a heterogeneous disease and a wide variety of associated syndromes have been described (2). Allgrove Syndrome, or 3-A syndrome is the most known among these which is characterized by isolated glucocorticoid deficiency, achalasia and alacrima (1).

Our case presented here, showed alacrima and achalasia but glucocorticoid deficiency was not present. Occasionally, symptomatic achalasia, with or without recognized alacrima, may precede the appearance of cortisol deficiency by several years (4). So it is possible that in a few years time our case will show all the characteristic findings of syndrome.

Allgrove syndrome is reported to be associated with autonomic or peripheral neuropathy, hyperkeratosis, delayed wound healing, short stature, ataxia, optic atrophy or mental retardation (5). Achalasia and microcephaly was reported to be a distinct syndrome (6,7). In the review of Grant et al, associated disorders in Allgrove syndrome were numerous neurological findings (hyperreflexia, increased limb tone, extensor plantar responses, muscle weakness, muscle wasting, dysarthria, nasal speech, ataxia, sensory impairment, optic atrophy, nerve deafness ad recurrent seizures), autonomic disturbances (postural hypotension, inequality of the pupils), impaired intellect, skin changes (hyperkeratosis, cutis anserina), multiple nasal polyps, scoliosis and cleft palate (8).

The case presented here had physical, motor and mental developmental delay, microcephaly, alacrima, camptodactly, typical facies, a nasal voice, scoliosis and achalasia. He developed afebrile seizures while on follow-up. The patient did not have adrenal insufficiency by history, physical examination or laboratory investigations at the time of evaluation. So he did not fulfill all the criteria to diagnose the Allgrove (or 3-A) syndrome. Our case represents an esophageal achalasia presented in early childhood with multisystemic manifestations which may be a new syndrome or he may be Allgrove syndrome in fact, not showing isolated glucocorticoid deficiency yet, but will appear in the future.

With this report we tried to point out the wide range of systemic findings associated with achalasia in childhood and although very rare we recommend that achalasia should be kept in mind in the differential diagnosis in a child with persistent vomiting especially if the patient has multiple manifestations not attributed to a specific entity.

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ABSENT PULMONARY VALVE SYNDROME WITH APICAL MUSCULAR VSD

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SUMMARY

The absent pulmonary valve syndrome includes absence or rudimentary development of the pulmonary valve leaflets, pulmonary annular hypoplasia, and dilated pulmonary arteries. Presentation is often in infancy with severe respiratory symptoms secondary to bronchial compression by the dilated pulmonary arteries or respiratory infections. This syndrome is usually associated with other congenital cardiac malformations. The following is a case report of an infant with absent pulmonary valve syndrome associated with an apical muscular VSD, which is, in our opinion the first case published.

Key Words: *Absent pulmonary valve syndrome, Apical muscular VSD*

Congenital absence of the pulmonary valve is a relatively rare cardiac malformation, called absent pulmonary valve syndrome (APVS). It consists of agenesis of the pulmonary valve with pulmonary insufficiency and annular pulmonary stenosis.

In the majority of cases, this syndrome is associated with a ventricular septal defect (VSD), obstructive pulmonary valve annulus, and massive dilation of the pulmonary arteries (1-3). This combination is often called tetralogy of Fallot with absent pulmonary valve. Type of the VSD is generally malalignment. It is known that apical muscular VSD is also a rare form of VSD's (4). We present a case of congenital absence of the pulmonary valve with apical muscular VSD diagnosed by echocardiography.

CASE REPORT

A three months old male infant, weighing 3,2 kg was referred for evaluation of respiratory distress and cyanosis. Delivery had been normal at term after a first pregnancy. He was cyanotic and tachypneic on the first week of life. He was treated conservatively and after stabilization was referred to our hospital.

He was tachycardic, cyanotic and in respiratory distress at presentation. On physical examination there was a grade 3/6 systolic ejection and diastolic murmurs with a to-and-fro quality over the right lower sternal border. The second heart sound was loud and single. The liver was palpable 4 cm below the right costal margin. The electrocardiogram showed right axis deviation and right ventricular hypertrophy. The chest radiograph revealed an enlarged heart with dilated pulmonary arteries, and hyperexpansion on the right side. The cross-sectional echocardiography demonstrated dilated pulmonary arteries with a narrow pulmonary annulus in the parasternal short-axis view (Figure 1). Diameter of the main pulmonary artery was measured 19.5 mm, the right and left pulmonary arteries were 12.5 and 14.5 mm. In the parasternal short-axis view, immobile rudimentary pulmonary valve tissue was identified in the stenotic annulus. Doppler echocardiography demonstrated both the accelerated antegrad systolic flow of stenosis across the pulmonic

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annulus and the retrograde diastolic flow of valve insufficiency in the pulmonary artery and right ventricular outflow tract. Apical trabecular VSD was visualized distal to the right ventricular moderator band with cross-sectional echocardiography. A colored jet was shown at the distal portion of the right ventricle below the moderator band with color flow Doppler imaging. Furthermore the diagnosis was confirmed with an increased systolic flow velocity at the apical region by pulsed and continuous wave interrogation.

After hospitalization intensive conservative medical care was started. Heart failure was treated with digitalis and furosemide. During three weeks hospitalization the respiratory distress was disappeared and he got hemodinamically stable with no carbondioxide retention nor hypoxia. Fortunately, immediate operation was not necessary for this patient and he was discharged after three weeks hospitalization.

DISCUSSION

APVS was first described by Cheevers in 1847 (4). It is a rare congenital cardiac lesion, the components of which include dysplasia and severe incompetance of the pulmonary valve, annular pulmonary stenosis, and dilatation of the pulmonary arteries leading to varying degrees of tracheobronchial compression. Aneurysmal dilatation of the pulmonary arteries results either from congenital weakness at the base of the pulmonary artery or from the hemodynamic consequences of the pulmonary stenosis in conjunction with severe pulmonary regurgitation. Compression of the tracheobronchial tree results in atelectasis and obstructive emphysema causing severe respiratory distress.

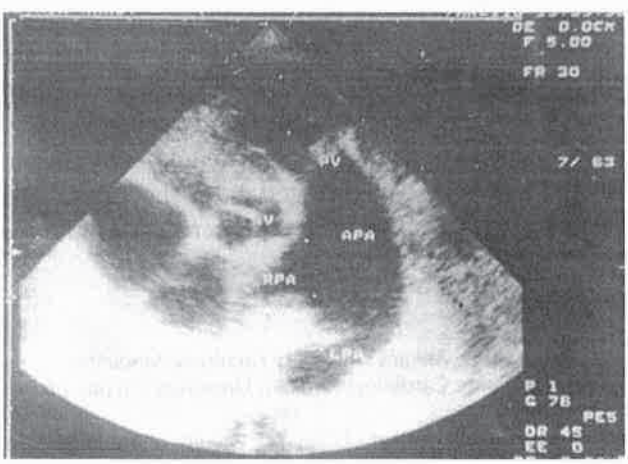

Figure 1. Cross-sectional echocardiogram of the pulmonary artery (parasternal short-axis view).

The diagnosis is not difficult because of its characteristic clinical, echocardiographic and angiographic features.

The diagnosis was made by cross-sectional and Doppler echocardiography in our patient without performing cardiac catheterization. The dilatation of pulmonary arteries were demonstrated by cross-sectional echocardiography in the parasternal short axis view. Moreover, pulmonary annulus was stenotic and the pulmonary valve was rudimentary. The diagnosis was confirmed with a retrograde diastolic and antegrade systolic flow pattern in the main pulmonary artery by Doppler echocardiography. The flow pattern in the main pulmonary artery may mimic that of patent ductus arteriosus, but demonstration of retrograde diastolic flow in the outflow tract will establish this reversal as pulmonary insufficiency. When considering the high risks involved for severely symptomatic infants undergoing cardiac catheterization, diagnosis should be established by the use of noninvasive methods (5).

APVS is usually associated with other congenital cardiac anomalies such as ventricular septal defect, tetralogy of Fallot, patent ductus arteriosus, atrial septal defect, double-outlet right ventricle, Marfan's syndrome , tricuspid atresia, transposition of the great arteries, coarctation of the aorta and Uhl's anomaly (1,6). Rarely it has also been presented as an isolated defect with intact septum (6,7). VSD is the most common lesion in association with APVS, but an apical muscular VSD has not been reported yet (1-3,6).

Apical muscular VSDs are difficult to detect with two-dimensional echocardiography, because of its localization. With the introduction of pulsed, continuous-wave, and color-flow Doppler techniques, the sensitivity in detecting these defects has improved considerably. Apical and subcostal four chamber views are particularly useful in assessing apical muscular VSDs. Since the large size of apical VSD in this patient, the diagnosis of the defect was not difficult with 2-D and color Doppler flow imaging. Up to now we reported 20 cases with congenital isolated apical muscular VSD (8). Except this case, the others had small apical muscular VSD and so that multiple echocardiographic planes were used for diagnosis.

Despite a variety of surgical intervention, appropriate management remains controversial. Operational mortality and morbidity, especially in infants with pulmonary complications is high, whereas in the older, minimally symptomatic group, elective operation carries a smaller risk (3,9). It is widely accepted though that asymptomatic infants will do well and may later undergo elective surgical repair (3,7,9). Our approach is to give intensive conservative medical therapy to symptomatic infants, and to delay surgical correction until late infancy. Early surgical intervention should be considered in infants who not respond to conservative medical therapy.

In conclusion, to our knowledge, this is the first reported case of APVS with apical muscular VSD. Furthermore, we wanted to emphasize that echocardiography is most reliable non-invasive method for diagnosis absent pulmonary valve syndrome with apical muscular VSD without catheterization.

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MUCOCELE OF THE APPENDIX AND COLORECTAL NEOPLASMS

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SUMMARY

We present herein the case of a 64 year-old woman with a huge mucocele of the appendix coexistent with an adenomatous polyp 2 cm. in diameter in the transverse colon. From the reports of Ahmed, Wolf and Higa we know that mucoceles may coexist with colorectal neoplasm's. Though the polyp in the transverse colon was not malignant, it had a potential source of becoming malignant in the future. We consider that once the diagnosis of mucocele has been made, every patient has to be searched for the possible coexistence of colorectal neoplasm's and all polyps in the colon have to be removed because these patients are at greater risk for developing colorectal cancers.

Key Words: *Colorectal Neoplasms, Mucocele of the Appendix*

Mucocele of the vermiform appendix is a descriptive term of an abnormal mucus accumulation distending the appendicial lumen regardless of the underlying cause. The incidence of mucocele in appendectomy specimens and autopsy series is about %0.25 (1)

Mucocele is usually an incidental finding during laparotomy for an unrelated condition. In actuality, there are three distinct clinicopathologic entities based on histologic differences.These are mucosal hyperplasia, cystadenoma, and mucinous cystadenocarcinoma of the appendix (2).

A case of a huge mucocele of the appendix vermiformis coexistent with a colon polyp is reported, that the diagnosis of mucocele was uncertain before the operation.

CASE REPORT

A 64 years old woman was admitted to our hospital with a right lower quadrant mass and pain . Cholecystectomy and thyroidectomy were performed three months ago. On physical examination there were right lower quadrant pain, a mass with undetermined margins, guarding and rebound tenderness. Mild leucocytosis was reported.

Barium enema revealed a polyp in the transverse colon (Fig.1a) and a filling defect in the region of cecum (Fig.1b). So we decided to perform colonoscopy and colonoscopy was able to show a polyp 2 cm. in length in the transverse colon. Endoscopic removal of this lesion revealed adenomatous polyp. With technical problems it was impossible to search the ascending colon and cecum. USG of the right lower quadrant showed a cystic homogenous, hypodens lesion in the expected region of the appendix (Fig.2).

Laparotomy revealed a cystic mass (12cm x 6cm), originating from the appendix (Fig.3). The patient was treated with appendectomy. There were neither pseudomyxoma peritonei nor any other pathologic conditions detected in the abdomen. Pathologic examination confirmed the diagnosis of mucocele(mucinous cystadenoma).

DISCUSSION

Usually a preoperative diagnosis of mucocele is rare. The differential diagnosis of an appendicial muco-

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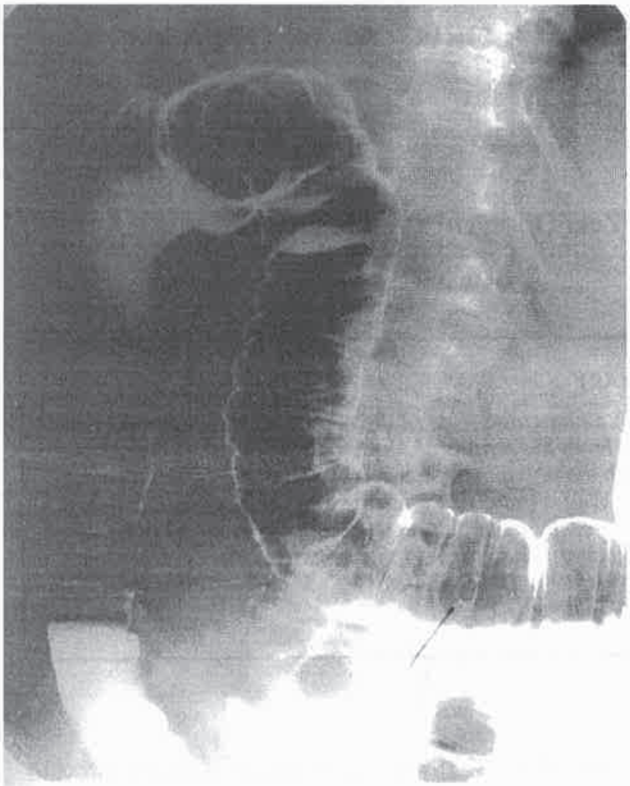

Figure 1a. Polyp in the transverse colon (arrow)

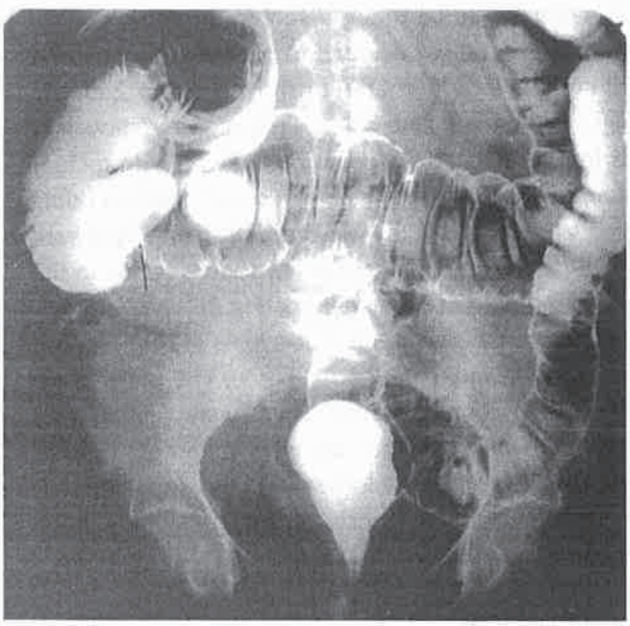

Figure 1b. Filing defect in the cecum (arrow). Note lateral and cephalad displacement of the cecum.

cele is broad and includes intraperitoneal and retroperitoneal lesions. Intraperitoneal masses to be considered include ovarian cysts and tumors, duplication cyst, mesenteric and omental cysts, mesenteric hematoma or tumor and abdominal abscess. Of the retroperitoneal disorders to be considered retroperitoneal inflammation, tumor and hemorrhage are important. Imaging with CT and USG usually can diferentiate between these entities and correct diagnosis is possible in a patient who has not had an appendectomy (3). Filling defect in the cecum after a barium enema is also an important finding in these patients. The cecum is often displaced laterally and or cephalad, depending on the location and size of the mucocele (4). In our case barium enema revealed lateral and cephalad displacement of the cecum (Fig.1b). Once the diagnosis of mucocele has been made colorectal neoplasm's has to be searched .

Appendicial mucoceles may be important in relation to other tumors. Wolf and Ahmed found an association between mucocele and other colonic tumors. Nine of their 42 patients had associated adenocarcinoma of the colon, representing a sixfold increase in risk compared with the general population and 4 patients had multiple colonic neoplasm's, as follows ; 4 benign lesions (2 adenomatous polyps, 2 papillary adenomas), 1 benign and 2 malignant lesions, 1 benign, and 1 carcinoma in 2 patients. In their review they included those cases in which adenomatous epithelium could be demonstrated, like in our case (5).Also in the series of Higa et al, of the 18 patients classified as mucosal hyperplasia, 5 were associated with adenocarcinoma of the large bowel and of the 46 cases classified as mucinous cystadenoma, 9 were associated with adenocarcinoma of the large bowel. Interestingly in Higa's study grup, a typical villous adenoma of the cecum extended into the appendix and, in so doing, gradually changed its appereance into that of a typical cystadenoma. Also Higa and his coworkers reported that at least some of the mucinous cystadenomas of the appendix might have begun as villous adenomas or adenomatous polyps and that the morphologic differences with the similarly called lesions of the colon are only due to the pressure effect of the accumulated mucus (2). We think that there are some adenomatous polyps in the colon of these patients, those that reside in cecum turn into mucocele and those that in the colon turn into cancer.

So every patient with mucocele has to be examined with either colonoscopy or barium enema, the former is more preferable. As in our case you may find an adenomatous polyp that has a malignant potential or already a malignant lesion. Every one must mention that these patients are carrying a high risk for colorec-

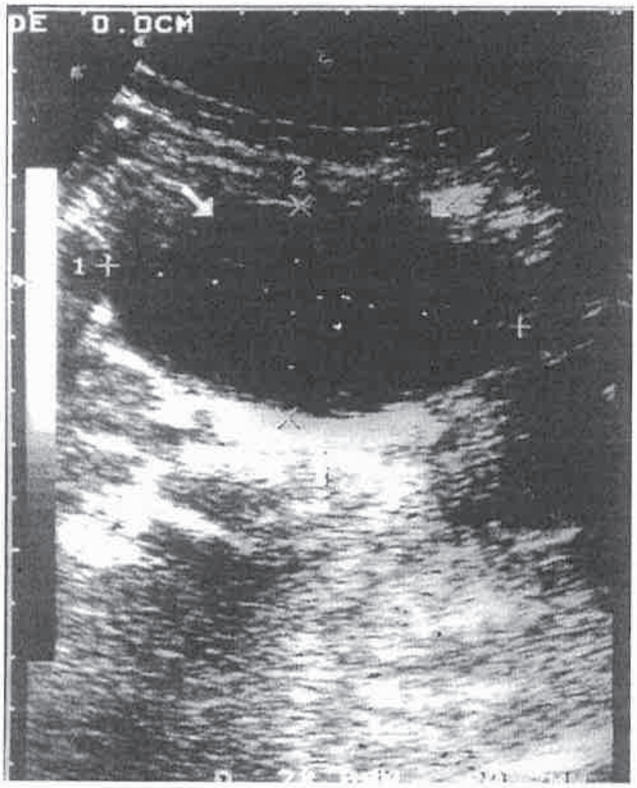

Figure 2. Abdominal ultrasonography revealed a cystic mass in the expected region of the appendix (arrow).

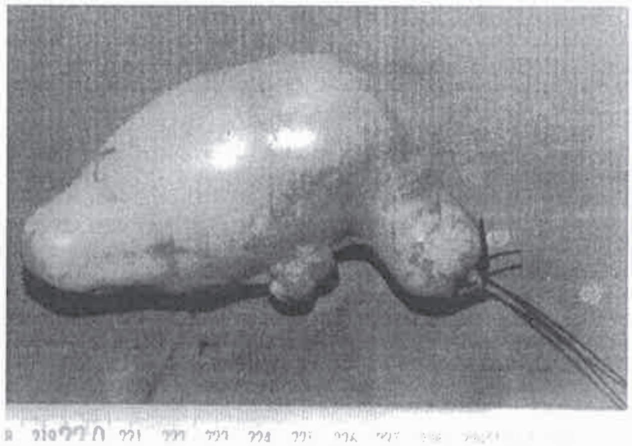

Figure 3. Mucocele (mucinous cytadenoma) of the appendix (12x6cm).

tal neoplasm's. Three months after discharge from the hospital the patient was reexamined by colonoscopy and no pathologic sign was found. Further follow-up is considered in this patient.

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PRONE POSITION IMPROVED ARTERIAL OXYGENATION IN A PATIENT WITH HELLP SYNDROME

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SUMMARY

A 25-year-old primigravid (25 weeks) was delivered by cesarean section because of abruptio placenta and fetal death. She was admitted to our ICU because of her respiratory insufficiency. Preeclampsia history, elevated liver function tests, low platelets and anemia suggested HELLP syndrome. A progressive dyspnea developed on the third day and the patient was intubated. Although she was ventilated with a F_iO_2 of 0.8 and a PEEP of 10cm H_2O, arterial hypoxemia persisted. Therefore, we considered ventilating her in prone position. In prone position, PaO_2 and postural drainage increased significantly compared to supine position. During this period, platelets increased virtually while liver function tests were decreasing to normal levels. She was turned to supine position after 48 hours. The patient was discharged without sequale 24 days after her admission to ICU. Our indication for the use of prone position in this case was; inadequate oxygenation despite high F_iO_2 and PEEP levels. We achieved optimum PaO_2 with the least F_iO_2 and better secretion removal in prone position.

Key Words: *HELLP Syndrome, Acute Lung Injury, prone position*

Hellp syndrome (Hemolysis, Elevated liver function tests, Low platelets) is considered secondary to microangiopathic hemolytic anemia. It occurs in approximately 10 per cent of patients with severe preeclampsia and 30 to 50 per cent of patients with eclampsia. Untreated disease can progress to pulmonary edema, adult respiratory distress syndrome (ARDS), renal failure, and multiple organ disease with disseminated intravascular coagulation (DIC) [1,2].

In patients with acute respiratory failure, arterial hypoxemia may often persist despite the administration of high F_iO_2 and PEEP [3]. An alternative method of increasing PaO_2 may be to turn them from supine to prone position [4].

The purposes of this clinical report are 1) to present Hellp syndrome in a primigravid with a history of preeclampsia, and 2) to show the effects of prone position on arterial oxygenation in that patient who developed acute respiratory failure.

CASE REPORT

A 25-year-old primigravid (25 weeks) woman whose pregnancy complicated with hypertension and proteinuria was delivered by cesarean section because of abruptio placenta and fetal death. On the postoperative first day, she was re-operated due to intraabdominal bleeding. At the end of the operation, she was admitted to our ICU, since the patient could not fulfill the extubation criterias.

On admission, vital signs, arterial blood gases analysis and laboratory findings were as below ; Blood pressure: 195/110 mmHg, heart rate: 120/min, urine output:40ml/hr, pH:7.20, PaO_2 : 61.9mmHg, $PaCO_2$: 59.2mmHg, $SatO_2$: 85.3%, BUN: 85, creatinin: 3.7, uric acid: 13.9, protein:5.1, albumin: 2.7, SGOT: 122U/L, SGPT: 113U/L, LDH: 950U/L, T. bilirubin: 1.05, Platelet: 39.000/mm^3, Hb: 12.4gr/dl. Chest x-ray showed pneumonic infiltration and density suggesting ARDS (Picture 1). The right costadiaphragmatic recess was closed. Abdominal ultrasonography revealed diffuse hepatomegaly and right pleural effusion. Preeclampsia history, elevated liver function tests, low platelets and absence of platelet aggregation on peripheral smear suggested HELLP syndrome in this patient.

Despite continous positive airway pressure (CPAP) therapy, progressive dyspnea developed on the third day. The patient was intubated because of arterial

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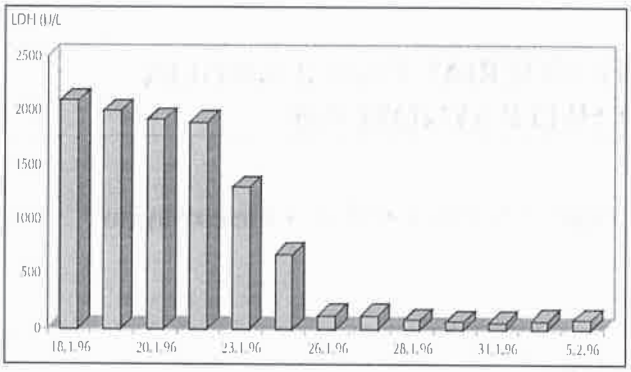


Figure 1. Blood thrombocyte levels.

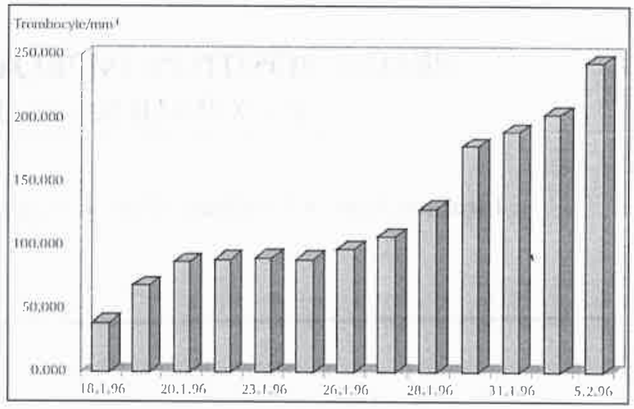
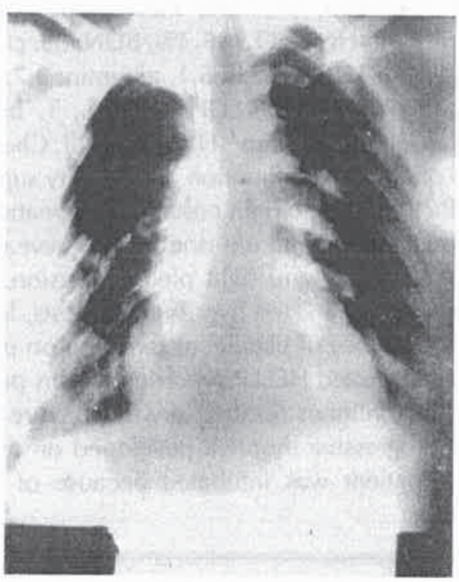
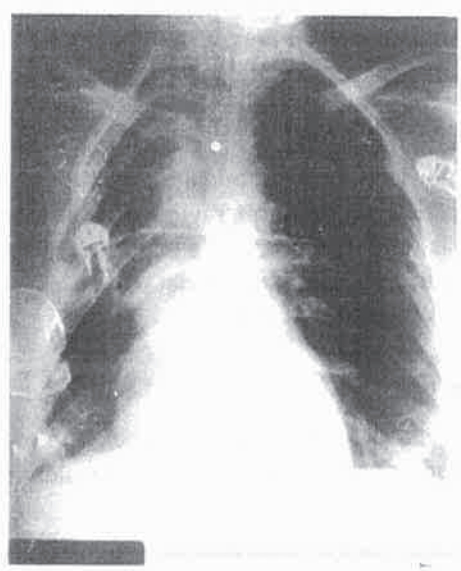


Figure 2. Blood LDH levels.

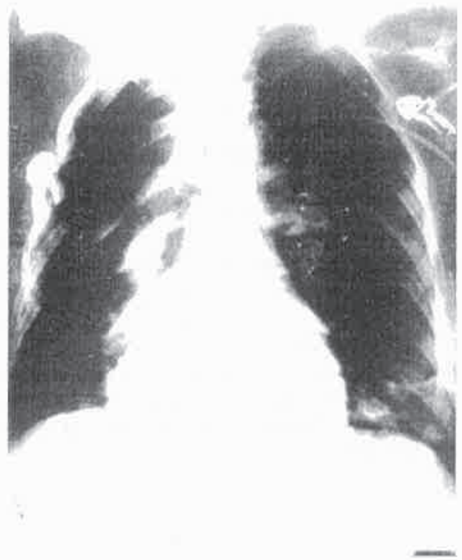
hypoxemia. Although she was ventilated with a F_iO_2 of 0.8 and a PEEP of 10cm H2O, arterial hypoxemia persisted. Therefore, we considered ventilating in prone position with supporting the upper thorax and pelvis with pillows and allowing the abdomen to protrude. After 30 minutes, PaO_2 increased to 420 mmHg. She was turned supine at the end of 24 hours, when her blood gases were in normal ranges with a F_iO_2 of 0.30. Pneumonic infiltrates and pleural effusion disappeared on chest x-ray (Picture 2). When her spontaneous breathing was adequate, she was extubated and therapy was continued with CPAP subsequently. Unfortunately, the patient couldn't cooperate with CPAP properly and arterial blood gases worsened gradually. Additionally, atelectatic regions were observed on the right hemithorax and mucous plugs were aspirated via fiberoptic broncoscopy, afterwards. However, arterial hypoxemia did not improve with this interventions and the patient was turned prone again. After turning to prone, postural drainage increased significantly compared to supine. During this period, platelets increased virtually while liver function tests decreased to normal levels (Figure 1,2). After 48 hours in prone position, she was turned to supine and chest x-ray was improved (Picture 3). Provided that she had adequate spontaneous breathing with a F_iO_2 of 0.21, the patient was extubated and O_2 therapy was applied by mask. During this period, blood gas analyses were in the normal ranges. The patient was discharged without sequale 24 days after her admission to intensive care unit. No abnormal laboratory or clinical findings were found out when she was called for check-up 20 days after discharge.



Picture 1. Chest x-ray of the patient on admisson to ICU.



Picture 2. Chest x-ray of the patient after 24 hours in prone position.



Picture 3. Chest x-ray of the patient after 48 hours in prone position.

DISCUSSION

Hellp syndrome is characterized with intravascular hemolysis, liver dysfunction, coagulation abnormalities and thrombocytopenia [2,5,6] in pregnant women with preeclampsia and eclampsia. In addition to platelet count, LDH level is one ofthe most important laboratory findings as it indicates both hemolysis and liver dysfunction [6].

In our preeclamptic patient, the existence of thrombocytopenia and hemolytic anemia, and increased levels of SGOT, SGPT, LDH and total bilirubin values, led us to consider Hellp syndrome. She was admitted to ICU because ofrespiratory failure, which is one of the complications of this syndrome [6].

In the present case, arterial hypoxemia persisted although mechanical ventilation was carried outwith high F_iO_2 and PEEP values for a long period. Bryan et al [3] tried prone position for patients requiring mechanical ventilation, suggesting that this position might enhanceexpansion and ventilation of the dorsal aspect of the lungs.Douglas et al [7] observed animprovement in arterial oxygenation with prone position by supporting the thorax and pelvis in patients with ARDS and acute respiratory failure on mechanical ventilation. While they considered that this improvement was secondary to increased functional residual capacity, Langer et al [8] explained this with better ventilation / perfusion ratios and with the help of CT scan they showed that edema fluid was collected in dorsal lung regions. Murdoch et al [9] used the prone position routinely in children with ARDS. Takashi et al [10], tried prone position in volume overloaded pigs. Albert et al [4] showed an improvement in $PaO_2$with prone position in experimentally ARDS induced dogs. All the authors above indicate that prone position allows a decrease in values of $F_iO_2$and/or PEEP.

The mechanism by which the prone position has this beneficial effect has not yet been elucidated. Proposed explanations include a prone position-induced 1) increase in functional residual capacity, 2) change in regional diaphragm motion, 3) redistrubition of perfusion along a gravitational gradient toward less injured lung regions, 4) better secretion removal [3,9,11]. Wealso observed an immediate improvement in arterial oxygenation by turning the patient from supine to prone.

Although the indications of prone position are not clear yet, a trial should be considered [3] when;

1) $PaO_2$is marginal despite maximal oxygen therapy by mask, particularly when a relative contraindicationto intubation is present.

2) $PaO_2$is adequate but the duration of exposure to a high $F_iO_2$may be excessive or PEEP is relatively contraindicated.

3) $PaO_2$is inadequate despite optimal ventilator therapy.

4) Postural drainage of dorsal regions is indicated and positions other than prone and supine are not tolerated.

Our indication for the use of prone position in this case was; inadequate oxygenation despitehigh $F_iO_2$and PEEP therapy. As itis pointed out by the authors above, we achieved optimum $PaO_2$with the least $F_iO_2$and better secretion removal when the patient was in prone position. This finding supports the premise, that an improvement in arterial oxygenation could be obtained in patients with acute respiratory failure by taking them to prone.

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ABDOMINAL AORTOILIAC ANEURYSM WITH SPÓNTANEOUS LEFT ILIO-ILIAC ARTERIOVENOUS FISTULA: Case report

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SUMMARY

Spontaneous rupture of the abdominal aortic aneurysm into the adjacent major veins is a very rare clinical entity. Herein a case is documented who was 74 year old woman with abdomino-iliac aneurysm and an arteriovenous fistula between the left iliac artery and left iliac vein.

Key words: *Aorta-iliac aneurysm, İlio-iliac fistula, Surgical repair*

Most of the abdominal aortic aneurysms (AAA) are located distal to the renal arteries and may involve the iliac arteries. Mostly atherosclerosis, but trauma, connective tissue disorders, syphilis, aortitis can lead the formation of aneurysm. The majority of patients are men over 60 year old and cigarette smokers, one half have associated hypertension and ischemic heart disease. Abdominal aortic aneurysms gradually enlarge and rupture if not repaired. The risk of rupture is higher when the diameter is greater than 6 cm. Rupture may occur into the retroperitoneum, gastrointestinal (sigmoid colon) and urinary tracts and adjacent major veins (vena cava inferior, iliac and renal veins) with a resultant aortacaval (arteriovenous-AV) fistula. Aortacaval fistulas are seen in 4% of all ruptured aneurysm and 1% of all AAA (1-4).

CASE REPORT

The patient was 74 year old woman and presented to a reference hospital of Social Insurance Institute with a history of left leg swelling which has developped suddenly 3 months ago. An abdominal ultrasound and aortography were performed there and the diagnosis of abdominal aortoiliac aneurysm with communication with the left iliac vein was established. She transferred to our hospital for operation.

She had no previous major illness until this time besides pustular psoriasis. She was hypertensive. She had no angina, dyspne and syncope attacks. She could not walk due to the left leg swelling. Physical examination revealed a continuous bruit over the left lower abdomen.There was a soft systolic murmur at the apex. Heart rate was 100/min and regular, blood pressure was 150/80 mm Hg. Arterial pulses were palpable. There was massive edema of the entire left lower extremity and wide spread skin lesions on the arms and legs. ECG revealed sinus tachycardia. Chest X-ray was normal. Blood cell counts and blood biochemistry were normal. Abdominal ultra sound revealed abdominal aortic aneurysm and aneurysms in both iliac arteries. Venous doppler ultrasound detected no deep vein thrombosis on the left leg. Aortography confirmed the diagnosis, an abdominal aortic aneurysm extending to both iliac arteries and another huge left iliac aneurysm which was opened into the left iliac vein (Fig. 1).

Exploratory laparotomy through standart transperitoneal approach was performed. There was a 10 x 10 cm aneurysm beginning just below the renal arteries.

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The left ovary and sigmoid colon was pushed anteriorly by the left iliac aneurysm filling the pelvis. Left ureter was dilated. After heparinization, aorta below the renal arteries and femoral arteries and veins were clamped. A bifurcated hemashield knitted vascular graft first anastomosed to the aorta and then right distal external iliac artery, clamps on the right were removed and blood flow to the right leg was reestablished. Aneurysmectomy was extended to the left iliac aneurysm, there was a 2 cm opening in the posterior aspect of the aneurysm to the iliac vein and hemorrhage from the fistula was controlled by fogarty catheter. Fistula was oversewn inside the aneurysm, graft was anastomosed to distal external iliac artery. Both internal iliac arteries were ligated. Postoperative course was uneventful. Early postoperative hypertension was treated with administration of nitroglycerine and Na nitropruside. Left lower extremity edema subsided in 7 days. She was discharged on 10 th postoperative day. The pathological specimens revealed the atherosclerotic changes in the aorta.

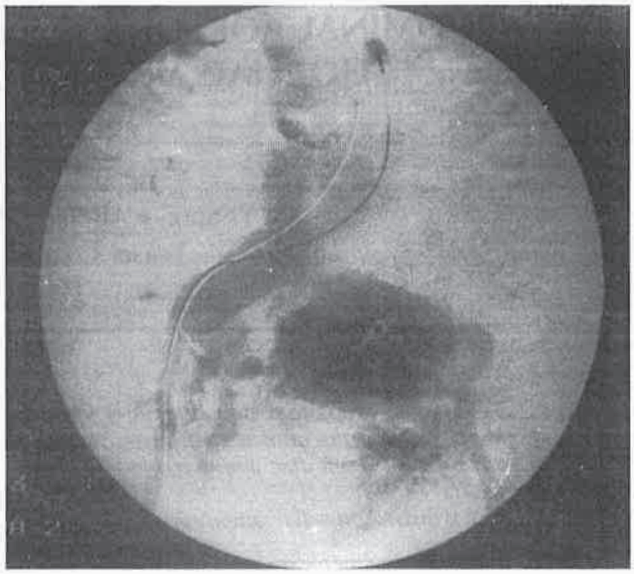

Figure1. Aortagram revealing the aortailiac aneurysm and ilio-iliac AVF.

DISCUSSION

Syme first described the aortacaval fistulas in 1831 (2-4). Most commonly it spontaneously occurs due AAA (80 %), trauma accounts for 15 % and iatrogenic causes (during lumbar laminectomy and in aortic false aneuryms) account for 5 % of cases. (3-8). Spontaneous aortocaval fistulas are atherosclerotic but occur in syphilis, in mycotic aneurysms, Ehler-Danlos syndrome, Marfan's syndrome, Takayashu arteritis, neoplasms (3-5). Spontaneous fistulas due to AAA occur between 48 - 78 years of age (mean 63), in Marfan's syndrome and syphilis occur 21 and 37 years respectively, in traumatic ones it is 22- 46 years (mean 32). The average diameter of the aneurysm when fistula occurs is 9.3 cm for aorta and 5,1 cm for iliac veins (3, 6). Fistula development is due to periaortic adventitial inflammatory reaction and pressure related necrosis of the aortic wall. Only 6% of cases were reported in women and 76 % of rupture occurs into the vena cava inferior (5). Rupture of the isolated iliac aneurysms into the iliac veins produce similiar physiologic consequences (6).

Aortacaval fistulas secondary to AAA results in circulatory disturbances but occasionally remains asymptomatic. Aldosterone levels are increased. Plasma volume increases and hemodilution occurs. Total peripheral resistance and mean arterial pressure decreases. Most cases cannot be diagnosed preoperatively. Abdominal or back pain, widened pulse pressure, acute elevated venous pressure, abdominal bruit, manifestations of acute heart failure (dyspnea, edema, cardiomegaly) which are present in 2/3 of cases, signs of venous compression by the aneurysm (hematuria, rectal bleeding, lower extremity edema) are the major signs and symptoms of rupture and aortocaval fistula (3, 4, 6).

Abdominal ultrasound, color coded duplex ultrasound, angiography, computed tomography, MRI, radioisotope scanning and measurement of the oxygen concentration are helpful in diagnosis of the fistula (3,4, 6).

In operation thrill over the vena cava inferior and Branham's sign (bradycardia and incraese in blood pressure) indicates the presence of fistula (4). Aorta must be gradually clamped not to increase the afterload suddenly and to lower the venous return abruptly which precipitates ventricular arrythmia and cardiac arrest (3). Proximal compression of the vena cava should be applied to prevent paradoxical emboli (3). Autotransfusion should also be used due to excessive bleeding. Mean blood loss is six lt (6). Excessive bleeding from the fistula should be controlled digitally or ballon catheters.

Reported operative mortality rate is 21-55 % for aortacaval fistulas and 5-10 % for iliac AV fistulas and post operative mortality is 20 % for aortacaval fistula.

Preoperative diagnosis reduces the mortality from 50% to 20% (6).

In our case massive leg swelling and the abdominal bruit are the only presenting signs.It was nearly an asymptomatic case. Excessive bleeding and the difficultiness in intrapelvic distal clamping were the major drawbacks. Iliac aneurysms extending nearly to the pelvic outlets of the iliac arteries must be considered in the inoperability criteria which makes the bleeding control very difficult.

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