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Address for Correspondence

Selimiye Mah. Tıbbiye Cad. 34668 Üsküdar, İstanbul

Phone: +90 216 418 96 16

E-mail: tipfakultesi@sbu.edu.tr

Issuing Body

Galenos Yayınevi Tic. Ltd. Şti.

Molla Gürani Mah. Kaçamak Sok. No: 21, 34093, Fındıkzade, İstanbul, Turkiye

Phone: +90 212 621 99 25

Fax: +90 212 621 99 27

E-mail: info@galenos.com.tr

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Current Methods of Treatment in Critical COVID-19 Patients

COVID-19 Kritik Hastalarında Güncel Tedavi Yaklaşımları

Yelda Balık[1], Osman Ekinci[2]

[1]*University of Health Sciences Turkey, İstanbul Haydarpaşa Numune Training and Research Hospital, Clinic of Intensive Care, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, İstanbul Haydarpaşa Numune Training and Research Hospital, Clinic of Anesthesiolgy and Reanimation, İstanbul, Turkey*

ABSTRACT

A new type of coronavirus was detected in China at the end of 2019 and spread across continents in a very short time. The World Health Organization declared pandemic in March 2020 due to the virus, which is highly contagious and occurs with respiratory failure. The virus, which had serious economic consequences, made health systems inoperable with the increasing number of patients. The virus, which causes critical illness in 5% of patients, appears with severe respiratory distress and impairements in other organ systems, especially in people with additional diseases, and requires multi-disciplinary observation and treatment approaches. Our aim is to summarize current literature on Coronavirus disease 2019 in intensive care units.

Keywords: Coronavirus disease 2019, intensive care, mechanical ventilation

ÖZ

2019 yılı sonunda Çin'de ortaya çıkan ve kısa sürede kıtalar arasında yayılım gösteren yeni tip bir koronavirüs saptandı. Oldukça bulaşıcı olan ve solunum yetmezliği ile seyreden virüs nedeni ile Dünya Sağlık Örgütü Mart 2020'de pandemi ilan etti. Ciddi ekonomik sonuçlar doğuran virüs, artan hasta sayıları ile sağlık sistemlerini de çalışamaz duruma getirdi. %5 hastada kritik hastalık meydana getiren virüs, özellikle ek hastalığı olan kişilerde ciddi solunum sıkıntısı ve diğer organ sistemlerinde bozulmalar ile karşımıza çıkmakta olup, multi disipliner takip ve tedavi yaklaşımlarını gerektirmektedir. Amacımız yoğun bakımda izlenen Koronavirüs hastalığı 2019'a karşı güncel bilgileri derlemektir.

Anahtar Kelimeler: Koronavirüs hastalığı 2019, yoğun bakım, mekanik ventilasyon

Introduction

A new coronavirus, named as Severe Acute Respiratory syndrome virus-2 (SARS CoV-2), caused pandemic. By now, this novel Cov has resulted in 18 million confirmed cases and more than 600,00 deaths (1). Neither overwhelming health systems nor highly infectious virus has opened new doors for healthcare workers. In the latest World Health Organization's (WHO) surveillance report, it was informed that 20% Coronavirus disease-2019 (COVID-19) patients needed hospitalization and 2% were treated in intensive care unit (ICU) (2). Lack of knowledge obligated data sharing. After outbreak, many publications were transmitted. Our aim is to summarize information about intensive care treatment in COVID-19.

Characteristics of the Patients Treated in ICU

First case has been reported to WHO on December 31, 2019 in Wuhan, China. After cluster of pneumonia cases with unknown origin, Chinese government started to investigate the outbreak. It has been proved that the virus belongs to coronavirus family which caused two epidemics in past twenty years (3,4). After first cases in China, the new, very contagious virus spread all over the World and WHO declared pandemic in March, 2020 (5). Clinical manifestations are defined as COVID-19 disease. All age groups seem to be affected by SARS CoV-2 but severity of disease is variable. Although some cases are asymptomatic, severe and critical disease can occur in some cases. According to a report from Chinese Center for Disease Control and Prevention, incidence of mild cases is 81%, that of severe cases is 14%, and that of critical cases is 5% (Table 1) (3).

Address for Correspondence: Yelda Balık, University of Health Sciences Turkey, İstanbul Haydarpaşa Numune Training and Research Hospital, Clinic of Intensive Care, İstanbul, Turkey

Phone: +90 555 297 52 09 E-mail: yelda_doseme@hotmail.com **ORCID ID:** orcid.org/0000-0001-8382-6569

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Table 1. Laboratory findings related to negative outcomes (9,11,12)
Thrombocytopenia
Lymphopenia
Elevated ferritin, lactate dehydrogenase, D-dimer, C-reactive protein, creatine phosphokinase
Elevated liver enzymes
Serum lactate >2 mmoL/L
Elevated cardiac enzymes (e.g. troponin)
Acute kidney injury

Classification of COVID-19 Disease (3)

Asymptomatic: No clinical symptoms, COVID-19 polymerase chain reaction (PCR) is positive (1% of cases).

Mild: Patients have upper respiratory tract infection symptoms (fever, cough, myalgia etc.), with/without pneumonia development.

Severe: Dyspnea, respiratory frequency ⩾30/min, blood oxygen saturation ⩽93%, PaO_2/FiO_2 <300 mmHg, and/or lung infiltrates >50% within 24 to 48 hours.

Critical: Multi-organ dysfunction/failure, septic shock.

Restricted health sources necessitate reasonable usage of all resources. After exposure to virus, symptoms usually start within 4-5 days (6). All patients should be carefully examined for hospitalization and intensive care. Viral pneumonia can cause acute respiratory distress that leads to mortality and morbidity. Real time PCR test should be performed for diagnosis. Meanwhile, all the patients who have respiratory tract infection symptoms, for example, cough, fever, difficulty breathing, fatigue and myalgia, have a potential for COVID-19 .

ICU administration was 26%, ICU mortality was 31% and 59% of patients treated in ICU had comorbidities. The most common comorbidity was cardiovascular disease, followed by hypertension and diabetes mellitus. In Italy, 14. 2% of COVID-19 patients have died and mortality rate is higher in the elderly and those with comorbidities (7). In the United States of America, mortality rate is 3.2% and 90% of patients treated in hospital have one underlying medical condition (most frequently hypertension, obesity, cardiovascular diseases metabolic diseases and chronic lung diseases) (8). According to the latest Turkish Ministry of Health COVID-19 guideline, patients who have symptoms below should be evaluated for critical care (Table 2).

Table 2. Suspected ICU admission
Dyspnea and respiratory distress
Respiratory rate ⩾30/minute
PaO_2/FiO_2<300 mmHg
Increase in O_2 demand
Despite 5 L/minute O_2 PaO_2<70 mmHg, SpO_2 <90%
Hypotension[a]
Hypoperfusion
Tachycardia (heart rate >100/minute)
Acute organ failure
Patients with immunosuppression
Arrhythmia
Macrophage activation syndrome
>2 points increase in SOFA[b] score

[a]: SOFA: Sequential organ failure assessment, [b]: SBP <90 mmHg, MBP <65 mmHg, drop off 40 mmHg from usual
ICU: Intensive care unit, SOFA: Sequential organ failure assessment

2. Critical Care Steps

COVID-19 can cause devastating results by Acute Respiratory Distress syndrome (ARDS), viral sepsis and hyper inflammatory syndrome. In severe cases, it should be carefully handled. COVID-19 treatment can be grouped as anti-viral therapies, immunmodulation and general support.

Recently, in a meta-analysis, nosocomial transmission of SARS CoV-2 is reported as 44% (9). In daily practice, various airborne factors are formed, which plays a major role in SARS CoV-2 transmission (e.g. endotracheal intubation, bronchoscopy, non-invasive mechanical ventilation, HFNC oxygen, open aspiration of mucus, nebulized drug application, manual ventilation, prone positioning, tracheostomy, cardiopulmonary resuscitation). Patients should be treated in negative pressure rooms to prevent spread of airborne particles if possible. In the lack of negative pressure rooms, isolated areas must be planned and increased patient numbers of COVID-19 obligated to cohorts (10). Viral exposure to health care providers can be decreased by using checklists before daily visits of patients.

Common complications of COVID-19 include acute respiratory distress, sepsis and septic shock, acute renal injury, cardiac injury (e.g. arrythmia, pericarditis, myocarditis, pericardial effusion) and hepatic dysfunction (11,12,13). Patients should be monitored carefully. Diagnostic tests should be performed to enlighten complications. To determine variance, daily ECG follow-up should be considered in patients who take medication that cause prolonged QT interval. Invasive arterial monitoring is determined to both blood gas samples and close blood pressure pursuit. Because of common usage of vasoactive drugs and fluids, central venous access should be applied. Current knowledge of hemodynamic approach is identical to latest sepsis guidelines.

During SARS CoV-2 infection, hypoxemic respiratory failure occurs in 19% of patients (6). To control hypoxemia, most cases require intubation and invasive mechanical ventilation. Up to this point, standard treatment therapies have not been designed.

Healthcare associated infections have been reported at the

rate of 44.5% in COVID-19. Longer length of ICU and hospital stay and higher mortality rate have been found to be related to HAI. In this paper, multidrug-resistant *Acinetobacter baumanii* has been isolated most commonly (9). According to current knowledge, HAI is more frequent in SARS Cov-2 patients (14). Deficiency in adaptation to bundles, exhausted medical staff, insufficient medical equipment, and high rate of intubated patients may bring on higher HAI incidence.

2.a Respiratory Support

Recent reports showed that 40-80% of patients required oxygen support, 2.5-5% required intubation and the prevalence of hypoxemic respiratory failure was 19% (11,15). Patients with underlying comorbidities, obesity, and smoking develop respiratory failure more frequently. WHO advises target SpO_2>90-92%, in pregnant patients as >92% (16).

According to surviving sepsis campaign, mechanically ventilated COVID-19 patients should be treated like acute respiratory distress syndrome (10). Nonetheless, Gattinoni reported that L type and H types of COVID-19 pneumonia were defined. According to this report, in L type, at the beginning of illness, low elastance, low ventilation/perfusion ratio, low lung weight, low lung recruitability and near normal compliance were described. In H type, high elastance, high right to left shunt, and high lung weight were observed (17). Following L type, clinics of patients can improve or worsen. Increased transmural pressure shifts by high respiratory drive may cause vascular oedema. Occurrence of dyspnea has been accused for clinical worsening. This phenomenon is called Patient self-inflicted lung injury (P-SILI) (18). Early intubation was suggested to reduce P-SILI (19,20). L type cases can reply to conventional oxygen therapies which include nasal cannula, high flow nasal cannula (HFNC) and non-invasive mechanical ventilation (NIV) support, although Actinon remarked this benefit as "questionable". In the recent paper, L type intubated patients should be ventilated with higher tidal volumes (<6 mL/kg). Prone positioning is defined only as rescue maneuver and high levels of positive end expiratory pressure (PEEP) (>8-10 cmH_2O) should be avoided because of low recruitability and hemodynamical side effects (17).

In literature, HFNC is associated with lower mortality rate, decreased ICU administration and decreased reintubation (21,22). Potential benefits of HFNC are high patient consistency, stable FiO_2 and reduced dead space. Surviving sepsis campaign suggests HFNC in patients unresponsive to supplemental oxygen and WHO recommends the usage of HFNC in selected patients (10,23). ROX index can be beneficial to diagnose failed HFNC (24). NIV can be preferred in patients with cardiogenic pulmonary oedema and chronic obstructive pulmonary disease. In the presence of hypercapnia, FNC is not recommended. Both HFNC and NIV could cause airborne transmission of SARS CoV-2, until the spread of virus is still undetermined (25). To define excessive transpulmonary pressure swings in spontaneous breathing patients, usage of work of breath and transpulmonary pressure measurement and lung imagining with computerized tomography or ultrasound can be beneficial. Both NIV and HFNC should be closely monitored. Up to this point, no certain timing for intubation has been settled. Non-uniform characteristic of disease should be kept in mind. Delayed intubation can cause clinical worsening. Stigmas of respiratory failure are mentioned in Table 3 (26,27).

In 2012, ARDS was defined by Berlin criteria (Table 4, the Berlin definition of ARDS) (28). In the light of current information, COVID-19 patients developing ARDS should be treated according to lung protective ventilatory interventions. Both volume and pressure controlled ventilatory modes can be applied. Tidal volume target should be 4-8 mL/kg of predicted body weight, plateau pressure should be below 30 cmH_2O, peep titration should be applied (Table 5, protective ventilatory strategies) (29). Despite lack of certain data about driving pressure, it can be useful for PEEP titration) (29). Neuromuscular blockade and prone positioning should be applied to patients with $PaO_2/FiO_2 \leqslant$ 150 mmHg (30). Prone positioning could improve oxygenation in mild and severe cases and should last more than 12 hours (31,32). There are few ongoing studies about extracorporeal membrane oxygenation (ECMO). According to extracorporeal life support organization COVID-19 Interim Guideline, patients should be unresponsive

Table 3. Respiratory failure indicators

Increased work of breath,
Rapid clinical worsening
Hypoxemia despite maximal oxygen support[a]
Hyper carbic respiratory failure
HFNC flow demand >40/L and FiO_2>0.6
Hemodynamic instability

[a]: Nasal cannula demand >6/, non-breather mask demand>10/L, HFNC: High flow nasal cannula

Table 4. The Berlin definition of ARDS

The Berlin definition of ARDS	
On set	The presence within 7 days of a known clinical insult, new or worsening respiratory symptoms
Chest imagining	Bilateral opacities not fully explained by heart failure or volume overload
Oxygenation	**Mild:** 200 mmHg<$PaO_2/FiO_2 \leqslant$300 mmHg with CPAP or PEEP ⩾5 cmH_2O
	Moderate: 100 mmHg< $PaO_2/FiO_2 \leqslant$200 mmHg with PEEP ⩾5 cmH_2O
	Severe: $PaO_2/FiO_2 \leqslant$100 mmHg with PEEP ⩾5 cmH_2O

ARDS: Acute Respiratory Distress syndrome, PEEP: Pasitive and expiratory pressure

to conventional ARDS therapies involving prone positioning. Veno-arterial ECMO should be applied to patients who have cardiac complications. Contraindications and indications for ECMO in SARS CoV-2 infection are similar and defined in Table 6 and Table 7. In overwhelmed capacities of ECMO and health care systems, triage becomes essential (32). Despite the absence of precise information, inhaled Nitric oxide (i NO) could dilate pulmonary vessels, may improve oxygenation and ventilation perfusion ratio, and has immunomodulatory effects. Routine usage of i NO is not recommended (32,33,34).

Table 5. Protective ventilatory strategies

Tidal volume	6 mL/kg PBW (range: 4-8 mL/kg PBW)
Plateau pressure	Less than 30 cm H_2O
Respiratory rate	Up to 35 breaths per minute, goal of pH 7.30-7.45 but may allow permissive hypercapnia with a pH >7.15
PEEP	Initiate at ⩾5 cm H_2O Titrate according to ARDS set lower PEEP/higher FiO_2 table
Oxygenation target	Titrate FiO_2 to: PaO_2 55-80 mmHg, SpO_2 88-95%

PBW: Predicted body weight, PEEP: Positive end expiratory pressure, ARDS: Acute Respiratory Distress syndrome

Table 6. Contraindications for ECMO in SARS CoV-2 infection

Relative contraindications	Absolute contraindications
Age ⩾65 years	Advanced age
Obesity BMI ⩾40 kg/m²	Clinical Frailty scale category ⩾3
Immunodeficiency	Mechanical ventilation>10 days
Lack of testamentary guardian	Significant underlying comorbidities[b]
Advanced chronic systolic heart failure	Severe acute neurologic injury, e.g., anoxic, stroke
High dose vasopressor requirement[a]	Uncontrolled bleeding
-	Contraindications to anticoagulation
-	Inability to accept blood products

[a]: Not under consideration for VA or V-VA ECMO, [b]: Cirrhosis, dementia, disseminated malignancy, Advanced lung disease, Uncontrolled diabetes with chronic end-organ dysfunction, severe deconditioning, protein-energy malnutrition, severe peripheral vascular disease, severe multiple organ failure, ECMO: Extracorporeal membrane oxygenation, SARS CoV-2: Severe Acute Respiratory syndrome virus-2, BMI: Body mass index

Table 7. Indications for ECMO in SARS CoV-2 infection

PaO_2/FiO_2<60 mmHg 6 hours[a]
PaO_2/FiO_2<50 mmHg 5 hours[a]
Ph <7.20 and $PaCO_2$>80 mmHg for >6 hours[a]

[a]: Without contraindications for ECMO, ECMO: Extracorporeal membrane oxygenation, SARS CoV-2: Severe Acute Respiratory syndrome virus-2

2b. COVID-19 Specific Treatment and Cytokine Storm Syndrome

Currently, no specific antiviral treatment is recommended. So far, lopinavir/ritonavir, hydroxychloroquine, remdesivir, umifenovir, favipiravir and many other drugs have been used. Consensus on standard treatment has not been established. Many ongoing trials may enlighten this issue.

Remdesivir has shown beneficial effects in patients of varying initial severity. A reduction in mean time for recovery resulted in higher probabilities of recovery on the 8-level sequential scale at day 15 and a statistically non-significant reduction in mortality in mild to severe COVID-19 patients. It also resulted in a statistically insignificant reduction in clinical recovery time with no effect on mortality rate in severe COVID-19 patients (35).

According to the latest Turkish Ministry of Health COVID-19 guideline, patients developing pneumonia should be treated with hydroxychloroquine with/or favipiravir (Figure 1). Current knowledge promotes early administration of antiviral therapies. If patients worsen under hydroxychloroquine, favipiravir should be added to the treatment. Multidrug and electrolyte imbalance can cause prolonged Qt and sudden cardiac death in intensive care unit. Other risk factors for prolonged Qt are hepatic and renal dysfunction, and sepsis. Drug interactions must be reviewed (36). All patients should be evaluated with electrocardiogram before hydroxychloroquine. During pregnancy, lopinavir/ritonavir is recommended for the treatment. Any potential benefits have been shown (37).

Defining superinfections and coinfections in COVID-19 is problematic. Both WHO and Surviving Sepsis Campaign recommend empiric antimicrobials in mechanically ventilated COVID-19 patients. Antimicrobial therapies should be daily evaluated for de-escalation, duration and appropriateness (10).

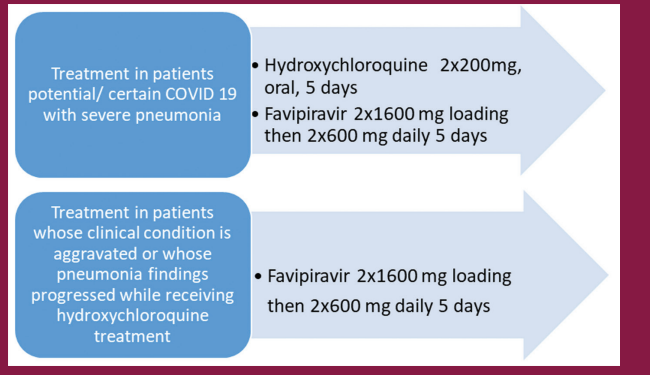

Figure 1. COVID-19 Treatment in adult patients (Adapted form: T.C. Sağlık Bakanlığı COVID-19 [SARS-CoV-2 Enfeksiyonu) (Bilim Kurulu Çalışması) Erişkin Hasta Tedavisi.; 2020].

SARS CoV-2: Severe Acute Respiratory syndrome virus-2, COVID-19: Coronavirus disease-2019

Table 8. COVID-19 immune (convalescent) plasma clinical use criteria
Fever >7 days
In 24-48 hours >50% infiltration increase in lung imaging
Respiratory rate >30/min
PaO_2/FiO_2<300 mmHg
Oxygen saturation <90%
Mechanical ventilation support
Two or more points increase in SOFA
Stigmas for rapid clinical worsening
Vasoactive drug administration
COVID-19: Coronavirus disease-2019, SOFA: Sequential organ failure assessment

Table 9. Thromboprophylaxis		
D-Dimer <1000ng/mL	**BMI <40 kg/m²**	**BMI >40 kg/m²**
CrCL ⩾30 mL/min	Enoxaparin 40 mg/day	Enoxaparin 40 mg/day twice
CrCL <30 mL/min	Standard heparin 5.000 U 2 or 3 times a day	50% of low-molecular weight heparin dosage
D-dimer ⩾1.000ng/mL	**BMI <40 kg/m²**	**BMI >40 kg/m²**
CrCL ⩾30 mL/min	Enoxaparin 0.5 mg/kg day	-
CrCL <30 mL/min	Standard heparin 5.000 U 2 or 3 times a day	-
BMI: Body mass index, CrCL: Creatinine clearance		

In recent years, convalescent plasma has been used to treat viral infections. In Mair-Jenkins metanalysis, convalescent plasma can reduce mortality by passive immunoterapy (38). At the beginning, in China, convalescent plasma has been given in small groups of COVID-19 patients and clinical improvement has been reported (39). Because of limited donor pool, efficiency in COVID-19 and effective dosage clinical approach remains still in dark. In cases with immunoglobulin A deficiency, cytokine storm syndrome and elongated SARS CoV-2 infection, convalescent plasma is not recommended (40). Indications of convalescent plasma are mentioned in Table 8 (40).

During viral infections, exaggerated immune response can cause endothelial damage or dysfunction and tissue edema and shock. Hyperinflammatory response can trigger multiorgan failure and causes mortality. Cytokine storm is thought as a major underlying clinical feature in severe cases. In a recent paper, IL-6 and IL-2 receptor levels have been found to be significantly higher in severe COVID-19 cases. In contrast, there were no statistically significant differences in serum tumor necrosis factor alpha (TNF-a), IL-1, IL-8, or IL-10 (41). In further investigations, higher concentrations of granulocyte colony stimulating factor, interferon-inducible protein 10, monocyte chemoattractant protein-1 and TNF-a were found in patients who required admission into an intensive care unit (42,43). Due to cytokine storm, ARDS and macrophage activation syndrome (MAS) may occur. Clinical and laboratory features of MAS are persistent fever, high/increasing CRP, high levels of ferritin (>700 mg/L), elevated D-dimer, lymphopenia, thrombocytopenia and elevated liver enzymes (44).

In RECOVERY trial, hospitalized patients receiving dexamethasone up to 10 days had a lower 28 mortality rate (45). In the latest treatment guideline of WHO, corticosteroid usage has been recommended. Corticosteroids can decrease mortality in severe and critical COVID-19 patients. Daily 6 mg dexamethasone or equivalent dosage is given intravenously or orally. Duration should be 7-10 days and glucose levels should be monitorized (46). Turkish Ministry of Health recommends the usage of 6 mg/day dexamethasone or 0.5-1 mg/kg prednisolone or equivalent methylprednisolone up to 10 days in patients who need oxygen therapy. Considering the risk factors of the patient, a higher dose of glucocorticoid (pulse, 250 mg/day methyl prednisolone) may be decided in patients whose need for oxygen has increased within 24 hours despite the treatment or whose acute phase response has increased (44).

In cases unresponsive to glucocorticoid, tocilizumab, which inhibits IL-6 or anakinra, IL-1 inhibitor, can reduce inflammatory response. Increased risk for infections should be kept in mind in those patients. Clinical response should be monitored with CRP, IL-6, fever and O_2 demand. Contraindications for toculizumab are pregnancy, neutropenia, active infections (tuberculosis, hepatitis B and C), allergy and hypersensitivity (47). Tocilizumab 8 mg/kg dos can be applied. In severe cases, when initial dose of 400 mg is administered, the dose can be repeated in the form of 200-400 mg within 12-24 hours according to the changes in values in clinical and laboratory findings. After treatment, patients should be carefully monitored for complications like infections, gastrointestinal perforation and ARDS like syndrome (44).

2c. Thromboprophylaxis

Although thromboprophylaxis is not a specific treatment for COVID-19, it is widely thought to be important considering the pathophysiology of the disease. Microvascular thrombosis may develop due to increased endothelial damage in COVID-19 patients. Increased fibrinogen and D-dimer levels and hypercoagulability also increase severity of disease. These patients are thought to have a high risk of developing pulmonary embolism. Therefore, low molecular weight heparin should be administered to every patient at prophylactic dose and to patients with high clinical thrombosis at the therapeutic dose except thrombocytopenic patients. At active hemorrhage and

thrombocytopenia states, intermittent pneumatic compression can be beneficial. In case of heparin induced thrombocytopenia, thromboprophylaxis can be ensured by fondaparinux. Without any drug interactions, oral anticoagulation is kept similiar (44). Thromboprophylaxis according to the body weight and renal function is summarized in Table 9.

Conclusion

Fight against pandemic still goes ahead. Although specific treatment has not been found, ongoing

trials and development of COVID-19 vaccine may enlighten our ways to a non-pandemic COVID-19 world. Until that day, the prevention of COVID-19 will play a major role.

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Validity of Histopathologic Lesions in the Diagnosis of Fibrotic Interstitial Lung Diseases

Fibrotik İnterstisyel Pnömoni Tanısında Histopatolojik Lezyonların Değeri

Halide Nur Ürer[1], Neslihan Fener[1], Nurcan Ünver[1], Erdoğan Çetinkaya[2]

[1]*University of Health Sciences Turkey, Yedikule Chest Disease and Thoracic Surgery Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Pulmonary Medicine, İstanbul, Turkey*

ABSTRACT

Background: Fibrotic interstitial pneumonia (FIP) is a group of dynamic and progressive interstitial diseases. Usual interstitial pneumonia (UIP), centrilobular fibrosis (CF), and fibrotic non-specific interstitial pneumonia (NSIP) are major pathologic patterns. Although not a typical pattern, intralobular fibrous obliteration with microcysts (IFOM) destroys the entire lobule, which can be another pattern. The present study investigated the role and importance of FIP patterns in pathology diagnosis. The lesions were categorized according to the UIP classification and the sensitivity and specificity of the findings were examined.

Materials and Methods: We reviewed and reexamined the cases of FIP. Fibrosis patterns were evaluated as UIP, CF, NSIP, and unclassified according to the current guidelines. Predominant and, if present, secondary patterns of interstitial fibrosis were determined in histologic examination. Evaluation for IFOM pattern was also included. Based on pattern and histologic examination, pathologic UIP diagnoses were categorized as definite, probable, indeterminate, and alternative diagnosis. Sensitivity and specificity values of the lesions were calculated. Relationships between morphological patterns and bronchiectasis, ossification, and emphysema were analyzed.

Results: A total of 226 cases with FIP were identified. Predominant patterns were found as CF in 80 (35.4%), IFOM in 74 (32.7%), NSIP in 44 (19.5%), unclassified in 17 (7.5%) and UIP in 11 (4.9%) cases. Secondary patterns were detected in 189 (92.5%) in cases. Predominant UIP pattern showed a significant difference in the exclusion of non-UIP diagnoses. The UIP and IFOM patterns were found to have diagnostic sensitivity and specificity of 75%, 87.5% and 95%, 73.7% respectively. Predominantly and secondary IFOM were observed in 59.3% of all cases.

Conclusion: Histopathologic FIP patterns include specific challenges. Although not a typical pattern, IFOM was second most common after CF among the predominant patterns observed. This indicates that when identifying lesions, coexistent patterns must be reported rather than a diagnosis. CF-focused diagnostic approach may be more accurate in FIP pathologic evaluation.

Keywords: Interstitial pneumonia, pulmonary fibrosis, pathology, sensitivity, specificity

ÖZ

Amaç: Fibrotik interstisyel pnömoni (FİP) akciğer interstisyumun ilerleyici ve dinamik bir hastalık grubudur. Usual interstisyel pnömoni (UİP), sentrilobüler fibrozis (SF), fibrotik non-spesifik interstisyel pnömoni (NSİP) majör paternlerdir. Tipik bir patern olmasa da kistik intralobüler obliteratif fibrozis (KİOF) lobülü tümüyle ortadan kaldıran bir diğer patern olabilir. Çalışmanın amacı FİP patoloji tanısında paternlerin önemini araştırmaktır. Lezyonları UİP sınıflamasına göre değerlendirerek sensitivite ve spesifiteyi belirlemektir.

Gereç ve Yöntemler: FİP tanılı olgular tekrar değerlendirilerek incelendi. Fibrozis paterni güncel rehberlere göre UİP, SF, NSİP ve sınıflanmayan olarak gruplandı. Baskın patern ve eğer varsa sekonder patern arandı. Ayrıca KİOF patern olarak değerlendirildi. UİP kesin, olası, belirsiz ve alternatif tanı olarak gruplandı. Lezyonların sensitivite ve spesifite değerleri hesaplandı. Morfolojik patern ile bronşektazi, ossifikasyon, amfizem arasında ilişki araştırıldı.

Bulgular: Toplam 226 FİP olgusu saptandı. Baskın patern SF 80 (%35,4), IFOM 74 (%32,7), NSİP 44 (%19,5), sınıflanmayan 17 (%7,5) ve UİP 11 (%4,9) olguda bulundu. Sekonder patern 189 (%92,5) olguda izlendi. Baskın UIP patern UİP dışı tanıyı dışlamada anlamlı

Address for Correspondence: Halide Nur Ürer, University of Health Sciences Turkey, Yedikule Chest Disease and Thoracic Surgery Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey

Phone: +90 505 265 93 65 E-mail: nururer@gmail.com **ORCID ID:** orcid.org/0000-0002-0549-9969

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ÖZ

fark gösterdi. UİP paternin tanısal sensitivite ve spesifitesi %75 ve %95 idi. Baskın ve sekonder IFOM paterni %59,3 bulundu. IFOM'un UİP tanısında sensitivite ve spesifite değeri %87,5 ve %73,7 idi.

Sonuç: Histopatolojik FİP paternlerin kendine özgü güçlükleri bulunur. IFOM tipik patern olmasa da SF'den sonra en sık saptanan paterndir. Bu durum tanıdan ziyade lezyonların tanımlanması gerekliliğini göstermektedir. SF odaklı tanısal yaklaşım FİP'nin patolojik değerlendirmesinde daha öncelikli olabilir.

Anahtar Kelimeler: İnterstisyel pnömoni, pulmoner fibrozis, patoloji, sensitivite, spesifite

Introduction

Fibrotic interstitial pneumonia (FIP) is a group of interstitial lung diseases with varying clinical, radiological, and pathological findings, each characterized by a unique pathological pattern.

The key point in the diagnosis and treatment of an interstitial disease is whether it is idiopathic pulmonary fibrosis (IPF). Current classifications recommend that the diagnosis of FIP should be based on a multidisciplinary clinicoradiologic/pathologic consensus (1,2). Marked clinical and radiologic findings are sufficient for diagnosis. If these findings are insufficient, biopsy is recommended (3). The presence and distribution of lesions in pathologic evaluation determine the specific histological pattern. Major fibrotic patterns are usual interstitial pneumonia (UIP), centrilobular fibrosis (CF), and fibrotic non-specific interstitial pneumonia (NSIP) (4). UIP is the pathologic diagnosis of IPF and CF is the prototype of the hypersensitivity pneumonia. Fibrosis lacking a characteristic pattern is defined as unclassified.

In cases with ambiguous clinicoradiologic findings, pathologic examination of biopsy specimens is important. The presence of unexpected lesions together with typical patterns can make diagnosis challenging. Although not a typical pattern, intralobular fibrous obliteration with microcysts (IFOM) destroys nearly the entire lobule and is an important lesion of progressive fibrosis (5). Because typical patterns are obliterated with the formation of diffuse fibrosis, the interstitium resembles a fireplace where histologic clues are lost. The histologic presentation may be equivalent to that of end-stage disease. A specific diagnosis is only possible if there is a typical pattern accompanying destructive fibrosis.

The present study investigated the role and importance of fibrotic interstitial lung disease patterns in pathology diagnosis. The lesions were categorized according to the UIP classification and the sensitivity and specificity of the findings were analyzed.

Material and Methods

Cases with a provisional diagnosis of interstitial lung disease, who underwent open or video-assisted wedge resection of the lung, were included in the study. Pathology reports from 2013 to 2019 were reviewed and cases diagnosed with interstitial fibrosis were selected. The cases' slides were reevaluated under light microscopy by the researchers (H.N.U., N.U., N.F.). Predominant and, if present, secondary patterns of interstitial fibrosis were determined in histologic examination. Fibrosis patterns were evaluated as UIP, CF, NSIP, and unclassified according to the current guidelines (Figure 1a,b,c,d) (1,2). Evaluation for IFOM pattern (obliteration of the lobular structure) was also included (Figure 2). Fibroblastic focus (FF) findings were graded as none, sporadic (fewer than 3 in field of view at low magnification), and diffuse (3 or more). Honeycomb fibrocysts, bronchiectasis, interstitial ossification, and emphysema were sought. In addition, minor changes such as well-formed and loose granuloma, centrilobular interstitial isolated giant cells, desquamative pneumonia, organizing pneumonia, smoking-related interstitial fibrosis (SRIF), pleuritis and inorganic dust accumulation, intense inflammation, and increase in lymphoid follicles were investigated. And also, pleuroparenchymal fibroelastosis was evaluated. Based on pattern and histologic examination, pathologic UIP diagnoses were categorized as definite, probable, indeterminate, and alternative diagnosis according to the current guidelines.

Interstitial diseases characterized by cysts were excluded even if FIP was present. Those were Langerhans cell histiocytosis, lymphangioleiomyomatosis, and Birt-Hogg-Dubé (BHD) syndrome. Cases with carcinoma were not included in the study.

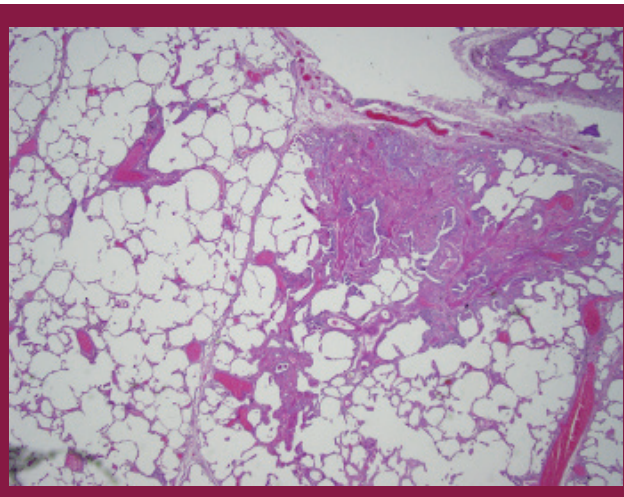

Figure 1a. Usual interstitial pneumonia pattern of irregular fibrosis in a peripheral and subpleural distribution

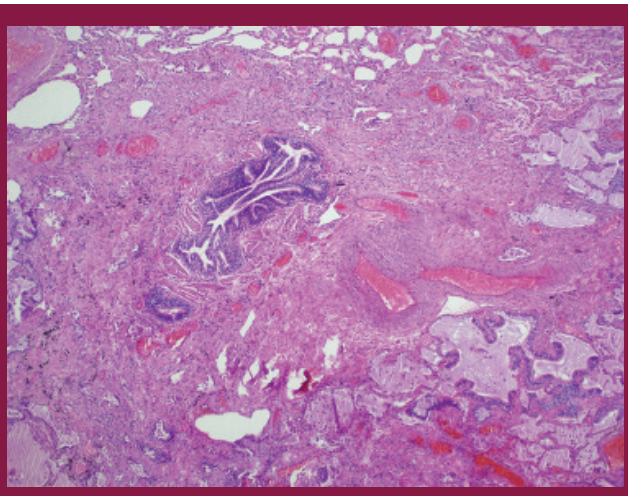

Figure 1b. Centrilobular pattern of fibrosis with airway-centered centrilobular fibrosis

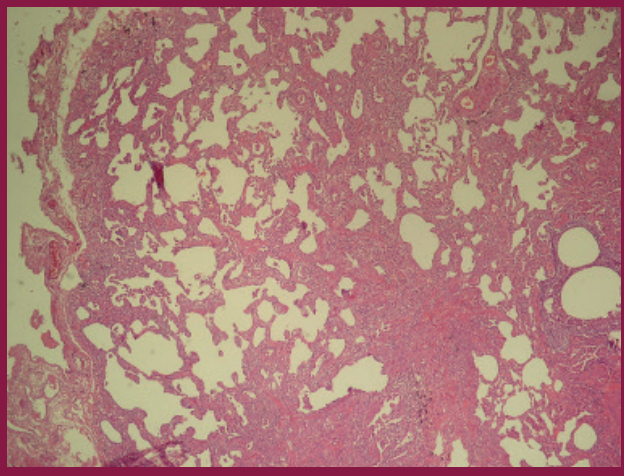

Figure 1c. Fibrotic non-specific interstitial pneumonia pattern of fibrosis showing diffuse involvement of the alveolar walls with thickening

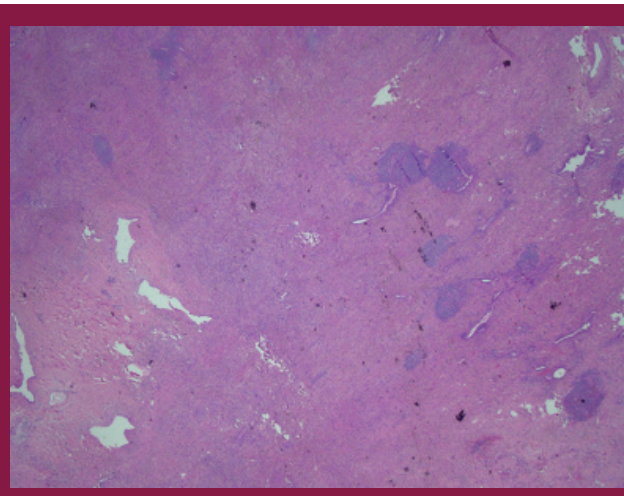

Figure 1d. Unclassified fibrosis with patternless distribution

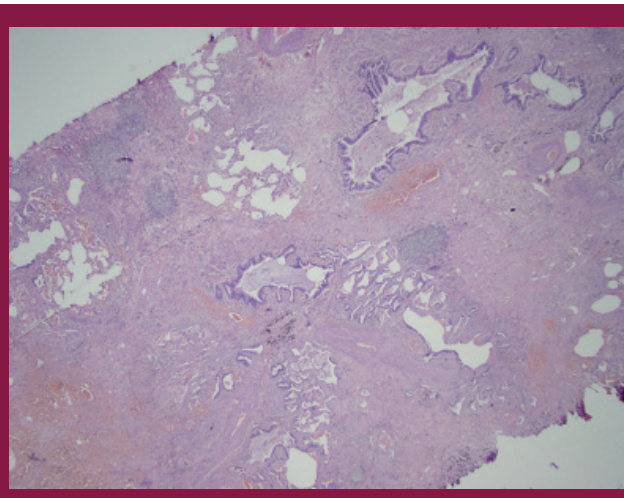

Figure 2. Intralobular fibrous obliteration with microcysts

Study design was approved by Local Ethical Committee (University of Health Sciences Turkey, İstanbul Training and Research Hospital). The study protocol number and date are 2259/20 (08/05/2020). And also, it was approved by Hospital Science Committee (protocol number is 244-5/20), and informed consents were obtained from all study patients.

Statistical Analysis

The data were evaluated using statistical methods. Sensitivity and specificity values were calculated for histologic lesions and diagnoses. Patterns defined as possible UIP and alternative diagnosis were grouped as non-UIP, while the others were grouped as UIP. Relationships between morphological patterns and bronchiectasis, ossification, and emphysema were analyzed. For categorical variables, frequencies were compared using chi-square, Student's t, Mann-Whitney U, and Fisher's Exact tests. Correlation analysis was performed using Spearman's correlation, Pearson's chi-squared test, linear model ANOVA, and bimodal logistic regression tests. Probability rate (p) less than 0.05 was accepted as statistically significant.

Results

A total of 226 cases with FIP were identified. The cases' demographic and clinical characteristics are shown in Table 1.

The characteristics of 17 cases whose predominant pattern was unclassified fibrosis are shown in Table 2.

Among all fibrotic cases, pneumoconiosis was detected in 5 cases (2.2%). Silicosis was detected in 3 cases, and 1 case each had talcosis and coal pneumoconiosis. CF was the predominant pattern in coal pneumoconiosis, while unclassified fibrosis pattern was predominant in the other pneumoconioses.

Table 1. Categorization of UIP patterns

Characteristics	Overall (n=226)
Gender	
Female	95 (42.0%)
Male	131 (58.0%)
Age (years)	
Mean (SD)	57.8 (11.2)
Range	25.0-80.0
Predominant pattern	
Unclassified	17 (7.5%)
NSIP	44 (19.5%)
CF	80 (35.4%)
UIP	11 (4.9%)
IFOM	74 (32.7%)
Secondary pattern	
None	37 (7.5%)
DP	2 (1.1%)
NSIP	38 (20.1%)
OP	11 (5.8%)
CF	55 (29.1%)
SRIF	1 (0.5%)
UIP	41 (21.7%)
IFOM	41 (21.7%)
Fibroblastic focus	
Rare	96 (42.5%)
Extensive	23 (10.2%)
None	107 (47.3%)
Bronchiectasis	
Yes	146 (64.6%)
No	80 (35.4%)
Honeycombing	
Yes	140 (61.9%)
No	86 (38.1%)
Ossification	
Yes	45 (19.9%)
No	181 (80.1%)
Emphysema	
No	134 (59.3%)
Yes	92 (40.7%)
UIP	
Alternative	159 (70.4%)
Indeterminate	43 (19.0%)
Probable	8 (3.5%)
Definite	16 (7.1%)

NSIP: Non-specific interstitial pneumonia, CF: Centrilobular fibrosis, UIP: Usual interstitial pneumonia, IFOM: Intralobular fibrous obliteration with microcysts, DP: Desquamative pneumonia, OP: Organizing pneumonia, SRIF: Smoking-related interstitial pneumonia, SD: Standard deviation

Table 2. Distribution of fibrosis cases with unclassified predominant pattern

Unclassified	17
Non-diagnostic fibrosis	9
Silicosis	3
PPFE	2
Sarcoidosis	1
Talcosis	1
Chronic eosinophilic pneumonia	1

PPFE: Pleuroparenchymal fibroelastosis

In terms of minor changes, 8 cases had loose granuloma and 5 had centrilobular isolated giant cells. Loose granuloma was the predominant pattern in 5.4% of IFOM and 5% of CF while isolated giant cells were detected in 4% and 2.5%, respectively. Both lesions were present in 9.4% of IFOM and 7.5% of CF.

Pleuritis and SRIF were detected in 1 case each. Intense inflammation was observed in 7 cases and prominent lymphoid nodular hyperplasia in 1 case. One case with eosinophilia was in the NSIP group and the other was in the unclassified group.

The most common pathology pattern in the UIP groups was alternative (70.4%) diagnosis and the least common was probable UIP (3.5%). Histopathologic characteristics were compared between the UIP and non-UIP diagnostic groups of the study population (Table 3).

In the comparison of UIP and non-UIP diagnoses, there was no difference according to sex. Although the mean age was not discriminatory, the UIP group was slightly older than the non-UIP group. In cases with definite and probable UIP diagnoses, the most common pattern was UIP, while IFOM and unclassified fibrosis were less common. Predominant UIP pattern showed a significant difference in the exclusion of non-UIP diagnoses. The UIP pattern was found to have diagnostic sensitivity and specificity of 75% and 95%, respectively.

IFOM was observed in 59.3% of all cases. It was associated with both predominant and secondary patterns (Figure 3). The prevalence of IFOM was significantly higher among cases with UIP diagnoses and was 26.2% in non-UIP. Its presence and absence were significant in the pathologic differential diagnosis. IFOM had a sensitivity of 87.5% and specificity of 73.7% in the diagnosis of UIP.

FF was observed in 83.3% of cases diagnosed with UIP. When compared to the non-UIP group, the difference was significant. The sensitivity and specificity of FF in UIP were 83% and 50%, respectively.

Honeycombing and bronchiectasis were significantly more prevalent in the UIP diagnosis group. The sensitivity and specificity of bronchiectasis for a UIP diagnosis were 95% and 39%, respectively. Ossification was detected in 19.9% of all cases and emphysema in 40%. Neither made a significant difference for UIP.

Table 3. Distribution of histopathologic lesion diagnoses

Characteristics	UIP (n=24)	Non-UIP (n=202)	Total (n=226)	p
Gender	-	-	-	0.177
Female	7 (29.2%)	88 (43.6%)	95 (42.0%)	-
Male	17 (70.8%)	114 (56.4%)	131 (58.0%)	-
Age	-	-	-	0.026
Mean (SD)	62.6 (7.9)	57.3 (11.4)	57.8 (11.2)	-
Range	45.0-76.0	25.0-80.0	25.0-80.0	-
Predominant pattern	-	-	-	<0.001
UIP	18 (75.0%)	9 (4.5%)	27 (11.9%)	-
NSIP	0 (0.0%)	56 (27.7%)	56 (24.8%)	-
CF	0 (0.0%)	119 (58.9%)	119 (52.7%)	-
Unclassified	6 (25.0%)	18 (8.9%)	24 (10.6%)	-
IFOM	-	-	-	<0.001
No	3 (12.5%)	149 (73.8%)	152 (67.3%)	-
Yes	21 (87.5%)	53 (26.2%)	74 (32.7%)	-
FF	-	-	-	0.001
No	4 (16.7%)	103 (51.0%)	107 (47.3%)	-
Yes	20 (83.3%)	99 (49.0%)	119 (52.7%)	-
Bronchiectasis	-	-	-	<0.001
No	1 (4.2%)	79 (39.1%)	80 (35.4%)	-
Yes	23 (95.8%)	123 (60.9%)	146 (64.6%)	-
Honeycombing	-	-	-	<0.001
No	0 (0.0%)	86 (42.6%)	86 (38.1%)	-
Yes	24 (100.0%)	116 (57.4%)	140 (61.9%)	-
Ossification	-	-	-	0.231
No	17 (70.8%)	164 (81.2%)	181 (80.1%)	-
Yes	7 (29.2%)	38 (18.8%)	45 (19.9%)	-
Emphysema	-	-	-	0.064
No	10 (41.7%)	124 (61.4%)	134 (59.3%)	-
Yes	14 (58.3%)	78 (38.6%)	92 (40.7%)	-

SD: Standard deviation, UIP: Usual interstitial pneumonia, IFOM: Intralobular fibrous obliteration with microcysts, FF: Fibroblastic focus, NSIP: Non-specific interstitial pneumonia, CF: Centrilobular fibrosis

Excluded cases included 16 with Langerhans cell histiocytosis X, 4 with lymphangioleiomyomatosis, 1 with BHD syndrome, and 5 with concomitant carcinoma and FIP.

Discussion

Our study has demonstrated which histologic lesions have greater validity in the pathologic diagnosis of FIP. Guidelines define UIP as combination of the fibrotic pattern, FF, and honeycomb cysts (1,2). Our study emphasizes that these lesions have an important place in diagnosis. On the other hand, while less common, it is a fact that the non-UIP group can also include these lesions. The characteristic interstitial fibrotic pattern model is undoubtedly important in decision-making (6,7). However, the presence of lesions in the histologic examination may not be enough to narrow down to a single diagnosis.

FIP is a group of dynamic and progressive diseases. The non-stop manner of fibrosis can destroy its characteristic patterns. IFOM, first described by Kradin (5), may be the endpoint of fibrosis. We determined that this lesion might be an important indicator in the diagnosis of UIP. The presence of IFOM as predominant or secondary pattern will obviously facilitate the pathology diagnosis of UIP. Bridging fibrosis in the center of the lobule extending to the septum or pleura causes a structural deformity similar to IFOM (4,8). This indicates that fibrosis may be more complex than expected in pattern determination (9). As a result, IFOM may be important both in the diagnosis of UIP and the demonstration of progressive fibrosis.

The provisional diagnosis of UIP most frequently encountered by the lung pathologist is often in reality an alternative diagnosis in daily practice. In the present study, 89.4% of our cases had a possible UIP or alternative diagnosis. Moreover, the fact that CF was most common in these cases is striking. In the literature, it has been emphasized that chronic hypersensitivity pneumonia is the most important disease in the differential diagnosis for UIP (10). It is suggested that a substantial proportion of cases were misdiagnosed as UIP in the past (11). For this reason,

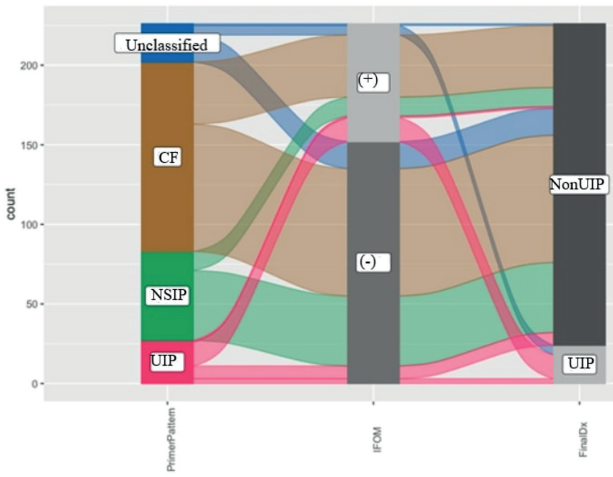

Figure 3. Distribution of IFOM in predominant patterns and diagnoses
IFOM: Intralobular fibrous obliteration with microcysts, UIP: Usual interstitial pneumonia, NSIP: Non-specific interstitial pneumonia, CF: Centrilobular fibrosis

quantitative analysis or scoring of the lesions is recommended (11,12). Despite all of these efforts, however, the coexistence of UIP and CF patterns in the same tissue is possible. The same difficulty arises when diagnosing NSIP (13). In the guidelines, honeycomb cysts are among the main diagnostic criteria for UIP. Although our study supports this approach, others have reported that chronic hypersensitivity can lead honeycomb cysts (8). Therefore, a CF-focused diagnostic approach may be more accurate in FIP pathologic evaluation. In addition, the differential diagnosis should include rare diseases such as pneumoconiosis and pleuroparenchymal fibroelastosis.

The combination of FIP and emphysema is not uncommon (14). Emphysema is usually accompanied by UIP and they often occur together in the lower lobe (15). Although there was no significant difference in our study in terms of the coexistence of emphysema and UIP, the fact that emphysema was present in 40.7% of all cases is quite important. Similarly, although it is a component of obstructive pulmonary disease, bronchiectasis develops when interstitial fibrosis destroys the alveolar structure and destroys the architectural framework. In particular, the presence of traction bronchiectasis, an important radiologic criterion, may be as valuable as FF and honeycomb fibrocysts in pathologic evaluation.

Study Limitations

There are some limitations of this study. First, the clinical and radiologic findings of the cases were excluded from the scope of the study. A connection could not be made between the lesions and etiology due to the lack of clinicoradiologic diagnosis. Another limitation is that only surgical biopsy cases were included in the study. Cases diagnosed with conventional transbronchial biopsy and cryobiopsy were not included due to the difficulty in detecting multiple patterns.

Conclusion

The pathological evaluation of FIP patterns involves specific challenges. Although not a typical pattern, it is interesting that IFOM, which completely obliterates the lobular anatomy, was second most common after CF among the predominant patterns observed in our study. This indicates that when identifying lesions, coexistent patterns must be reported rather than a diagnosis. CF-focused diagnostic approach may be more accurate in FIP pathologic evaluation.

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Ethics

Ethics Committee Approval: Study design was approved by Local Ethical Committee (University of Health Sciences Turkey, İstanbul Training and Research Hospital). The study protocol number and date are 2259/20 (08/05/2020). And also, it was approved by Hospital Science Committee (protocol number is 244-5/20).

Informed Consent: Informed consents were obtained from all study patients.

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Authorship Contributions

Surgical and Medical Practices: H.N.Ü., N.F., N.Ü., E.Ç., Concept: H.N.Ü., Design: H.N.Ü., Data Collection or Processing: H.N.Ü., N.F., N.Ü., Analaysis or Interpretation: H.N.Ü., E.Ç., Literature Search: H.N.Ü., Writing: H.N.Ü.

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Effects of Obstructive Sleep Apnea Syndrome on the Eye

Obstrüktif Uyku Apne Sendromunun Göz Üzerindeki Etkileri

Asiye Yavuz[1], Berrak Şekeryapan[2], Mevlüt Karataş[3], Aziz Gümüş[4], Halit Çınarka[5], Ünal Şahin[4], Deniz Doğan[6]

[1]*Ankara City Hospital, Clinic of Chest Diseases, Ankara, Turkey*

[2]*University of Health Sciences Turkey, Ulucanlar Eye Training and Research Hospital, Clinic of Eye Diseases, Ankara, Turkey*

[3]*University of Health Sciences Turkey, Occupational and Environmental Diseases Hospital, Clinic of Chest Diseases, Ankara, Turkey*

[4]*Recep Tayyip Erdoğan University Faculty of Medicine, Department of Chest Diseases, Rize, Turkey*

[5]*University of Health Sciences Turkey, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, Clinic of Chest Diseases, İstanbul, Turkey*

[6]*University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Chest Diseases, Ankara, Turkey*

ABSTRACT

Background: The purpose of this study is to investigate the eye pathologies, primarily glaucoma and Floppy Eyelid syndrome (FES), of patients with Obstructive Sleep Apnea syndrome (OSAS).

Materials and Methods: One hundred sixty two patients with OSAS, who were diagnosed through polysomnography (PSG), were consulted to the ophthalmology clinic. The patients were classified on the Apnea-hypopnea index (AHI). It was accepted that AHI⩽5 was normal, 5⩽ AHI <15 was mild OSAS, 15⩽ AHI <30 was moderate OSAS, and AHI ⩾30 was severe OSAS.

Results: The mean age of the patients was 48.9±10.6 years. Statistically, there was a significant correlation between age and body mass index for the groups. It was observed that moderate and severe OSAS groups had FES more frequently for both eyes. There was no increase in intraocular pressure (IOP) and no presence of optic disc edema, which might cause glaucoma, in any of our patients. We could not find a correlation between AHI and peripapillary retinal nerve fiber layer, IOP and C/D ratio and there was no significant difference among the study groups.

Conclusion: For the moderate and severe groups, the frequency of FES was significantly correlated for both eyes of patients. The etiological studies have shown relatively more frequent OSAS among the patients with non-arteritis ischemic optic neuropathy (NAION) and glaucoma in the literature. Therefore, we believe patients with OSAS need to be examined for glaucoma and NAION for a long term. Moreover, it would be helpful to refer pulmonology clinics for PSG for patients who has FES, glaucoma and NAION with an unknown etiology.

Keywords: OSAS, FES, PSG, AHI, glaucoma

ÖZ

Amaç: Bu çalışmanın amacı, Obstrüktif Uyku Apne sendromu (OUAS) hastalarının başta glokom ve Floppy Göz Kapağı sendromu (FES) olmak üzere göz patolojilerinin araştırılmasıdır.

Gereç ve Yöntemler: Polisomnografi (PSG) ile tanı alan 162 OUAS hastası oftalmoloji kliniğine konsülte edildi. Hastalar Apne-hipopne indeksine (AHİ) göre sınıflandırıldı. AHİ⩽ 5 normal, 5⩽ AHİ<15 hafif OUAS, 15⩽ AHİ<30 orta OUAS ve AHİ ⩾30 şiddetli OUAS olarak kabul edildi.

Bulgular: Hastaların ortalama yaşı 48,9±10,6 yıldı. İstatistiksel olarak, yaş ve vücut kitle indeksi gruplar arasında anlamlı idi. Orta ve ağır OUAS gruplarında her iki gözde daha sık FES olduğu görüldü. Hastalarımızın hiçbirinde göz içi basıncında (GİB) artış ya da glokoma neden olabilecek optik disk ödemi görülmedi. AHİ ile peripapiller retina sinir lifi tabakası, GİB ve C/D oranı arasında bir ilişki ve çalışma grupları arasında anlamlı bir fark bulamadık.

Sonuç: Orta ve şiddetli grup için, FES sıklığı, hastaların her iki gözü için önemli ölçüde ilişkiliydi. Etiyolojik çalışmalar literatürde non-arteritis iskemik optik nöropati (NAION) ve glokomlu hastalarda nispeten daha sık OUAS olduğunu göstermiştir. Bu nedenle,

Address for Correspondence: Deniz Doğan, University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Chest Diseases, Ankara, Turkey
Phone: +90 532 602 13 39 E-mail: dr_denizz@yahoo.com **ORCID ID:** orcid.org/0000-0003-2596-3113

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ÖZ

OUAS hastalarının glokom ve NAION açısından uzun süreli muayene edilmesi gerektiğine inanıyoruz. Ayrıca etiyolojisi bilinmeyen FES, glokom ve NAION hastalarında PSG için pulmonoloji kliniklerine yönlendirilmesi faydalı olacaktır.

Anahtar Kelimeler: OUAS, YES, PSG, AHİ, glokom

Introduction

Sleep is essential for healthy life and it occurs in almost one third of life. Basically, it can be described as unconscious status which can be taken up by stimuli like sound, light or touching (1). Physiology of sleep has been revealed partially after the 20th century through the use of electroencephalogram (EEG). Respiratory effects of sleep were shown for the first time by Gastaut in 1965 by using polysomnography (PSG) (2) which is accepted as "gold standard" for the diagnosis of Sleep Apnea syndrome (3).

Obstructive sleep apnea is a syndrome (OSAS) characterized by episodic obstruction of upper respiratory tract (total obstructions cause apnea; partial obstructions cause hypopnea) and a decrease in the levels of O_2 saturation during sleep (3). Risk factors for the syndrome have not been revealed completely except certain risk factors such as age (over 65 years), obesity, male gender (4,5), and familial history of OSAS (6). However, mechanisms of this syndrome have not been elucidated yet due to complicated anatomic, muscular, neuromuscular, neural factors and other involving factors.

OSAS leads to many complications in the cardiovascular and neuropsychiatric systems and also in many other systems in the body. The eye is one of the organs that is affected by this syndrome. Forty percent of patients diagnosed with moderate and severe OSAS have significantly higher eye symptoms when compared to the control group (7).

In this study, we evaluated the eye signs and vision of patients who underwent all-night PSG with a pre-diagnosis of OSAS. Thus, we aimed to get an idea about referring patients with OSAS to eye clinics for routine eye examination and non-routine eye examinations.

Material and Methods

Approval of this study was received from the Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine in March, 2013 (2013/54). The study was performed on 324 eyes of 162 patients who did not have any diagnosis for ophthalmologic disorders and were hospitalized for PSG survey in Department of Pulmonology. Patients who underwent all-night PSG in the sleep laboratory of Recep Tayyip Erdoğan University with a pre-diagnosis of sleep apnea between April 2013 and November 2013 were included in the study. Written informed consent was obtained from all patients who met the study criteria, and the patients were referred to the ophthalmology clinic on the morning of the test. Patients under the age of 18 years, who had any known eye disease, history of head injury or cranial operation, previously known chronic renal failure, and a diagnosis of Diabetes Mellitus and who stated that they did not want to participate in the study, were excluded from the study. Demographic characteristics such as age, gender and body mass index (BMI), duration of complaints, Epworth sleepiness scale score, PSG results (AHI, oxygen desaturation index, minimum and mean oxygen saturations) and all eye examination findings were recorded.

PSG

PSG (Grass Technologies Comet, EEG/PSG with as40 Amplifier System, 2008, Ohio/USA) examinations have been proceeded with 4 EEG channels as C3/A2, C4/A2, O1/A2, O2/A1; 2 electrooculography channels as ROC/A1, LOC/A1; 3 electromyography channels as one submandibular, two tibial; electrocardiography; an air-flow sensor (nasal-oral thermistor); thoracic and abdominal piezoelectric belts, and pulse-oximeter. Every 30 seconds of measurements have been accepted as one "epoch unit". Patients have been measured for at least 6 hours. Sleepiness score, based on American Academy of Sleep Medicine 2007, was done according to R&K (Rechtschaffen A. & Kales A.) standard scoring system (8). Patients were classified into four groups based on the Apnea-hypopnea index (AHI). It was accepted that AHI⩽5 was normal, 5⩽ AHI <15 was mild OSAS, 15⩽ AHI <30 was moderate OSAS, and AHI ⩾30 was severe OSAS.

Eye Examination

After signing consent form, patients were referred to department of ophthalmology. Visual acuity was examined via Snellen Chart and autorefractometer. Ocular tension [intraocular pressure, (IOP)] was measured by the Goldman Applanation Tonometer. Central cornea thickness (CCT) was calculated by a corneal pachymeter (NIDEK; noncontact tonometer NT-2000, 2008 Japan). Anterior and posterior chambers were examined by biomicroscope. Dilated-fundus examinations were performed after pupils were enlarged with 1% tropicamide. Optic nerve and retinal nerve fiber layer (RNFL) thickness was examined with optical coherence tomography (OCT); (Carl Zeiss Meditec, Dublin, CA, USA). Findings were evaluated with laboratory results.

Statistical Analysis

Data were recorded into SPSS 16.0 for Windows (IBM Corp., Armonk, New York, ABD). Descriptive statistics were used for demographic data, BMI, AHI, minimum and mean O_2 saturation and eye findings. Median values were given for continuous variables; categorical variables were shown in percentage (%). Chi-square tests were used for categorical comparison to define a relationship between independent variables. ANOVA with post-hoc Tukey HSD test was used for comparison among the groups. P-values lower than 0.05 were accepted as significant.

Results

Forty-three of patients were female (27%), and 119 were male (73%). According to the PSG results, the AHI was below 5 in 23 patients. On the other hand, 33, 19 and 87 patients were observed in the mild, moderate and severe OSAS group, respectively. The mean patient age of the entire cohort was 48.9±10.6 (minimum: 25-maximum: 73) years. The mean age was 42±8 years (29-54 years) for the AHI normal patient group, 46.1±9.5 years (27-62 years) for the mild OSAS group, 49.5±9 years (31-65 years) for the moderate OSAS group, and 50.4±11 years (25-73 years) for the severe OSAS group. There was a statistically significant difference among the groups in terms of age (p=0.011). However, this significance was observed only between the normal patient group and the patient group with severe OSAS. The mean BMI was 33.6±6.4 kg/m^2 in the entire group. The mean BMI was 29.3±6.8 kg/m^2 in the normal patient group, 31.8±5.4 kg/m^2 in the mild OSAS group, 33.7±4.8 kg/m^2 in the moderate OSAS group, and 35.2±6.4 kg/m^2 in the severe OSAS group (p=0.001). BMI values were significant among the groups and this significance originated from the patient group with severe OSAS.

The average score in ESS was 7.2±4.1 and there was a significant difference among the groups (p<0.001). The average AHI was 31.7±23.9 (minimum: 1.3, maximum: 137), the average O_2 desaturation index was 20±22.2, the lowest O_2 saturation (minO_2 hr) was 80.3±8.1%, and the average O_2 saturation (mean/average O_2 hr) was 92.3±2.7%. When the relationship between OSAS severity and O_2 desaturation index, minO_2 and meanO_2 values was examined, it was seen that there was a statistically significant difference among the groups (p<0.001). This significance was also due to the severe OSAS patient group. All demographic characteristics and PSG results of the study population are summarized in Table 1.

In the study, when compared to the AHI normal group and mild OSAS group, right eye floppy eyelid and left eye Floppy Eyelid syndrome (FES) were found to be significantly higher in the moderate and severe OSAS group (p=0.016 vs. p=0.024, respectively). Statistically, there was no significant difference among the groups in terms of IOP, RNFL, CCT and C/D ratio. 62 patients had blepharitis. Although there was no significant difference in blepharitis among the groups, the highest rate (46%) was seen in the severe OSAS group.

There was no significant difference in papillary conjunctivitis among the groups; however, conjunctivitis was observed more frequently in the moderate (47%) and severe (43%) OSAS groups. Adjusted visual acuities were found to be normal but there was no significant difference in refraction values among the groups.

None of our patients had glaucoma in IOP measurements and ophthalmic examination. There was no OSAS patient developing optic disc edema, central serous chorioretinopathy and filamentous keratitis. The eye examination findings of the entire study population according to the OSAS severity are summarized in Table 2.

Discussion

In this prospective study, we aimed to determine the frequency of eye-related pathologies in patients who underwent all-night PSG with a pre-diagnosis of sleep apnea. Data of totally 163 patients, including 43 women and 120 men, were evaluated in the study.

Obesity is a part of the metabolic syndrome and is a condition that is closely related to OSAS (9). For this reason, BMI should definitely be measured in patients with suspected OSAS. Obesity can cause OSAS directly by causing collapse in the upper airways. It also has an effect on the loss of respiratory muscle strength and an increase in inflammation through cytokines released from the adipose tissue (10). In our study population, the mean BMI was 33.6±6.4 kg/m^2, and the group with the highest BMI was the severe OSAS group.

FES is a condition characterized by easily rotating and drooping lids, papillary conjunctivitis, and corneal epithelial erosions (11). The prevalence of FES in the general population ranges from 2.3% to 3.8% (12). In a meta-analysis involving 6 studies with a total of 767 patients on the prevalence of FES in OSAS, it was shown that FES was statistically significantly more common in OSAS patients than in non-OSAS patients. The authors also stated that FES prevalence increased (odds ratio=2.56, 4.62, and 7.64 for mild, moderate, and severe OSAS, respectively) with disease severity, but there is a necessity for prospective cohort studies to determine whether FES is an independent risk factor for OSAS (13). In our study, in accordance with the literature, the incidence of FES according to OSAS severity differed among the groups.

On the other hand, when the IOP, RNFL, CCT and C/D ratios were evaluated, no statistically significant difference was found among the patient groups in our study population. In a study conducted in our country, Tapan et al. (14) evaluated the changes in the cornea and choroid layers of the eye in patients with OSAS of different severities and in the healthy control group by measuring

Table 1. General features of groups (n=162)

Groups/data	Normal (n=23)	Mild OSAS (n=33)	Moderate OSAS (n=19)	Severe OSAS (n=87)	p
Age (year)	42±8	46.1±9.5	49.5±9	50.4±11	0.011
BMI (kg/m^2)	29.3±6.8	31.8±5.4	33.7±4.8	35.2±6.4	0.001
Time of symptoms (year)	3.5	3.8	5.3	6.2	0.002
AHI (/hour)	3.8	8.3	17.3	48.1	<0.001
Epworth sleepiness scale	2	4	4	8	<0.001
Desaturation index	2	5	10	31	<0.001
Min O_2 saturation (%)	87	85	81	76	<0.001
Average of O_2 saturation (%)	94	93	92	91	<0001

OSAS: Obstructive Sleep Apnea syndrome, BMI: Body mass index, AHI: Apnea-hypopnea index

Table 2. Eye findings (n=162)

Groups/findings	Normal (n=23)	Mild OSAS (n=33)	Moderate OSAS (n=19)	Severe OSAS (n=87)	p
Number of patient (F/M)	4/19	11/22	6/13	20/67	0.560
Right eye IOP (mmHg) ± SD	15±3	15±3	15±2	15±3	0.910
Left eye IOP (mmHg) ± SD	15±3	16±2	16±2	16±2	0.300
Right eye RNFL (µm) ± SD	95±12	90±11	92±10	91±9	0.230
Left eye RNFL (µm) ± SD	93±11	90±13	93±10	91±11	0.670
Right eye CCT (µm) ± SD	547±43	548±39	553±28	540±66	0.760
Left eye CCT (µm) ± SD	549±48	548±39	552±52	550±32	0.970
Right eye C/D ratio	0.3±0.06	0.29±0.08	0.3±0.06	0.3±0.01	0.072
Left eye C/D ratio	0.31±0.08	0.3±0.09	0.3±0.06	0.3±0.09	0.976
Right eye (refraction) (decreased/normal)	6/17	11/22	6/13	36/51	0.723
Left eye (refraction) (decreased/normal)	6/17	13/21	5/13	35/52	0.821
Right eye ptosis (+/-)	0/23	0/33	0/19	0/87	-
Left eye ptosis (+/-)	0/23	0/33	0/19	1/86	0.855
Right/left eye floppy eyelid (+/-)	5/18	6/27	9/10	38/49	0.060
Right/left eye blepharitis (+/-)	4/19	12/21	6/13	40/47	0.270
Right/left eye filamentous keratitis (+/-)	0/23	0/33	0/19	0/87	-
Right eye papillary conjunctivitis (+/-)	6/17	10/23	9/10	37/50	0.455
Left eye papillary conjunctivitis (+/-)	6/17	10/23	9/10	38/49	0.450
Right/left eye optic disc edema (+/-)	0/23	0/33	0/19	0/87	-
Right/left eye optic neuropathy (+/-)	0/23	0/33	0/19	0/87	-
Right/left eye retinal vascular tortuosity (+/-)	1/22	1/32	1/18	2/85	0.780
Right/left eye central serous chorioretinopathy (+/-)	0/23	0/33	0/19	0/87	-

SD: Standard deviation, RNFL: Retinal nerve fiber layer thickness, IOP: Intra ocular pressure, C/D ratio: Cup/Disc ratio, CCT: Central cornea thickness

with OCT. At the end of the study, the researchers found that there was no significant difference in corneal thickness between the patients with OSAS and healthy controls, and the choroidal thickness became thinner as the severity of OSAS increased (14). Blepharitis is a chronic inflammation of the rim of the eyelid. It is often caused by non-virulent staphylococcus and seborrheic dermatitis and it has been shown to be associated with sleep apnea (15,16). In our patient group, the rate of blepharitis was 38%, and the highest rate was seen in the severe OSAS group (46%).

Glaucoma was not detected in any of the patients in our study population according to IOP values and optic nerve head examination. In the literature, it has been reported that the prevalence of glaucoma in OSAS patients is 7.2%, and primary open-angle glaucoma, normotensive glaucoma and related RNFL thinning and visual field defects are more common in OSAS patients (17). However, studies evaluating RNFL thickness in OSAS patients present different results. Bayhan et al. (18) evaluated 92 OSAS patients, and they stated that the nasal and upper quadrant RNFL was thinner in the OSAS group. On the other hand, as in our study results, there are studies reporting that RNFL thickness is not different in patients with and without OSAS (19). While Yavaş et al. (20) reported that they observed increased frequency of OSAS in patients with central serous chorioretinopathy, Brodie et al. (21) showed in their study that there was no increased risk for central serous chorioretinopathy in OSAS patients. In our study, no patient had central serous chorioretinopathy.

Conclusion

It is almost inevitable to get affected for eyes which need high oxygen supply with well-vascularized structure in a disease which has neurovascular complications and hypoxia-hypercapnia episodes like OSAS. Statistically, only FES was found to be significantly high in patients with OSAS among the ophthalmologic disorders that were investigated in this study. The reason for that, as we believed, might be the lower average age compared to other studies and different AHI cut-off values. Further investigations are needed to elucidate the role of these variables. Nevertheless, the current literature information has shown that physicians who deal with OSAS patients should be aware of ophthalmologic complications of this syndrome. On the other hand, OSAS should be considered as an etiologic factor in patients with ophthalmologic disorders.

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Ethics

Ethics Committee Approval: Approval of this study was received from the Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine in March, 2013 (2013/54).

Informed Consent: Written informed consent was obtained from all patients who met the study criteria, and the patients were referred to the ophthalmology clinic on the morning of the test.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., M.K., H.Ç., Concept: A.Y., B.Ş., M.K., H.Ç., Ü.Ş., Design: A.Y., B.Ş., A.G., Ü.Ş., D.D., Data Collection or Processing: A.Y., M.K., H.Ç., Analysis or Interpretation: A.Y., B.Ş., A.G., H.Ç., D.D., Literature Search: A.Y., M.K., A.G., H.Ç., D.D., Writing: A.Y., B.Ş., Ü.Ş., D.D.

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Student Views on Playing Classical Music in the Background and Its Effects on Anatomy Practice Lessons

Arka Planda Klasik Müzik Çalınmasının Anatomi Uygulama Derslerine Etkisi Üzerine Öğrenci Görüşleri

Erengül Boduç

Kafkas University Faculty of Medicine, Department of Anatomy, Kars, Turkey

ABSTRACT

Background: The aim of this study is to reduce the fear and anxiety towards the cadaver in the anatomy practice lesson with the effect of classical music playing in the background.

Materials and Methods: One hundred fity seven students participated in the study. The questions asked were created with a 5-point Likert scale and the students answered the questions via mail. Answers were analyzed on the system and then statistically calculated.

Results: According to the statistics of the chi-square test of first and second grade answers, there was a significant difference only in the first (p=0.017) and fourth (p=0.015) questions (p<0.05). Participation in the ninth, tenth and eleventh questions was quite high both in the first and second grades.

Conclusion: There are very few studies in the literature with the effect of classical music playing in the light background in the anatomy laboratory. It is important to include student responses in this study in the literature, so it is thought that the effect of classical music in the anatomy laboratory will reduce the stress and fear arising from the cadaver.

Keywords: Anatomy education, background music, five likert scale

ÖZ

Amaç: Bu çalışmanın amacı, arka planda klasik müzik çalmanın etkisi ile anatomi uygulama dersinde kadavralara yönelik korku ve kaygıyı azaltmaktır.

Gereç ve Yöntemler: Araştırmaya 157 öğrenci katıldı. Sorulan sorular 5'li Likert testi ile oluşturuldu ve öğrenciler soruları mail yoluyla cevapladılar. Cevaplar sistem üzerinde analiz edildikten sonra istatistiksel hesaplamalar yapıldı.

Bulgular: Birinci ve ikinci sınıf cevaplarının ki-kare testi istatistiğine göre, sadece birinci (p=0,017) ve dördüncü (p=0,015) sorularda anlamlı fark vardı (p<0,05). Dokuzuncu, onuncu ve on birinci sorulara katılım hem birinci hem de ikinci sınıflarda oldukça fazlaydı.

Sonuç: Anatomi laboratuvarında klasik müzik çalmanın hafif arka planda etkisi ile literatürde çok az çalışma vardır. Bu çalışmada öğrenci yanıtlarının literatüre dahil edilmesi önemlidir, bu nedenle klasik müziğin anatomi laboratuvarındaki etkisinin kadavradan kaynaklanan stres ve korkuyu azaltacağı düşünülmektedir.

Anahtar Kelimeler: Anatomi eğitimi, arka plan müziği, beşli likert test

Introduction

Cadaver has been an important teaching tool in anatomy education for years and still continues (1). Although 3D digital software has tried to replace cadavers in recent years, its success in raising physicians has been lacking in replacing cadaveric education (2,3,4). Moreover, the cadaver is actually the first patient of the students (5).

Cadaver education is actually laborious, it requires knowledge and effort (6,7). Besides being beneficial, this training has some

Address for Correspondence: Erengül Boduç, Kafkas University Faculty of Medicine, Department of Anatomy, Kars, Turkey
Phone: +90 530 784 95 86 E-mail: erenboduc@gmail.com **ORCID ID:** orcid.org/0000-0001-8872-1993
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disadvantages as well (7,8). The anatomy laboratory should be suitable for cadaver education. Cadaver tanks or pools should be stainless and attention should be paid to the toxic effects of the solutions that provide cadaver protection (9). Another negative disadvantage is the feeling of anxiety caused by seeing a cadaver (10).

Unfortunately, the cold and morgue appearance of the anatomy laboratory creates an emotional sense of anxiety in the instructors and students. Especially touching the cadaver to dissect it, spending time with it and the silence of the environment can sometimes negatively affect a person in this environment. Getting used to a dead body and a sense of death in students who have just taken the anatomy lesson can stress students at first. The same situation may be similar for instructors and postgraduate students (10,11,12).

One of the recommended methods to reduce anxiety and stress caused by cadavers is education with music. When the studies on this subject are examined, it is observed that education with music is very beneficial in overcoming cadaver anxiety (10). In this study, students' opinions were taken for the adaptation of the classical music played in the light background to overcome the cadaver fear and to adopt the cadaver in the sense of anxiety faced by medical students in the anatomy laboratory. It is thought that the study will benefit cadaveric anatomy education.

Material and Methods

This study was approved by the Ethics Committee of Medicine Faculty of Kafkas University (approval number: 2020/06/ decision 11). The study was carried out on the first and second year medical students of Kafkas University Medicine Faculty in the 2019-2020 academic year. The data collection forms used in the study were prepared on the web and sent to the students by e-mail. 157 students (87 from first class, 70 from second class) answered the questions in the data collection form. Data collection questions were prepared with a five-point Likert scale (totally agree, agree, undecided, disagree, totally disagree) (13,14). The answers given by the students were automatically analyzed through the web system and the results were obtained through the software. The answer options given were calculated automatically on the system with the calculation of frequency and percentage.

Statistical Analysis

The first and second years were compared according to the answers given by the students. Statistical analysis was carried out using SPSS 22.0 version software program for Windows. Descriptive statistics for categorical variables were expressed as frequency and percentage values. A chi-square test was used in the analysis of categorical data. The results were evaluated at a 95% confidence interval, and a p-value of <0.05 was considered significant.

The study was approved by the Ethics Committee of Kafkas University (approval number: 2020/06/ decision 11). The study was performed following the aid of the ethical standards down in the 1964 Declaration of Helsinki and its later amendments.

Results

The first and second years were compared according to the answers given by the students. Participation rate of first graders to the first question opinion was higher than that of second graders (43.7% agree, 24.2 totally agree, p=0.017). On the other hand, the number of undecided participants was almost equal. Participation to the second question opinion was high in the first year, while the rate of undecided people was higher in the second year (36.8% agree, 27.3% undecided, p=0.057). Participation to the third question opinion was high in the first year, while the rate of those who did not agree with the third question was higher in the second year (41.4% agree, 30.3% disagree, p=0.032). The numbers of first and second year students who absolutely disagreed with the fourth question were almost the same (37.9% disagree, 34.4% disagree, p=0.015). Participation in the opinion of the fifth question was high in the first grade, while the rate of undecided ones was high in the second grade (36.8% agree, 27.3% undecided, p=0.244). The numbers of participants who participated in the sixth question opinion in the first and second grades and did not agree were almost equal to each other (23.7% agree, 24.2 agree; 23.6% disagree, 24.2% disagree; p=0.961). The numbers of those who totally agreed and agreed with the seventh question opinion in the first year were equal (36.8%). In the second year, the number of participants was not very high; the numbers of those who disagreed and who were undecided were equal (15.4% undecided-disagree). The p-value in the comparative statistics of the two classes was 0.090. Participation to the eighth question opinion was quite high both in the first and second grades (51.7%-42.4% agree, p=0.558). Participation in the ninth, tenth and eleventh questions was quite high both in the first and second grades. The frequency percentages for these questions are given in Table 1 and Table 2. According to the statistics of the chi-square test of first and second grade answers, there was a significant difference only in the first and fourth questions (p<0.05) (Table 3).

Discussion

The main tool of the anatomy laboratory has been the cadaver (15). However, cadaver education has some disadvantages (7,8). One of them is the fear and anxiety created by the cadaver (10). The cold and morgue air of anatomy laboratories further increases the feeling of intense stress in meeting a dead body. It takes quite a bit of time to get used to this situation, such as

Table 1. Frequencies (f) of answers given by the first year students to the questions					
First year of the medicine faculty students n=87	**5**	**4**	**3**	**2**	**1**
1- I love to learn the anatomy practice lesson in company with classical music playing soft and low-pitched sounds in the background.	10.3	43.7	21.8	13.8	10.3
2- Learning and studying the anatomy practice lesson accompanied by classical music playing soft and low-pitched music increases my concentration.	9.2	36.8	24.1	14.9	14.9
3- While learning the anatomy practice lesson, there should be classical music playing a soft and low voice in the background.	8	41.4	17.2	14.9	18.4
4- While learning the anatomy practice lesson, other music with spoken can be used instead of classical music that plays soft and low sounds in the background.	3.4	4.6	9.2	37.9	44.8
5- Classical music playing soft and low sounds in the background during anatomy practice lessons can reduce fear and stress in encountering cadavers.	21.8	36.8	19.5	8	13.8
6- In anatomy practice lessons, if there is classical music playing a soft and low voice in the background, the noise that may occur during free study decreases, and thus, the concentration and understanding of the lesson increase.	14.5	23.7	20.8	17.4	23.6
7- In anatomy practice lessons, if there is a different style of music instead of classical music that plays a soft and low voice in the background, the concentration and understanding of the lesson decreases and the lesson is not understood at all.	36.8	36.8	11.5	4.6	10.3
8- If the number of cadavers belonging to the anatomy department was large, performing a dissection accompanied by classical music playing a soft and low sound in the background would reduce fear and stress and enable students to learn the lesson better and be equipped.	20.7	51.7	12.6	4.6	10.3
9- Dissection accompanied by classical music playing a soft and low voice in the background in the classes where the students of the faculty of medicine receive anatomy lessons overcomes fear and stress, and provides adaptation to the first patient cadaver and prepares the ground for surgical lessons.	19.5	54	14.9	2.3	9.2
10- Classical music playing soft and low sounds in the background in anatomy practice lessons can soften the coldness and gloom of the laboratory, which is like a morgue unit, and reduce stress.	17.2	60.9	8	3.4	10.3
11- While learning the anatomy practice lesson, other non-verbal instrumental music can be used instead of classical music that plays soft and low-pitched sounds in the background.	19.5	51.7	11.5	8	9.2
5: Totally agree (%), 4: Agree (%), 3: Undecided (%), 2: Totally disagree (%), 1: Disagree (%)					

dissection, education or research, and sometimes these stress conditions cannot be adapted. In the studies conducted, it has been observed that playing soft background music in the anatomy laboratory reduces the fear and anxiety conditions arising from the cadaver. In addition, it has been observed that the concentration-increasing weft of the music increases the efficiency of scientific studies by providing easier orientation to the dissection (10,11,12).

In this study, the perspective of first-year and second-year students to anatomy education with classical music playing in the light background is quite positive. When the questions are examined, it can be said that the first graders like to do the anatomy practice lesson with soft music in the background and this has a positive effect on their concentration. In the second grade, they were mostly eager to teach the lesson in the accompaniment of classical music playing in the light background, but they were unsure that the music increased their concentration. This situation may show that second graders are more used to cadavers than first graders. While the first grade participated in the view that classical music must be in the anatomy laboratory, the rate of students who agree with this view was low. In this case, we can say that the second graders are used to seeing cadavers. In general, both first and second year students did not find it appropriate to use other music with lyrics instead of classical music. However, all classes showed a high degree of participation in the suggestion of using other non-verbal instrumental music instead of classical music. The following conclusion can be drawn here; students' interest in non-verbal instrumental music is more preferable than music with lyrics.

Students generally participated in the fact that the music played in the light background dissipated the cold gloom of the anatomy laboratory in the air of the morgue unit. In addition, participation in the view that music playing in the light background reduced fear and stress in approaching the cadaver, but provided better quality dissection, was quite high. Both first and second graders generally showed an indecisive attitude to the view that music playing in a light background reduced the rate of noise that might occur in the lesson, and the rate of those who disagreed with this view was quite high.

From the data obtained in this study, it can be said that the students liked to learn the anatomy practice lesson with classical

Table 2. Frequencies (f) of answers given by the second year students to the questions					
Second year of the medicine faculty students n=70	**5**	**4**	**3**	**2**	**1**
1- I love to learn the anatomy practice lesson in company with classical music playing soft and low-pitched sounds in the background.	24.2	21.2	21.2	22.7	10.6
2- Learning and studying the anatomy practice lesson accompanied by classical music playing soft and low-pitched music increases my concentration.	19.7	19.7	27.3	10.6	22.7
3- While learning the anatomy practice lesson, there should be classical music playing a soft and low voice in the background.	16.7	22.7	21.2	9.1	30.3
4- While learning the anatomy practice lesson, other music with spoken can be used instead of classical music that plays soft and low sounds in the background.	6.2	20	12.3	34.4	26.2
5- Classical music playing soft and low sounds in the background during anatomy practice lessons can reduce fear and stress in encountering cadavers.	13.6	25.8	27.3	12.1	21.2
6- In anatomy practice lessons, if there is classical music playing a soft and low voice in the background, the noise that may occur during free study decreases, and thus, the concentration and understanding of the lesson increase.	15.2	24.2	22.7	13.6	24.2
7- In anatomy practice lessons, if there is a different style of music with lyrics instead of classical music that plays a soft and low voice in the background, the concentration and understanding of the lesson decreases and the lesson is not understood at all.	16.9	43.1	15.4	9.2	15.4
8- If the number of cadavers belonging to the anatomy department was large, performing a dissection accompanied by classical music playing a soft and low sound in the background would reduce fear and stress and enable students to learn the lesson better and be equipped.	19.7	42.4	12.1	9.1	16.7
9- Dissection accompanied by classical music playing a soft and low voice in the background in the classes where the students of the Faculty of Medicine receive anatomy lessons overcomes fear and stress, and provides adaptation to the first patient cadaver and prepares the ground for surgical lessons.	15.2	45.5	16.7	12.1	10.6
10- Classical music playing soft and low sounds in the background in anatomy practice lessons can soften the coldness and gloom of the laboratory, which is like a morgue unit, and reduce stress.	15.2	50	7.6	9.1	18.2
11- While learning the anatomy practice lesson, other non-verbal instrumental music can be used instead of classical music that plays soft and low-pitched sounds in the background.	18.2	33.3	13.6	18.2	16.7
5: Totally agree (%), 4: Agree (%), 3: Undecided (%), 2: Totally disagree (%), 1: Disagree (%)					

Table 3. P-values of first and second year students' answers to each question with chi-square test	
Questions	**Chi-square test of 1st and 2nd grade students P**
1- I love to learn the anatomy practice lesson in company with classical music playing soft and low-pitched sounds in the background.	0.017
2- Learning and studying the anatomy practice lesson accompanied by classical music playing soft and low-pitched music increases my concentration.	0.057
3- While learning the anatomy practice lesson, there should be classical music playing a soft and low voice in the background.	0.032
4- While learning the anatomy practice lesson, other music with spoken can be used instead of classical music that plays soft and low sounds in the background.	0.015
5- Classical music playing soft and low sounds in the background during anatomy practice lessons can reduce fear and stress in encountering cadavers.	0.244
6- In anatomy practice lessons, if there is classical music playing a soft and low voice in the background, the noise that may occur during free study decreases, and thus, the concentration and understanding of the lesson increase.	0.961
7- In anatomy practice lessons, if there is a different style of music with lyrics instead of classical music that plays a soft and low voice in the background, the concentration and understanding of the lesson decreases and the lesson is not understood at all.	0.090
8- If the number of cadavers belonging to the anatomy department was large, performing a dissection accompanied by classical music playing a soft and low sound in the background would reduce fear and stress and enable students to learn the lesson better and be equipped.	0.558

Table 3 continued	
9- Dissection accompanied by classical music playing a soft and low voice in the background in the classes where the students of the faculty of medicine receive anatomy lessons overcomes fear and stress, and provides adaptation to the first patient cadaver and prepares the ground for surgical lessons.	0.194
10- Classical music playing soft and low sounds in the background in anatomy practice lessons can soften the coldness and gloom of the laboratory, which is like a morgue unit, and reduce stress.	0.334
11- While learning the anatomy practice lesson, other non-verbal instrumental music can be used instead of classical music that plays soft and low-pitched sounds in the background.	0.073

music playing in the light background. However, in the upper classes who are accustomed to seeing cadavers, participation in this situation is not too much. Because as you get used to seeing the cadaver, the stress and fear towards the cadaver decrease and the sense of anxiety awakened in the students is not much. All students have adopted that classical music playing on a light background increases the interest in the lesson, reduces stress and makes it easier to concentrate.

For anatomy practice lessons, light background classical music can be a recommended option for the interest and comfortable adaptation to the lessons. This study was a preliminary study for this option. Getting feedback from students also made a significant contribution to the educators.

Study Limitations

The study is limited with the answers of students who participated in the survey. The collected information was assumed to be true; the subjects involved in the study were assumed to give their answers honestly. The questionnaire was not a standardized instrument and could be validated in future studies.

Conclusion

For anatomy practice lessons, light background classical music can be an alternative for adaptation and learning to the lesson. There are very few studies on this in the literature. According to the data in the literature, students' approach to this type of education is quite positive. In this study, a preliminary study was conducted on student approaches to this education model in our country, and the approach and satisfaction of the students were positive.

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Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Kafkas University (approval number: 2020/06/ decision 11).

Informed Consent: Patient approval is not required as it is a survey study.

Peer-review: Externally peer-reviewed.

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When is the Appropriate Time for Superficial Corneal Metallic Foreign Body Removal?

Kornea Yüzeyindeki Metalik Yabancı Cisimleri Çıkarmanın En Uygun Zamanı Nedir?

Abdullah Aşur[1], Onur Gökmen[2]

[1]*University of Health Sciences Turkey, Van Training and Research Hospital, Clinic of Ophthalmology, Van, Turkey*

[2]*Yüzüncü Yıl University Faculty of Medicine, Department of Ophthalmology, Van, Turkey*

ABSTRACT

Background: This study aims to compare the differences of corneal epithelial defects after the removal of foreign body (FB) according to clinic arrival dates.

Materials and Methods: Patients with metallic FB removed from the corneal surface were examined and divided into three groups according to their clinic arrival dates. The diameter of the FB was measured before removal, and the width and length of the epithelial defect were measured, and the area of the defect was calculated and compared between the groups.

Results: In this prospective study, totally 110 patients with metallic FB burrs in the cornea were examined. There were 54 patients in the first arrival day group, 34 patients in the second day group and 22 patients were in the third day and after arrival group. The FB diameter was 0.97±0.5 mm in the first day group, and the mean area of the epithelial defect after removal was 3.59±2.3 mm^2. In the second group, FB diameter was 1.05±0.4 mm, and the epithelial defect was 3.16±1.6 mm^2, and in the third group, FB diameter and epithelial defect was respectively 1.01±0.41 mm and 1.68±1.5 mm^2, and less iatrogenic epithelial defects were observed in the patients who had FB removed after the third day compared to the 1st and the 2nd groups. (p=0.002, p=0.050, respectively).

Conclusion: It may be more beneficial to remove the FB after epithelial regeneration and cup formation, by waiting 1-2 days under topical antibiotic prophylaxis rather than increasing the iatrogenic corneal damage by trying to scrape the rust ring under panic and stress.

Keywords: Metallic foreign body, eye trauma, rust ring, cornea, epithelial defect

ÖZ

Amaç: Bu çalışma, korneal yabancı cisim (YC) çıkarıldıktan sonra oluşan epitel defektlerinin, hastaların kliniğe varış sürelerine göre karşılaştırmasını amaçlamaktadır.

Gereç ve Yöntemler: Kornea yüzeyinden metalik YC çıkarılan hastalar muayene edildi ve kliniğe geliş tarihlerine göre üç gruba ayrıldı. YC'nin çapı çıkarılmadan önce ölçüldü ve epitel defektinin genişliği ve uzunluğu değerlendirildi, defektin alanı hesaplandı ve gruplar arasında kıyaslandı.

Bulgular: Bu prospektif çalışmada, korneada metalik YC olan toplam 110 hasta incelendi. İlk gün gelen 54 hasta, ikinci gün 34 hasta, üçüncü gün ve sonrasında gelen ise 22 hasta vardı. Birinci gruptaki YC çapı ortalama 0,97±0,5 mm, çıkarıldıktan sonra oluşan epitel defekti alanı ise 3,59±2,3 mm^2 idi. İkinci gruptaki YC çapı 1,05±0,4 mm ve epitel defekti 3,16±1,6 mm^2 idi. Üçüncü grupta ise YC çapı ve epitel defekti sırasıyla 1,01±0,41 mm ve 1,68±1,5 mm^2 olup, üçüncü günden sonra YC çıkarılan hastalarda 1. gruba ve 2. gruba göre daha az iyatrojenik epitel defekti görülmüştür (sırasıyla p=0,002, p=0,050).

Sonuç: Panik ve stres altında pas halkasını kazımaya çalışarak iyatrojenik kornea hasarını artırmaktansa, epitel rejenerasyonu ve cup formasyonundan sonra, topikal antibiyotik profilaksisi altında 1-2 gün bekleyerek YC'nin çıkarılması daha faydalı olabilir.

Anahtar Kelimeler: Metalik yabancı cisim, göz travması, pas halkası, kornea, epitel defekti

Address for Correspondence: Onur Gökmen, Yüzüncü Yıl University Faculty of Medicine, Department of Ophthalmology, Van, Turkey
Phone: +90 507 467 07 67 E-mail: onurgkmen@gmail.com **ORCID ID:** orcid.org/0000-0002-6058-4226

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Introduction

The damage caused by foreign body (FB) on the corneal surface is the most common and preventable eye trauma in the eye. Metallic FB is the most common of these FBs (1). Patients usually present to the outpatient clinic on the day of the trauma because of pain due to trauma to the cornea. In the classical approach, the FB is removed immediately, the existing corneal rust is cleaned, antibiotic and lubrication drops are given, and corneal wound healing of the affected eye is provided, and it is called to control by keeping it closed until this healing is completed (2,3). However, some patients reach the polyclinic days after the occurrence of trauma, and in these patients, corneal button formation and rust ring formation can be seen and wound healing takes a different course (4). In this study, we aimed to compare the differences between epithelial defects occurring between the immediate removal of the FB and the removal of the FB after days in the eye injury due to corneal metallic FB.

Material and Methods

In this prospective study, patients admitted to the eye clinic of University of Health Sciences Turkey, Van Training and Research Hospital between 2016 and 2018 due to metal burr trauma in the cornea were included. Patients were divided into three groups, the first group consisted of patients whose metallic body was removed on the first day of trauma, the second group consisted of patients whose FB was removed on the second day of trauma, and the third group consisted of patients whose FB was removed on the third day and after trauma. FB was removed on the same day in all patients admitted to the outpatient clinic. Patients with previous corneal trauma, recurrent epithelial defects, corneal degeneration or dystrophy, with previous keratitis corneal scar, and previous ocular surgery were excluded from the study. Patients under 18 years of age and over 50 years of age were excluded from the study.

The study was approved by the Local Ethics Committee (date: 21.07.2016-number: 2016/7). The research was adhered to the tenets of the Declaration of Helsinki, and detailed written informed consent was obtained before each individual's participation in the study.

All the patients were Turkish Caucasians. First, demographic data of the participants, including age and sex, were obtained. Thereafter, anterior segment examination was performed with a biomicroscope to the patients and the FB diameter was measured with the light of a slit lamb microscope and noted with other examination findings. Then, for topical anesthesia Alcaine® (0.5% proparacaine) drop was instilled into the eyes of the patients. The corneal metallic FB was scraped out of the cornea by the same physician at the head of the biomicroscope with minimal trauma to the stroma and epithelium with the help of 23 gauge insulin syringe tip (AA). After FB removal, the eyes of all patients were closed for 24 hours with tobramycin ophthalmic pomade, thereafter lubricant drops and ofloxacin antibiotic drops were used 4 times a day for 5 days.

After that, corneal epithelial defects were stained with fluorescein coated strips (Haag Streit®) and the width and length of the defect were again measured by slit lamb light of the biomicroscope and the area of the defect was calculated as the multiplication of the width and length of this defect.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS, Inc, Chicago, IL). Normality analyses of variables were checked by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical variables were shown as mean-standard deviation or median (minimum-maximum). Categorical variables were expressed as frequency and percentage. ANOVA test was used to evaluate statistical differences, and post-hoc Tukey test was performed between the groups. Values of $p<0.05$ were considered statistically significant.

Results

In this prospective study, 110 patients with corneal metallic FB burrs were examined. FB in the cornea of 54 patients was removed on the first day of trauma, it was removed on the second day in 34 patients, 22 patients were admitted to the outpatient clinic after the third day after the trauma and FB was removed, and they were included in the study and grouped.

Of the 54 patients in the first group, 52 (96.3%) were male and 2 (3.7%) were female; in the second group, 33 (97.1%) were male and 1 (2.9%) was female; all of (100%) the third group were male. The mean (± standard deviation) age of the participants was 30.9±6.5 years in the first group, and 29.35±5.1 and 30.0±5.5 years in the second group and third group, respectively. No significant differences were observed among the study groups with respect to age and sex ($p=0.470$, and $p=0.640$ respectively).

No keratitis, corneal abscess formation or corneal scar formation was observed in any of the patients with FB removal. While rust ring formation was present in 45 (83%) patients in the first group, rust ring developed in all patients in the second and third groups.

The FB diameter, width, length and size of the epithelial defect after the removal of the FB in each group are shown in Table 1. The comparisons among the groups are shown in Table 2.

Discussion

Corneal abrasions and corneal FB have an incidence of approximately 0.2-0.3% and constitute the majority of eye patients presenting to the emergency department. They frequently

Table 1. Mean values of groups

Groups		Patient number	Minimum	Maximum	Range	Mean	± SD
First day clinic arrival	Foreign body diameter (mm)	54	0.50	2.50	2.00	0.97	±0.5
	Defect width (mm)	54	0.50	3.50	3.00	1.77	±0.6
	Defect height (mm)	54	0.75	3.50	2.75	1.85	±0.7
	Age (years)	54	21.00	45.00	24.00	30.9	±6.5
	Defect size (mm^2)	54	0.75	10.50	9.75	3.59	±2.3
Second day clinic arrival	Foreign body diameter (mm)	34	0.50	2.25	1.75	1.05	±0.4
	Defect width (mm)	34	1.00	2.75	1.75	1.76	±0.4
	Defect height (mm)	34	0.75	3.00	2.25	1.72	±0.5
	Age (years)	34	20.00	43.00	23.00	29.35	±5.1
	Defect size (mm^2)	34	1.13	7.5	6.38	3.16	±1.6
Three days and after clinic arrival	Foreign body diameter (mm)	22	0.50	2.00	1.50	1.01	±0.4
	Defect width (mm)	22	0.75	2.50	1.75	1.30	±0.5
	Defect height (mm)	22	1.00	2.25	1.25	1.20	±0.3
	Age (years)	22	22.00	37.00	15.00	30.0	±5.5
	Defect size (mm^2)	22	0.75	5.63	4.88	1.68	±1.5
	SD: Standard deviation						

Table 2. Comparison of groups according to foreign body diameter, defect width, defect height and defect size

Post hoc Tukey tests		
	Mean difference	**p**
Foreign body diameter		
Group 1 vs Group 2 Group 1 vs Group 3 Group 2 vs Group 3	-0.08388 -0.04377 0.04011	0.705 0.931 0.905
Defect width		
Group 1 vs Group 2 Group 1 vs Group 3 Group 2 vs Group 3	0.00844 0.47769* 0.46925*	0.997 0.003* 0.007*
Defect height		
Group 1 vs Group 2 Group 1 vs Group 3 Group 2 vs Group 3	0.1266 0.64268* 0.51604*	0.598 0.001* 0.006*
Defect size		
Group 1 vs Group 2 Group 1 vs Group 3 Group 2 vs Group 3	0.50708 1.90614* 1.39906*	0.535 0.002* 0.050*
* The mean difference is significant at the 0.05 level		

present to the emergency department with the complaints of red-eye, photophobia, watery eyes, and blepharospasm (5). The FB seen on the cornea is removed from the cornea with a routine approach. Prophylactic, antibiotic, lubrication or therapeutic contact lenses are applied to the patients and followed-up. This approach is practiced by almost all emergency physicians and ophthalmologists in routine practice (2,6). But, are superficial metallic corneal FBs really an ophthalmic emergency? When is the appropriate time for corneal FB removal? When we see a FB in the cornea, do we really treat the patient by scraping from the cornea under emergency conditions, or do we cause a lot more iatrogenic damage to the cornea? To our knowledge, there are very few studies in the literature that can satisfactorily answer the above questions. In this study, we aimed to find answers to the above questions by evaluating the iatrogenic epithelial defect that occurs after the removal of FB in the cornea and the times when the FB was removed. FB was removed on the first day of trauma in 54 out of 110 patients and the mean epithelial defect was 3.59±2.3 mm^2. Epithelial defect was found to be 3.16±1.6 mm^2 in 34 patients in the second group. The mean epithelial defect was found to be 1.68±1.5 mm^2 in 22 patients in the third group and removed after the third day. In the patients whose FB was removed after the third day, less iatrogenic epithelial defects were found to be statistically significant than the first and second groups. (p=0.002, p=0.050 respectively).

There is a possibility of infectious keratitis and corneal scar formation due to FB on the surface of the cornea, but infectious keratitis is more likely to develop due to organic FB damage. The risk of infectious keratitis due to inorganic objects such as metal, plastic and stone is very low. As a matter of fact, cases of stone fragments that can remain asymptomatic in the eye for 60 years without any medical treatment (7), as well as cases of contact lenses that remain uninfected with topical antibiotic drops on the cornea for 7 years, have been reported (8). In a study on 100 people performed by Ramaknishnan et al. (9) with superficial corneal metallic bodies, only 1 (1%) patient admitted on the first

day developed infectious keratitis and was treated with topical antibiotic drops. Another risk may be siderosis bulbi, the earliest occurrence being reported after 18 days for an intraocular metallic body. It can be predicted that this risk will be much lower in the metallic FB on the corneal surface (10). The metallic object is exposed to high temperatures during hammering or after welding. This may have a sterilizing effect on the body and reduce the risk of developing keratitis, but this hypothesis needs to be supported by further studies. Another problem that may occur when the FB waits on the cornea is the formation of rust ring. The rust ring is formed by the diffusion and oxidation of the iron deposits around the metallic object (4,11). Another formation to be followed here is the formation of rust ring around the FB in the 1st hour after the trauma and formation of a cup with a white ring developing around the rust ring from the 1st day (Figure 1). The white ring around the rust ring contains white cells and is responsible for corneal scar formation (11,12). According to our observations in this study, this cup comes out more easily with the rust ring in patients coming after the 3rd day (Figure 2, 3). In corneal superficial iron FB, immediate intervention to the patient within the first hour may be important in order to avoid scarring in the cornea because rust has not yet formed in this circuit. If this period has passed, the urgency of the case has disappeared since rust formation has started. At this stage, removing the FB may be against the patient, not in the favor of the patient because the patient is irritated and painful at this stage. By removing the blepharospasm due to these, the removal of the FB and the rust ring formed may be partially possible under difficult conditions. It may even result in the spread of rust and rust ring on the corneal surface. It may be in the best interest of the patient to wait for cup formation at this stage in the removal of the corneal superficial iron FB, and then remove the FB in a much shorter time and with less iatrogenic damage to the cornea.

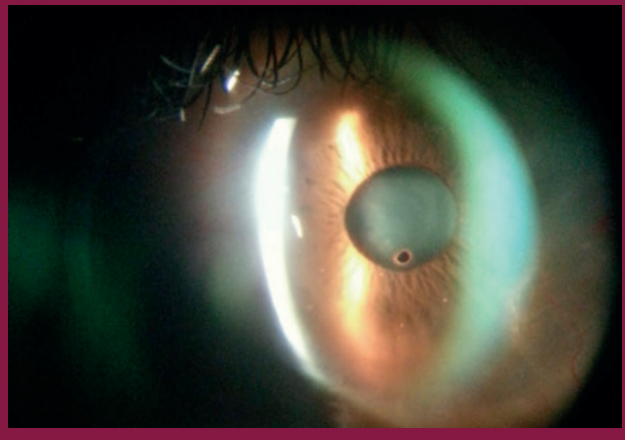

Figure 1. The rust ring around the FB in the middle and the white ring surrounding it and the cup starting from the first day
FB: Foreign body

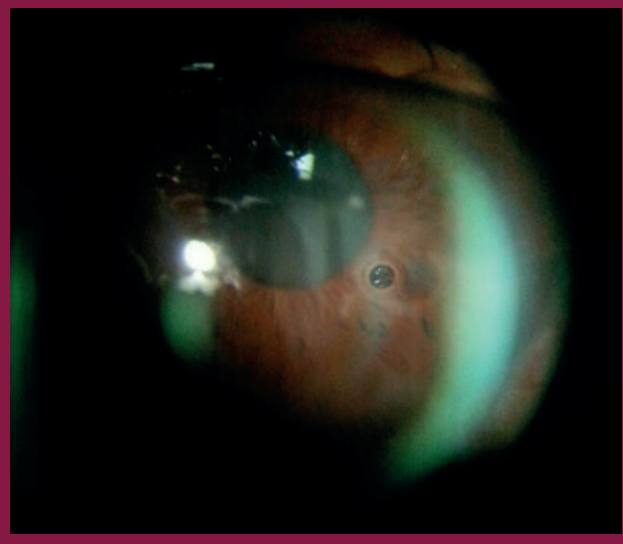

Figure 2. In another patient presenting after the seventh day, the FB in the middle, the transparent ring surrounding it and the outermost dirty white ring and the formation of the completed cup
FB: Foreign body

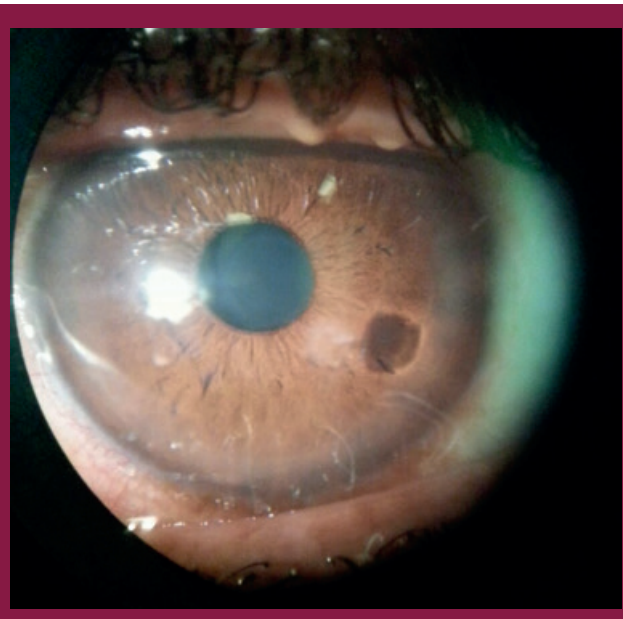

Figure 3. Same patient at Figure 2, after the removal of the FB and the cup. After the FB was easily removed, there was no rust or scar in the cornea. (The shadow of the corneal laceration on the iris appears on the right side of the lesion and after 24 hours the laceration is completely lost)
FB: Foreign body

Conclusion

If the metallic FB remains on the cornea for more than 1 hour, rust ring formation usually develops. Therefore, after the first hour, we think that the superficial metallic corneal FB is not an

ophthalmic emergency. When we see the patient who is agitated with stress and panic after the formation of the rust ring, rather than attempting to remove the rust ring, we suggest that it may be more beneficial to remove FB with less iatrogenic damage by waiting 1-2 days under topical antibiotic prophylaxis and observing the formation of the cup. However, this hypothesis should be supported by further studies.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee (date: 21.07.2016-number: 2016/7).

Informed Consent: Written informed consent was obtained before each individual's participation in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., Concept: A.A., Design: A.A., Data Collection or Processing: A.A., Analysis or Interpretation: O.G., Literature Search: O.G., Writing: O.G., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Appendicitis in a Pediatric Patient with Cystic Fibrosis: Difficulties in the Path to Diagnosis

Kistik Fibrozisli Pediyatrik Hastada Apandisit: Tanıya Giden Yoldaki Zorluklar

Sabri Cansaran

Tokat State Hospital, Clinic of Pediatric Surgery, Tokat, Turkey

ABSTRACT

The production of non-fluid mucus and secretions in the lungs, gastrointestinal tract, pancreas, hepatobiliary and reproductive system is the most prominent feature of cystic fibrosis (CF) disease. In this study, it was aimed to present the diagnostic challenge in a pediatric appendicitis case with CF.

A 3.5-year-old girl with the complaint of abdominal pain that had been going on for four days was consulted with thesuspicion of acute abdomen. She had been diagnosed as CF with gastrointestinal involvement and had tenderness in the right lower quadrant with deep palpation on initial examination. After proper follow-up, because repeated ultrasonography revealed that the diameter of the appendix increased (10 mm) compared to the previous one, the response to compression decreased and there was minimal fluid in the pericecal area, it was decided to perform laparotomy. During the operation, there was a hard structure filling the whole appendix lumen and extending into the cecum. It was observed that the structure in the lumen was a hardened mucus plug causing partial obstruction.

Ultrasonography is a highly effective method in the diagnosis of appendicitis in younger children and can be easily repeated if necessary. Pediatric CF patients with refractory or unexplained abdominal symptoms deserve a higher index of suspicion. With the help of diagnostic tools, surgical intervention is both diagnostic and therapeutic, especially in patients who do not improve clinically.

Keywords: Cystic fibrosis, appendicitis, pediatric, mucus plug

ÖZ

Akciğerler, gastrointestinal yol, pankreas, hepatobiliyer ve reprodüktif sistemde akışkan olmayan mukus ve salgıların üretilmesi, kistik fibrozis (KF) hastalığının en belirgin özelliğidir. Bu çalışmada, KF'li bir pediyatrik apandisit olgusunda tanısal zorlukların sunulması amaçlanmıştır.

Dört gündür devam eden karın ağrısı şikayeti ile başvuran 3,5 yaşında kız hasta akut batın şüphesi ile konsülte edildi. Daha önce gastrointestinal tutulumlu KF tanısı almış hastanın ilk muayenesinde sağ alt kadranda derin palpasyonla hassasiyet mevcuttu. Uygun takip sonrası tekrarlanan ultrasonografide apendiksin çapının bir öncekine göre arttığı (10 mm), kompresyona yanıtın azaldığı ve periçekal bölgede minimal sıvı olduğunun görülmesi üzerine laparotomi yapılmasına karar verildi. Operasyonda, apendiksin tüm lümenini dolduran ve çekuma uzanım gösteren sert bir yapı mevcuttu. Lümen içindeki yapının, kısmi obstrüksiyona neden olan sertleşmiş bir mukus tıkacı olduğu görüldü.

Ultrasonografi, küçük çocuklardaki apandisit tanısında oldukça etkili bir yöntemdir ve gerekirse kolaylıkla tekrarlanabilir. İnatçı veya açıklanamayan abdominal semptomları olan pediatrik KF hastalarında daha şüpheci bir yaklaşım gereklidir. Tanı araçlarının da yardımıyla cerrahi müdahale, özellikle klinik olarak düzelmeyen hastalarda hem tanısal hem de tedavi edicidir.

Anahtar Kelimeler: Kistik fibrozis, apandisit, pediyatrik, mukus tıkacı

Address for Correspondence: Sabri Cansaran, Tokat State Hospital, Clinic of Pediatric Surgery, Tokat, Turkey
Phone: +90 356 214 54 00 E-mail: sabrican@hotmail.com **ORCID ID:** orcid.org/0000-0001-8466-6595

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Introduction

Since associated morbidity and mortality conditions generally develop due to pulmonary complications, cystic fibrosis (CF) is considered more as a lung disease. The pathology in CF is associated with abnormal chloride and bicarbonate transport caused by CF transmembrane regulator gene variants on chromosome 7 (1). The production of non-fluid mucus and secretions in the lungs, gastrointestinal tract, pancreas, hepatobiliary and reproductive system is the most prominent feature of CF disease. This condition causes luminal obstruction in these organs and the emergence of clinical signs related to the disease (2,3).

Pancreatic dysfunction is a key expression for CF disease. In all patients with CF, secretin-induced biological substance release from the pancreatic ducts is reduced (4). The most common complication of CF related to the gastrointestinal tract is pancreatic insufficiency. Approximately 85% of patients experience pancreatic insufficiency at some time in their lives and it is present in most of them from birth (5).

Appendicitis is less common in patients with CF than in the general population. However, the diagnosis is difficult because it can mimic distal intestinal obstruction syndrome (DIOS) and other intestinal diseases associated with CF and cause atypical symptoms (6). In this study, it was aimed to present the diagnostic challenge in a pediatric appendicitis case with CF.

Case Report

A 3.5-year-old girl with the complaint of abdominal pain that had been going on for four days was consulted with the suspicion of acute abdomen. It was learned from her history that she was diagnosed as CF with gastrointestinal involvement and received 3x30 mg oral pancreatin (equivalent to 2,000 IU lipase) treatment. On abdominal examination, she had tenderness in the right lower quadrant with deep palpation. Her fever was within normal limits (36.6 °C). Except for severe constipation, no feature was observed on abdominal X-ray (Figure 1). In laboratory findings, there was 7,300/dL neutrophil count (1,500-8.000) within normal limits and 13,500/dL leukocytosis (4,500-12,000). Biochemistry parameters were normal and C-reactive protein value was negative. The abdomen ultrasound revealed that the appendicular transverse diameter increased to 9 mm and the response to compression decreased. Since abdominal physical examination findings did not significantly support acute appendicitis, follow-up decision with intravenous fluid resuscitation was made. On the second day, the patient's leukocytosis regressed (8,500/dL) and the C-reactive protein value was again negative. The patient who tolerated oral feeding on the same day did not have fever or vomiting. On the third day of follow-up, ultrasound was performed again due to recurrent abdominal pain and anorexia. Repeated ultrasound showed that the diameter of the appendix increased (10 mm) compared to the previous one, the response to compression decreased and there was minimal fluid in the pericecal area. Therefore, it was decided to perform laparotomy. During the operation, the appendix was distant with a very slight hyperemia, and there was a hard structure filling the whole lumen and extending into the cecum. After appendectomy, it was observed that the structure in the lumen was a hardened mucus plug causing partial obstruction (Figure 2). The patient was discharged on the second postoperative day with healing. Outpatient follow-up was uneventful and according to the pathology report, the specimen was compatible with acute appendicitis and the lumen was partially obliterated.

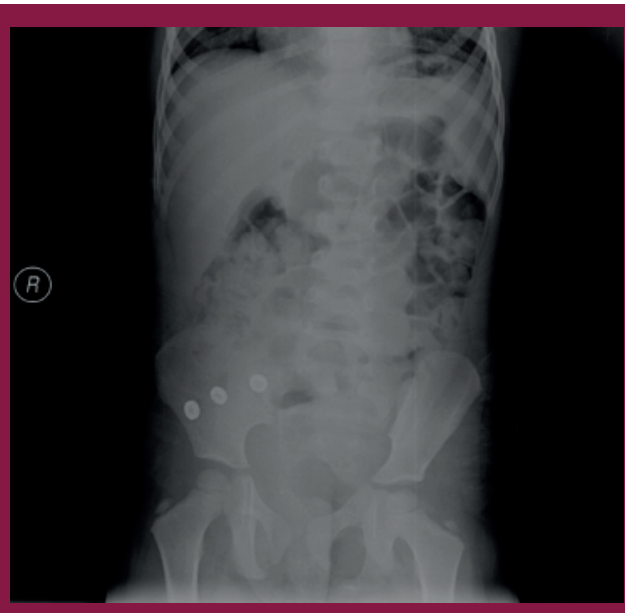

Figure 1. Fecal impaction in the abdominal X-ray of the patient at initial admission

Figure 2. Hardened mucus plug in the lumen of the appendix

An informed consent was obtained from the patient's parents for the publication of this case report containing photographs of the operation.

Discussion

Due to the increasing life expectancy, gastrointestinal problems have become a prominent element of morbidity in patients with CF. Although conditions such as gastroesophageal reflux and constipation are not specific to disease, they are common in patients with CF (7,8). Some complications, such as DIOS, are specific to CF and require special knowledge during the diagnosis and treatment stages.

It is noteworthy that the incidence of acute appendicitis in patients with CF is low compared to the general population. The incidence of appendicitis was reported as 1% in a study including cases with CF (9). Similarly, McCarthy et al. (10) reported the incidence of appendicitis in cases with CF as 1-2% compared to 7% of the general population. These authors attributed the low incidence of appendicitis in cases with CF to the absence of complete obstruction due to the consistently produced thick viscous mucus and the distention it provides. Probably, periodic regression of the complaints and physical examination findings in our case were related to the same reason. The mucus plug that fills the entire lumen and extends into the cecum has revealed this result due to partial obstruction. On the other hand, the same authors noted that the low incidence of appendicitis might also be due to prophylactic antibiotics used by patients with CF. Usage of antibiotics is able to hide the symptoms of acute appendicitis in these cases.

The defect in the release of chloride and water into the intestine, increased acidity in the lumen and loss of bile salts contribute to the development of DIOS (11). The lower right quadrant pain, nausea, vomiting, abdominal distention, failure to pass flatus or stool are the characteristic findings in these CF patients (11,12). The abdominal X-ray is recommended in DIOS, but may fail to distinguish ileus from other abdominal pathologies seen in CF (13). Due to the proximity of anatomical regions and the similarity of their clinical presentations, appendicitis may mimic DIOS. The similar features of many abdominal pathologies such as DIOS, volvulus, intussusception, Crohn's disease, fibrosing colonopathy and colon carcinoma in CF increase the risk of misdiagnosis, especially in terms of appendicitis (6). Our patient applied with similar complaints and initial physical examination findings were not compatible with acute abdomen. There was significant constipation appearance in abdominal X-ray. The septic markers became negative during the follow-up period and this prolonged the accurate diagnosis process. Although there were no significant findings compatible with acute appendicitis in serial physical examinations, markers suggesting acute appendicitis in repeated ultrasound were effective in laparotomy decision. Computed tomography was not preferred due to intense radiation exposure in this case.

Conclusion

Although the incidence of appendicitis is low in patients with CF, there is no easy way to make an accurate and rapid diagnosis. Ultrasound is a highly effective method in the diagnosis of appendicitis in younger children and can be easily repeated if necessary. Although DIOS is the most common cause of abdominal pain in the right iliac fossa in patients with CF, acute appendicitis should also be kept in mind. Pediatric CF patients with refractory or unexplained abdominal symptoms deserve proper follow-up, extensive research and a higher index of suspicion. With the help of diagnostic tools, surgical intervention is both diagnostic and therapeutic, especially in patients who do not improve clinically.

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Ethics

Informed Consent: Informed consent was obtained from the patient's parents for the publication of this case report containing photographs of the operation.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

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CASE REPORT

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Purple Urine Bag Syndrome; A Rare but Important Manifestation of an Important Disease

Mor İdrar Torbası Sendromu; Önemli Bir Hastalığın Nadir Fakat Önemli Bir Belirtisi

Ümran Keskin, Polen Balin Kahraman, Pelin Özel, Kadir Kayataş

University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

ABSTRACT

Purple Urine Bag syndrome (PUBS) is a rare and startling clinical situation commonly associated with urinary tract infection in patients with a urinary catheter. In previous reports, the underlying pathogens and mechanisms were found quite similar and there is not a report with a different further diagnosis in PUBS. In this report, we present a patient with PUBS for which the underlying pathogen and diagnosis is quite unique.

Keywords: Urine color, urinary tract infection, urothelial cancer, urinary catheter

ÖZ

Mor İdrar Torbası sendromu (PUBS) nadir ve çarpıcı bir klinik durum olup genellikle üriner kateter taşıyan hastalardaki idrar yolu enfeksiyonu ile ilişkilendirilmiştir. Geçmiş raporlarda altta yatan patojenler ve mekanizmalar oldukça benzer olarak bulunmuş olup PUBS'de farklı bir tanıya yönlendiren olgu rapor edilmemiştir. Bu yazıda altta yatan patojen ve tanısı oldukça benzersiz olan bir PUBS olgusu sunmaktayız.

Anahtar Kelimeler: İdrar rengi, idrar yolu enfeksiyonu, ürotelyal kanser, üriner kateter

Introduction

Urine color can be an important finding of various disorders and clinical situations. For example, white urine indicates lipiduria or chyluria, pink urine indicates glomerulonephritis, tea color urine indicates hemolysis or myoglobinuria, orange urine indicates rifampicin use, and blue-green urine indicates pseudomonas infection. Oxford urine table is dedicated to make a proper diagnosis in patients with abnormal urine colors (1). Purple Urine Bag syndrome (PUBS), which was first reported in 1978, is another rare clinical situation that might point to urinary tract infection (UTI) (2). Additionally, purple urine can be seen in pediatric patients with Drummond syndrome (3). PUBS is usually seen in geriatric and immobilized patients with inserted Foley catheter, who is complicated with UTI (4). In this case report, we present a patient with bladder cancer, who was admitted to emergency department with PUBS.

Case Report

A 92-year-old male patient was admitted to our emergency department with the complaints of dysuria, hypotension, oliguria, and purple urination. The patient had a history of heart failure and chronic obstructive pulmonary disease and was hospitalized due to pneumonia in intensive care unit three weeks ago. He was followed-up with a urinary catheter in this period and discharged two days ago after the removal of the catheter. The patient did not have another systemic disorder. In physical examination, no abnormalities were found in flank region. The patient looked dehydrated and lethargic. The patient's bladder was palpable and suprapubic region was painful on palpation. Other systems' examination was normal. After the insertion of urinary catheter, we noticed that the urinary catheter bag and the urine within it had become a purple color (Figure 1). The urine test was positive nitrites, hemoglobin and

Address for Correspondence: Ümran Keskin, University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Cardiology, İstanbul, Turkey

Phone: +90 553 545 14 54 E-mail: drumrankeskin@gmail.com **ORCID ID:** orcid.org/0000-0002-7494-2733

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Figure 1. The purple discoloration of urine which was observed after the insertion of urinary catheter

leucocytes and had a pH of 8.4. White blood cell count was 5.2 10^3/μL and neutrophil count was 3.1 10^3/μL. C-reactive protein was at 1.8 mg/dL, and procalcitonin at 0.46 ng/mL. Abdominal ultrasound demonstrated focal bladder wall thickening and contour irregularities. Post-void residual urine volume was 250 mL. The patient was administered an empirical ciprofloxacin 500 mg, antibiotherapy twice a day after bacteriological sampling of urine. Urine culture for aerobic bacteria, anaerobic bacteria and yeast was carried out before the administration of antibiotics. *Morganella morganii* culture results showed significant growth after 24 hours, which was sensitive to ciprofloxacin. After the administration of ciprofloxacin therapy (400 mg q12h) for two days, the urine returned to a clear yellow color. After the completion of antibiotherapy, the patient underwent transurethral cystoscopy to take a biopsy from the bladder. Pathological examination of the sample revealed a low grade papillary urothelial carcinoma. The patient underwent transurethral resection of bladder tumor and was discharged without a complication.

The patient and his relatives gave consent for this case report.

Discussion

PUBS is a rare and relatively benign clinical situation and commonly associated with the UTI in patients with urinary catheter. PUBS has been reported as a benign, harmless and asymptomatic situation in most studies (5,6,7,8,9,10,11,12). There are some high-risk clinical situations for PUBS patients, such as those who are elderly, women, immobilized patients, patients with an indwelling catheter, chronic constipation, alkaline urine, or poor hygiene, and those with catheter bags and tubes made of certain types of plastic. One of the other reasons for the occurrence of PUBS is the increased concentration of bacteria in the urine as a result of urinary outflow obstruction (5,13).

The UTI has been considered as the main cause, and trigger of PUBS and some pathogens such as *Escherichia coli* (28%), *Enterococcus species* (13%), *Pseudomonas aeruginosa* (6%), *Providencia retgerii* (8%), *Klebsiella pneumoniae* (9%), *Citrobacter species,* group B *Streptococci* (2%) and *Morganella morganii* were found as responsible (4). The causative bacteria produce sulphatases and phosphatases through tryptophan metabolism and these reactions result in the formation of indigo and indirubin pigments. The purple color comes from chemicals resulting from this tryptophan metabolism. Interaction between the plastic urine bag and the aforementioned pigments, as well as a high bacterial load, is important precipitating factor for PUBS (6,7,8,9).

M. morganii is an opportunistic infection often seen in post-operative wound and urinary tract infections. According to literature, *M. morganii* is very rarely associated with PUBS and underlying-associated urothelial cancer has not been reported yet (4). Liu et al. (14) considered *M. morganii* as an opportunistic and a non-neglient pathogen and they reported that this pathogen might be considered as a cause of PUBS. Our patient had a different clinical scenario from the other cases in the literature. First, according to literature, the plastic urinary catheters were found as responsible in PUBS and whole cases in the literature with PUBS had a urinary catheter at admission (4). However, our patient admitted to emergency department with purple discoloration of urine had no urinary catheter. Second, there is no case report demonstrating an association between the newly diagnosed cancer and UTI with PUBS. In literature review, we did not encounter a case with PUBS, who had no indwelling catheter at the time of diagnosis. Our patient had serious comorbid situations and a urinary catheter insertion history before the latest admission. Underlying urothelial cancer, accompanying comorbid situations might differentiate this patient from previous reports and explain this situation.

Morganella morganii has been known as a rare opportunistic pathogen that is associated with the infection of urinary tract

(14). However, it is rarely associated with PUBS, there is no report demonstrating that this pathogen was a preliminary finding of urothelial cancer. Malignant urothelial cancer accompanying UTI was probably the main cause of this unique and distinctive clinical situation. Although there is no direct relation between the urothelial cancer and PUBS, all these comorbid situations, atypical pathogen and previous urinary catheter insertion might have caused to this clinical scenario. The isolation of an atypical pathogen as the cause of UTI might be an important clue for differential diagnosis.

Ethics

Informed Consent: The patient and his relatives gave consent for this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ü.K., P.B.K., P.Ö., K.K., Design: Ü.K., P.B.K., P.Ö., K.K., Literature Search: Ü.K., P.B.K., P.Ö., K.K., Writing: Ü.K., P.B.K.

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CASE REPORT

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Hepatosplenic *Bartonella henselae* Infection in an Immunocompetent Patient

Bağışıklık Sistemi Yeterli Bir Hastada Hepatosplenik *Bartonella henselae* Enfeksiyonu

Servet Öztürk[1], Derya Öztürk Engin[1], Semra Toprak Kavas[1], Onur Çolak[1], Adnan Somay[2], Canan Ağalar[1]

[1]*University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey*

ABSTRACT

Cat scratch disease often presents with limited regional lymphadenomegaly. In addition, atypical manifestations such as retinitis, tendinitis, osteomyelitis, oculaglandular syndrome, encephalopathy and granulomatous hepatitis have been reported.

The patient was hospitalized with a diagnosis of fever of unknown origin. Apart from fever, no clinical complaints and no pathological examination findings were found. Since the patient identified erythema migrans-like lesions before the application, doxycycline treatment was started with the suspicion of Lyme disease. However, *Borrelia burgdorferi* immunoglobulin (IgM) and IgG resulted as negative. A fever response was received from the patient at the 48th hour to doxycycline treatment, and *Bartonella henselae* IgG (IFA) evaluation was requested because the patient said they had a cat. *Bartonella henselae* IgG was positive in 1/512 titers and the diagnosis of bartonellosis was made. A liver biopsy was performed with positron emission tomography-computed tomography because of malignancy and microabscess suspicion. Histopathological findings have been reported to be compatible with granulomatous inflammation in the liver. Doxycycline treatment was discontinued and rifampicin was completed on the first day as 14 mg 600 mg/day + azithromycin 500 mg and 250 mg. The patient was discharged with healing. No relapse occurred after his first year of follow-up. *Bartonella henselae*, which is often the cause of cat scratch disease, can rarely cause hepatosplenic involvement secondary to bacteremia. As in our case, it should be kept in mind in the etiology of fever of unknown origin.

Keywords: *Bartonella henselae*, cat scratch disease, hepatosplenic involvement

ÖZ

Kedi tırmığı hastalığı, genellikle sınırlı bölgesel lenfadenomegali ile kendini gösterir. Ancak retinit, tendinit, osteomiyelit, okuloglandüler sendrom, ensefalopati ve granülomatöz hepatit gibi atipik klinik tablolar da bildirilmiştir.

Hasta nedeni bilinmeyen ateş tanısı ile yatırıldı. Hasta başvurudan önce eritema migrans benzeri lezyonu tanımladıktan sonra borreliyoz şüphesi ile doksisiklin tedavisi başlatılmıştır. Ancak *Borrelia burgdorferi* immünoglobulin (IgM) ve IgG negatif sonuçlandı. Doksisiklin tedavisine 48. saatte ateş yanıtı alınan hastadan, evde kedisi olması nedeniyle *Bartonella henselae* IgG (IFA) istendi. *Bartonella henselae* IgG, 1/512 titrede pozitif olarak sonuçlandı ve hastaya bartonelloz tanısı konuldu. Pozitron emisyon tomografi-bilgisayarlı tomografide malignite ve mikroabselerden şüphelenildiği bildirildiği için karaciğer biyopsisi yapıldı. Histopatolojik bulguların karaciğerdeki granülomatöz enflamasyonla uyumlu olduğu bildirilmiştir. Doksisiklin tedavisi kesildi ve rifampisin ilk gün 14 mg 600 mg/gün + azitromisin 500 mg ve 250 mg olarak tamamlandı. Hasta iyileşerek taburcu edildi. İlk takip yılı bitiminde nüks görülmedi. Sıklıkla kedi tırmığı hastalığı etkeni olan *Bartonella henselae*, çok nadir olarak bakteriyemiye sekonder hepatosplenik tutuluma neden olabilir. Olgumuzda olduğu gibi nedeni bilinmeyen ateş etiyolojisinde bartonelloz akılda bulundurulmalıdır.

Anahtar Kelimeler: *Bartonella henselae*, kedi tırmığı hastalığı, hepatosplenik yayılım

Address for Correspondence: Servet Öztürk, University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

Phone: +90 505 527 04 60 E-mail: serwetozturk@hotmail.com **ORCID ID:** orcid.org/0000-0002-9114-5090

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Introduction

Bartonella is an oxidase and catalase negative, facultative, intracellular gram negative bacteria (1). *Bartonella henselae*, *Bartonella quintana* and *Bartonella bacilliformis* can infect healthy people (2). Cat scratch disease often presents itself with limited regional lymphadenomegaly. Papules or pustules occur 3-10 days after animal contact. Growth and pain in the ipsilateral lymph nodes occurs 1-2 weeks later (3). Fever, weakness, myalgia, arthralgia, headache, and sore throat can be observed. Atypical manifestations such as hepatosplenic involvement, neuroretinitis, endocarditis, tendinitis, osteomyelitis, oculoglandular syndrome and fever of unknown origin have been reported. Hepatosplenic bartonellosis is a clinical condition that makes lesions characterized by granulomatous inflammation in the liver and spleen, after the bacteria pass into the systemic circulation. *Bartonella* infections should be considered in the case of fever of unknown origin. The aim of this case report is to present the case who was being observed due to fever or unknown origin, that was diagnosed with isolated hepatosplenic bartonellosis without the presence of lymphadenopathy.

Case Report

A 48-year-old female patient was admitted to our outpatient clinic due to fever that had been ongoing for a month. She had 39.5 ºC degrees of fever every evening for a month; the patient had no additional complaints. There was no chronic disease except hypothyroidism and using levothyroxine. There was no history of traveling abroad, and no smoking and alcohol use. The patient had a history of visiting the countryside but did not describe a tick contact. The only animal that the patient contacted was her cat at home. In her family history, her father had only diabetes mellitus. It was learned that he had received meropenem + vancomycin treatment in a private hospital 15 days before her application to our hospital, and then she used levofloxacin for five days on suspicion of atypical pneumonia. There was no regression in the patient's fever with the current treatments. No pathological examination findings were found. The patient was hospitalized with a diagnosis of fever of unknown origin. In routine examinations, C-reaktive protein resulted in 8.4 mg/dL (range <0.5), sedimentation was 85 mm/hour, ferritin was 456 ng/mL. Other biochemical and complete blood count results were within normal limits (white blood cell: 8,900, leukocyte: 5,400, lymphocyte: 2,600, hemoglobin: 11 g/dk, plotelet (Plt): 414,000/u). There were no atypical cells in the peripheral smear; malaria parasite was not found in thin and thick smear preparations. Infiltration-cavitation-consolidation or mass image was not detected on lung X-ray. Cytomegalovirus (CMV) immunoglobulin (IgM): 1.68 (0-0.84) and CMV inmunglobulin (IgG): >250 (0-5.9) were obtained in serological examinations. Hepatitis B, hepatitis C, toxoplasmosis, brucella, Epstein-Barr virus (EBV) and syphilis tests of the patient were negative. Because the CMV IgG avidity test was high (83.3), acute infection possibility was disregarded. antinuclear antibody, rheumatoid factor and Quantiferon tests were negative; C3-C4 was within normal limits. Vegetation was not observed in transthoracic echocardiography for endocarditis exclusion. "Liver and spleen sizes were normal and diffuse hypoechoic smooth limited millimetric (the largest is 9 mm in diameter) multiple lesions" was observed in the abdominal ultrasonography. Thereupon, upper abdominal magnetic resonance (MR) with contrast was planned. *Borrelia burgdorferi* IgM and IgG were sent for the patient who described the lesion in the forearm in Figure 1 before applying to hospital. Doxycyclin 2x100 mg was started after getting this information. *Borrelia burgdorferi* IgM and IgG resulted as negative. After the 48th hour of doxycycline treatment, the patient's fever did not recur, and his CRP and sedimentation values decreased after the treatment. Because the patient's fever resolved after doxycycline treatment, we started to research which bacteria that doxycycline killed. Multiple millimetric lesions were detected in the liver by abdominal ultrasonography. Abdominal MR showed hypointense in T1 sequence, hyperintense in T1 and T2, and diffusion

Figure 1. Erythema migrans-like lesion on the left forearm

sequence in necular lesions in the T1 sequence, heterogeneity in the spleen parenchyma, and intra-parenchymal lesions in the spleen. The radiologist evaluated the current findings as metastasis if the patient had a history of primary malignancy. In addition, it was stated that it should be evaluated for specific granulomatous infections and microabscess. The infections that caused granulomatosis infections in the liver namely, tuberculosis, brucellosis, secondary syphilis, toxoplasmosis, CMV, EBV, hepatitis A, B, C were disregarded after necessary tests. *Bartonella henselae* IgG (IFA) was requested from the patient who had a clinical and laboratory response to doxycycline therapy, which was started with the suspicion of Lyme. The patient was found to be positive at *Bartonella henselae* IgG 1/512 titer*, and thus was diagnosed with bartonellosis. Doxycycline treatment was discontinued and rifampicin was completed to 14 days as 600 mg/day + azithromycin 500 mg on the first day and 250 mg on maintenance. Positron emission tomography-computed tomography (PET-CT) was taken to the patient because malignancy and infectious processes could not be distinguished in abdominal MR. A liver biopsy was performed in PET-CT as the lesions were reported as suspicious for malignancy and microabscess. Histopathological findings were reported as compatible with granulomatous inflammation in the liver (Figure 2). The patient was discharged with healing.

*Indirect immunofluorescence assays (IFA) were performed using the *Bartonella henselae* (IgG) kit (Euroimmun, Lübeck, Germany) in Istanbul Sistem Tıp Laboratory.

Conclusion

Bartonella henselae can be presented with atypical clinical pictures besides cat scratch disease and bacillary angiomatosis.

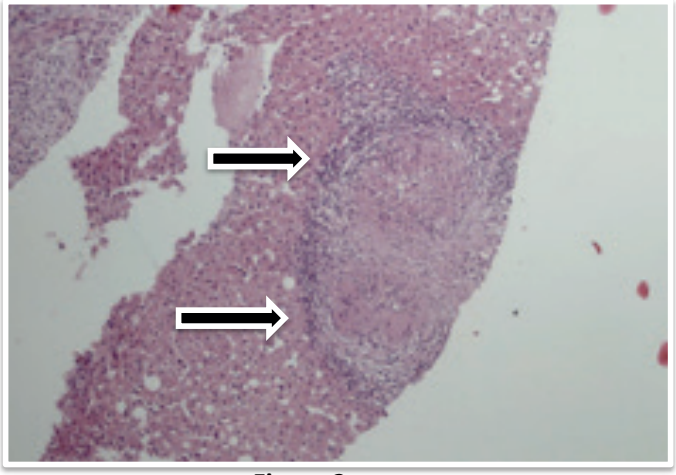

Figure 2a

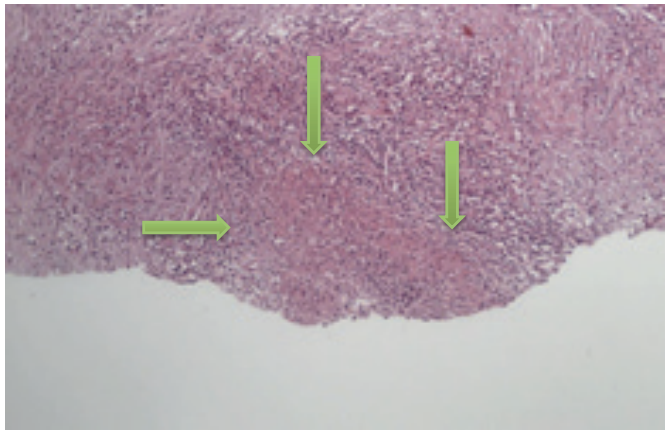

Figure 2b

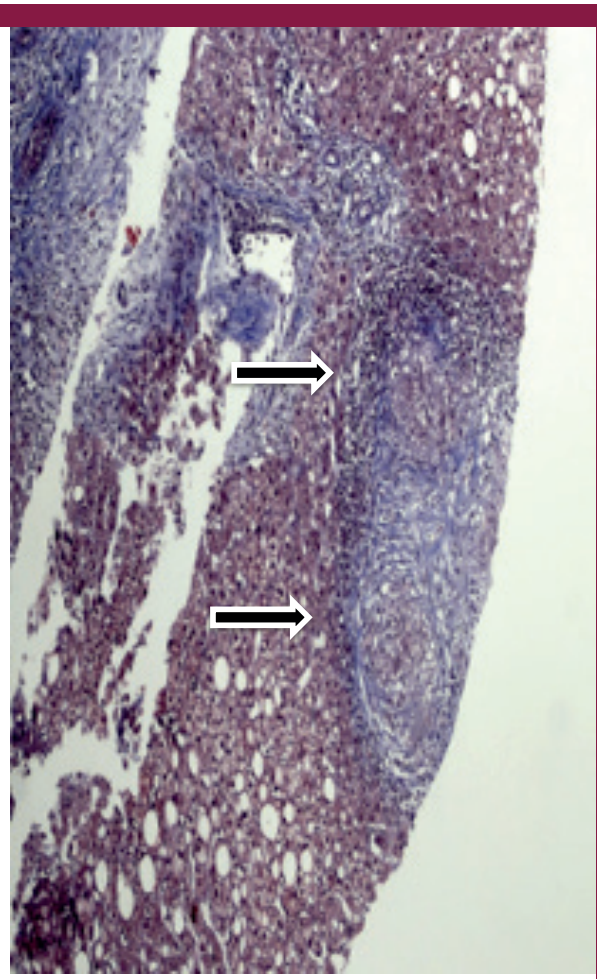

Figure 2c

Figure 2. (a) Two non-necrotizing granulomas in the enlarged portal area, (b) Irregular granuloma structure consisting of epithelioid histiocytes in the portal area with minimal necrosis in the center. H&E X100, (c) Two portal non-necrotizing granulomas surrounded by fibrosis. Masson Trichrome X100

Delays may occur in the diagnosis of atypical course of bartonellosis. The most important diagnostic step in rare infections is the suspicion of the disease. For that, it is very crucial that animal contact is questioned during anamnesis. As in our case, hepatosplenic involvement without lymphadenopathy can progress as an atypical course of bartonellosis (4). In our case, *Bartonella henselae* IgG was positive at 1/512 titers. Culture tests are not used in routine practice because it is difficult to perform. Molecular methods (PCR) and serological tests (IFA) are performed routinely. While titers of *Bartonella henselae* IgG 1/64 and above indicate possible infection, titers above 1/256 strongly suggest acute and recent infection (5,6). Low titer *Bartonella henselae* IgG positivity was found in healthy asymptomatic individuals with cat contact, and serology alone causes deficiencies in diagnosis (7). In fact, false PCR and serology negativities are also observed in blood tests due to temporary and low bacteremia (8). It may be beneficial to go to tissue diagnosis in patients with clinical suspicion whose PCR and serology tests are negative.

There is no consensus in the treatment of cat scratch disease. In the treatment of classical cat scratch diseases, azithromycin is used (6). In the case of bacteremia and endocarditis, gentamicin + doxycycline is used, and in the presence of neuroretinitis and neurological involvement, *erythromycin* + doxycycline (with or without rifampin combination) is generally used (6). Some clinicians apply long-term (four months) combination therapies to minimize the possibility of sequestration in immunological niches such as thymus, bone marrow, and lymph node (9). In fact, the majority of uncomplicated cases regress without antibiotics (10). In complicated cases, trimethoprim-*sulfamethoxazole*, ciprofloxacin or azithromycin are recommended. Gentamycin can be reserved for serious patients. We prescribed two-week rifampicin + three-day azithromycin treatment to our patient. No relapse occurred after his first year of follow-up. PET-CT was not taken again because the patient had no suspicion of malignancy and granulomatosis infection was detected in liver biopsy.

Ethics

Informed Consent: The patient signed a written consent form for this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ö., D.Ö.E., S.T.K., O.Ç., C.A., Concept: S.Ö., C.A., Design: S.Ö., D.Ö.E., S.T.K., O.Ç., C.A., Data Collection or Processing: S.Ö., D.Ö.E., S.T.K., O.Ç., A.S., C.A., Analysis or Interpretation: S.Ö., D.Ö.E., S.T.K., O.Ç., A.S., C.A., Literature Search: S.Ö., D.Ö.E., S.T.K., O.Ç., C.A., Writing: S.Ö., D.Ö.E., S.T.K., O.Ç., C.A.

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