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Review

Internal Medicine

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Medical Journal

Evaluation Of Post-Covid-19 Patients In Terms Of Internal Medicine Practice

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ABSTRACT

COVID-19 can primarily involve the lung, causing multi-organ failure and ultimately death. Acute respiratory complications result in prolonged ICU stay, and this is one of the main causes of morbidity and mortality. For this reasons, the diagnosis and treatment of chronic changes and sequelae caused by the virus in the lungs and other organs in people with severe disease will be important in terms of controls after discharge.

According to the National Institute for Health and Care Excellence (NICE) guideline, the period we call the post-COVID-19 period was defined as the persistence of symptoms and signs after COVID-19 infection for more than 12 weeks and the exclusion of other causes that would explain this situation. In addition, the continuation or re-emergence of symptoms and signs after acute COVID-19 infection was defined as long-COVID. This period includes the prolonged symptomatic period and the post-COVID period. The most commonly reported post-COVID-19 symptoms are fatigue, shortness of breath, cough, arthralgia and chest pain.

COVID-19 disease can have some physical and psychological effects on patients even after the acute symptoms has resolved. Therefore, it would be beneficial to carry out the post-COVID situation, which requires a multidisciplinary approach, under the coordination and responsibility of an internal medicine specialist. In order for post-COVID patients to be followed up regularly and necessary precautions to be taken early, special COVID-19 follow-up outpatient clinics should be established for these patients.

Keywords: post covid, long covid, internal medicine practice

In December 2019, a case of pneumonia of unknown etiology was reported that spread rapidly from Wuhan, China to all over the world.[1] In January 2020, it was discovered that this pneumonia due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[2] One month later, the World Health Organization (WHO) named the disease as Coronavirus Disease-2019 (COVID-19).[3] This new coronavirus spread all over the world in a short time and was declared a pandemic by WHO. [3]

COVID-19 can primarily involve the lung, causing multi-organ failure and ultimately death.[4] Acute hypoxemic respiratory failure, hypercapnia and acute respiratory distress syndrome (ARDS) are the most common complications with a rate of 60-70% in patients treated in the intensive care unit (ICU).[5] Shock (30%), myocardial dysfunction (20-30%), acute kidney injury (10-30%) and arrhythmias (44%) have been reported in ICU patients.[5] Acute respiratory complications result in prolonged ICU stay, and this is one of the main causes of morbidity and mortality.[5, 6] For this reasons, the diagnosis and treatment of chronic changes and sequelae caused by the virus in the lungs and other organs in people with severe disease will be important in terms of controls after discharge.

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Post-COVID-19 Period and Symptoms

According to the National Institute for Health and Care Excellence (NICE) guideline, the period we call the post-COVID-19 period was defined as the persistence of symptoms and signs after COVID-19 infection for more than 12 weeks and the exclusion of other causes that would explain this situation.[7] In addition, the continuation or re-emergence of symptoms and signs after acute COVID-19 infection was defined as long-Covid. This period includes the prolonged symptomatic period and the post-COVID period.[7] Risk factors for long-COVID-19 were stated as > 50 years of age, hypertension, female gender, asthma and obesity.[8]

The most commonly reported post-COVID-19 symptoms are fatigue, shortness of breath, cough, arthralgia and chest pain.[9] All post-COVID-19 symptoms are shown in table 1. In a study conducted in Italy, 83% of 143 patients hospitalized for COVID-19 continued to have at least 1 symptom an average of 60 days after discharge.[10] In another Swiss study, of the 669 post-COVID patients, 32% showed at least one symptom after an average of 43 days.[10]

Time to resolution of symptoms varies in post-COVID patients. This varies depending on the severity of the acute illness and the characteristics of the symptoms experienced by the patient, as well as the pre-disease risk factors. Hypertension, obesity and mental status can be risk factors for the persistence of symptoms.[11] The incidence and recovery times of symptoms after COVID-19 are shown in Table 2. It has been thought that all these prolonged COVID-19 symptoms may be related to virus or immune-mediated disruption of the autonomic nervous system (autonomic dysfunction) resulting in orthostatic intolerance syndromes.[12] Orthostatic intolerance syndromes include orthostatic hypotension, vasovagal syncope and postural orthostatic tachycardia syndrome. The pathophysiology relies on the abnormal autonomic response to orthostasis (standing). In orthostatic intolerance, the release of epinephrine and norepinephrine causes marked tachycardia experienced as palpitations, shortness of breath, and chest pain. Very high catecholamine levels can lead to paradoxical vasodilation, withdrawal of sympathetic activity and activation of the vagus nerve, resulting in hypotension, dizziness, and ultimately syncope.[13, 14] These syndromes may be also exacerbated by hypovolemia from the initial infection or by deconditioning with bed rest. Prolonged bed rest leads to decreased cardiac output and stroke volume, hypovolemia, baroreflex dysfunction, and withdrawal of the sympathetic neural response.[15]

One of the most important post-COVID complaints is fatigue. In studies on fatigue, it was shown that fatigue was not associated with baseline disease severity and there was no relation between proinflammatory cytokines or immune cell groups and fatigue. Pre-existing depression was associated with severe post-COVID fatigue.[10]

Post-COVID Follow-up

Although COVID-19 mainly affects the respiratory system, it has been shown to cause extensive endothelial damage.[16] Therefore, the disease should be evaluated systemically and evaluated in terms of the potential for the development of complications related to all organs and systems. For this reason, we think that the follow-up of these patients by an internal medicine specialist and consultation or referral to other branches when necessary would be a more accurate approach.

Patients who are hospitalized in the intensive care units and have signs of severe disease should be invited for control after discharge. They should be re-

Table 1. Post- COVID symptoms.

Dyspnea	Tiredness
Post-exercise fatigue	Mood cahnges
Cough	Chest pain
Headache	Palpitations, tachycardia
Artralji	Myalgia
Paresthesia	Abdominal pain
Diarrhea	Insomnia
Fever	Rash
Anosmia	Dysgeusia

Table 2. Frequency and duration of post-COVID symptoms

Symptoms	Frequency	Duration of symptoms
Common		
Tiredness	15-87%[10, 11, 26–29]	> 3 months
Dyspnea	10-71%[9, 10, 18-20]	> 2-3 months
Chest pain	12-44%[9, 10]	2-3 mpnths
Cough	17-34%[10, 11, 27, 30]	> 2-3 months
Anosmia	10-13%[10, 11, 22, 31]	> 1 months
Less common		
Arthralgia, myalgia	< 10%[10, 26, 29]	Unknown
Headache, insomnia		
Taste disturbance		
Anorexia		
Sweating, diarrhea		
Psychological and neurocognitive		
Post traumatic stress disorder	7-24%[27, 28]	6 weeks to 3 months, or longer
Poor memory	18-21%[27, 32]	Weeks to months
Lack of concentration	16%[27]	Weeks to months
Anxiety/depression	22–23%[26, 28, 29, 33]	Weeks to months
Decreased quality of life	> 50%[33]	Unknown (possibly weeks to months)

questioned about COVID-19 symptoms and physical examination should be performed thoroughly. The persistence of symptoms or the presence of new symptoms should be investigated, and care should be taken in terms of reinfection. Patients should be evaluated in detail in terms of inflammatory and immunological reactions caused by the disease, side effects due to medications, changes in lifestyle and effects of psychological stress.

Post-COVID Laboratory Evaluation

Hemogram, C- reactive protein (CRP), coagulation tests (INR, d-dimer) and abnormal biochemical tests at discharge should be evaluated at first visit. If possible, the COVID antibody test should be measured at quantitatively to assess antibody response. In addition, patients should be evaluated in terms of common internal diseases such as for hypertension, diabetes, dyslipidemia and obesity. Care should be taken to measure blood pressure in both arms at the first control of the patients

Post-COVID Radiological Evaluation

If there are no persistent or newly developing symptoms in patients with positive PCR test but no radiological findings or who show complete radiological recovery at discharge, there is no need for routine chest X-ray control. It is known that radiological recovery may occur after clinical recovery. For this reason, it should be kept in mind that not every persistent lesion on chest X-ray or tomography indicates active disease after the treatment is completed. Pulmonary fibrosis, thromboembolic events, small airway diseases, pulmonary hypertension, bronchiectasis and organizing pneumonia are the pulmonary findings that can be seen in COVID-19 patients.[16, 17]

The long-term radiological findings of COVID-19 are not clearly known. However, experience from SARS and MERS outbreaks has shown us that 20-60% of patients have signs of pulmonary fibrosis.[9] Therefore, COVID-19 pneumonia may be expected to cause permanent damage to the lung parenchyma in some patients. In a case series of patients with mild symptoms, some radiological findings can be detected on computed tomography (CT) despite complete clinical recovery in a significant part of the patients 3 months after discharge.[18]

Patients with severe COVID-19 pneumonia followed in the ICU should be evaluated for ongoing or newly developed respiratory symptoms. The

course of existing symptoms over time and, if any, newly developed symptoms should be evaluated. This patient group should undergo a full clinical evaluation and chest X-ray at the end of week 12.[18] If the chest X-ray is normal except for small segmental atelectasis and the clinical findings are normal, it can be excluded from follow-up. However, if the expected improvement in the chest X-ray has not been achieved, a pulmonologist consultation should be made. However, if the expected improvement in the chest X-ray did not occur, should be consulted to a chest diseases specialist. It is recommended to perform pulmonary function tests and lung CT in patients with normal control chest X-rays and laboratory examinations, and who continue to have respiratory distress.[18] To save patients from unnecessary radiation exposure, tomography requests should be determined correctly and attention should be paid.

Post-COVID Neurological Symptoms, Smell and Taste Disorders

Severe COVID-19 patients may encounter acute conditions such as encephalitis and stroke, as well as long-term neurological symptoms and persistent neurocognitive impairments.[19-21] Therefore, in the first examination of the patient, a neurological examination including orientation and cooperation status, muscle strength assessment, and gait analysis should be performed. If the patient's system query, neurological examination and tests are normal, the control is completed. However, if an abnormality is detected, consultation from a neurologist should be sought.

As COVID-19 can affect neuronal cells by both direct and indirect mechanisms, this can lead to a variety of neurological manifestations, including anosmia and hypogeusia. Anosmia and hypogeusia are present in both mild/moderate and severe cases of COVID-19.[21,22] Patients with anosmia, hypogeusia, hearing loss, facial paralysis, hoarseness, dysphagia and vertigo are referred to an ear-nose-throat (ENT) specialist.

Post-COVID-19 Psychiatric Evaluation

It has been reported that the COVID-19 pandemic causes mental problems such as anxiety, depressive symptoms, insomnia and fear of death [20]. In addition to these, it was observed that the patients had depression, anxiety disorder, obsessive compulsive disorder and post-traumatic stress disorder in their follow-up.[23] Mental status of patients can be evaluated with simple questions and patients with abnormality should be referred to psychiatry.

Post-COVID Treatment Recommendations

Patients presenting with dyspnea, which is the most important complaint at presentation, should be evaluated in terms of lung pathologies, and if no abnormality is detected, muscle fatigue, coordination disorder and psychiatric causes should be evaluated. Saturation monitoring should be recommended for silent hypoxemia. If necessary, patients should be included in pulmonary rehabilitation programs and breathing exercises should be performed.[24] It is predicted that patients who are discharged with oxygen support due to hypoxemia will need oxygen therapy at home for an average of 6-8 weeks.[25] There is no data on the treatment of patients who continue to have dyspnea or develop pulmonary fibrosis despite the completion of COVID-19 treatment. These patients must be evaluated by a pulmonologist and followed closely at home if necessary.

According to the recommendations of the Ministry of Health of our country, patients should be evaluated for venous thromboembolism (VTE) and prophylaxis should be performed. New generation oral anticoagulants should be used in patients who are considered for long-term VTE prophylaxis, due to ease of follow-up (except in cases where warfarin or heparin is mandatory, such as prosthetic valve, valvular atrial fibrillation (AF).[26]

CONCLUSION

COVID-19 disease can have some physical and psychologic effects on patients even after the acute symptoms has resolved. Although it is essential to make a decision to the patient, they should be followed up especially at 1, 3 and 6 months after discharge. Severe COVID-19 patients should continue their controls at 12, 18 and 24 months and should be screened for the pathologies described above.

As a result, it is necessary to determine the current status of individuals with Covid-19 disease, and their controls should be followed in a standard and multidisciplinary manner for at least 2 years. Therefore, it would be beneficial to carry out the post-COVID situation, which requires a multidisciplinary approach, under the coordination and responsibility of an internal medicine specialist. In order for post-COVID patients to be followed up regularly and

necessary precautions to be taken early, special COVID-19 follow-up outpatient clinics should be established for these patients.

Authors' Contribution

Study Conception: EA,; Study Design: EA, İBT, MÇ,; Supervision: EA,; Materials: EA, İBT, MÇ,; Data Collection and/or Processing: EA, İBT, MÇ,; Statistical Analysis and/or Data Interpretation: EA,; Literature Review: EA, İBT, MÇ,; Manuscript Preparation: EA, İBT, MÇ and Critical Review: EA, İBT, MÇ.

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Original Article

Internal Medicine & Hematology

DAHUDER Medical Journal

Clinical features of patients with monoclonal gammopathy

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ABSTRACT

Objectives: In this study, we aimed to demonstrate ordered immunofixation electrophoresis (IFE) testing for distinct indications from different inpatient and outpatient clinics, interrelate the IFE results and patients' clinical and laboratory characteristics, and classify the confirmed cases of monoclonal gammopathy (MG).

Methods: We included 4,474 IFE tests conducted between December 2013 and July 2016 in this study. Out of these, the tests of 472 patients with MG were retrospectively evaluated.

Results: The patients' median age was 64 years (range, 17–90). Seventy-four percent of the IFEs were ordered by Hematology, 13.1% by the General Internal Medicine Department, 5% by other internal medicine departments, and the rest were ordered by different clinics. Moreover, 59.5% of IFEs were ordered as diagnostic workups for multiple myeloma, 13.3% for lymphoma; 2.5% for polyneuropathy, and 0.4% for amyloidosis. Among the patients with definitive diagnosis and MG, 44.5% had plasma cell diseases and 14.6% had lymphoproliferative diseases. The most common non-hematological condition associated with MG was rheumatic disease.

Conclusion: Clinicians should be aware of other indications for ordering IFE in diagnostic workups of rare diseases with different clinical presentations, such as unexplained polyneuropathies or autoimmune diseases, which may be associated with MG.

Keywords: Monoclonal gammopathy, Immunofixation electrophoresis, Plasma cell disorders, Lymphoma, Rheumatologic disorders

The monoclonal gammopathies are a group of disorders characterized by the proliferation of a single clone of plasma cells or lymphoplasmacytic cells; this produces an immunologically homogenous protein, commonly referred to as a paraprotein or monoclonal protein (M-protein), which can be detected via immunofixation of serum, urine, and/or other body fluids. The finding of a monoclonal protein represents one of the most common laboratory abnormalities in adults and one of the most frequent causes of hematology consultation. The presence of an M-protein in the serum or urine indicates, among other disorders, an underlying clonal plasma cell or lymphoproliferative, connective tissue, dermatological, or infectious disorder.[1, 2]

Although there have been several prevalence and incidence studies of monoclonal gammopathy of undetermined significance (MGUS) performed in the literature.[3, 6], there has been no research study indicating the aim of ordering immunofixation electro-

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phoresis (IFE) tests in different medical departments. Therefore, in this study, we aimed to evaluate the ordered IFE testing for different indications from different inpatient and outpatient clinics, interrelate the IFE results and patients' clinical and laboratory characteristics, and classify the confirmed cases of monoclonal gammopathy (MG).

METHODS

Patients and Study Design

We conducted a retrospective study of the all patients in whom immunofixation studies were done at a multidisciplinary hospital, over a nearly 2-year period (December 2013–July 2016). Of the 4,474 patients tested with IFE, 472 were identified with confirmed MG positivity. The available medical files and biological results of all IFE-positive patients were retrospectively reviewed. Age, gender, serum, and urine IFE results, indications for IFE testing, clinical data, and final diagnoses were analyzed in these patients. Subgroups of monoclonal proteins were recorded. Patients were then grouped according to their immunofixation findings, and associations with the above demographic, diagnosis, clinical, and laboratory variables were assessed.

Ethical considerations

The study protocol was approved by the institu-

Table 1. Distribution of medical departments that ordered the immunofixation electrophoresis

DEPARTMENT	Ordered IFEs		M band +	
	n (4474)	%	n (472)	%
MEDICAL DEPARTMENT				
Hematology	2003	44.8	349	74
General Internal Medicine	1076	24	62	13
Physical Therapy and Rehabilitation	472	10.6	13	2.9
Nephrology	*234*		*9*	
Rheumatology	*109*		*6*	
Gastroenterology	*40*		*1*	
Oncology	*35*		*2*	
Endocrinology	*22*		*1*	
Neurology	161	3.6	8	1.7
Cardiology	64	1.4	2	0.4
Pulmonary Medicine	55	1.2	2	0.4
Infectious Diseases	47	1	7	1.5
Dermatology	10		1	0.2
SURGICAL DEPARTMENT				
Neurosurgery	52	1.1	2	0.4
Transplant Centre	37	0.9	4	0.8
Otorhinolaryngology	17		0	
General Surgery	12		1	0.2
Gynecology	11		0	
Thoracic Surgery	7		1	0.2
Orthopedic Surgery	4		0	
Plastic and Reconstructive Surgery	3		0	
Ophthalmology	3		0	
TOTAL	**4474**			

Abbreviations; IFE; immunofixation electrophoresis

tional ethics committee (date/number:17.08.2016/468) and conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. There was no sponsor for the study.

Statistical analysis

All statistical analyses were performed using the SPSS 20.0 program (SPSS, Chicago, Illinois, USA). The chi-square test was used for categorical data. The findings are given as the median, minimum, and maximum for age. Descriptive values for the other data are given as numbers (percent).

RESULTS

In this study, we investigated which clinical department performed the IFE for 4,474 patients (Table 1). Of the patients tested, 472 (10.5%) had positive immunofixation test results. The mean age for the patients who had positive immunofixation test results was 64 (range, 17–94) years, comprising 247 men and 225 women. The preliminary diagnoses of the 472 patients are given in figure 1. The most common preliminary diagnoses were multiple myeloma (59.5%), lymphoma (13.3%), neuropathic diseases (2.5%), and amyloidosis (0.4%), but for 114 (24.3%) patients, there were various other reasons for performing IFE, including pancytopenia, thrombocytopenia, neutropenia, muscle weakness, and unknown.

The reasons for performing IFE and which department performed the testing were evaluated. The reasons for performing IFE in the department of endocrinology were not clear. In the other departments, IFEs were performed infrequently for cancer screening in patients presenting with consistent symptoms and laboratory results, including unexplained fatigue, weight loss, anemia, and elevated sedimentation rates. These patients were then diagnosed with multiple myeloma (MM) or myelodysplastic syndrome.

The definitive diagnoses of 472 patients are given in figure 2. As expected, plasma cell neoplasms were the most frequent disorder; 144 (87.6%) patients were diagnosed with multiple myeloma and 69 with lymphoproliferative disorder. Most of them were non-Hodgkin lymphoma (NHL; 72.5%). Diffuse large B-cell lymphoma cases were the most common subtype of NHL cases. However, lymphoma subtype analysis could not be performed or the data could not be retrieved for about half of the NHL cases. The distribution of diagnoses for the 84 patients in figure 2a labelled ‘other’ are given in table 2. Rheumatoid arthritis and ankylosing spondylitis were the most frequently detected rheumatological disorders. In 11 patients with known chronic kidney disease and MG who had been followed up in other services, sufficient data could not be obtained.

Heavy- and light-chain distributions of plasma cell disorders, lymphoproliferative disorders, rheumatological disorders, chronic kidney diseases, and myelodysplastic syndromes are presented in Tables 3, 4, and 5, respectively. The most commonly observed monoclonal protein subtype was immunoglobulin G (IgG) kappa. Heavy and light chain distributions of rheumatological disorders, chronic kidney disease and

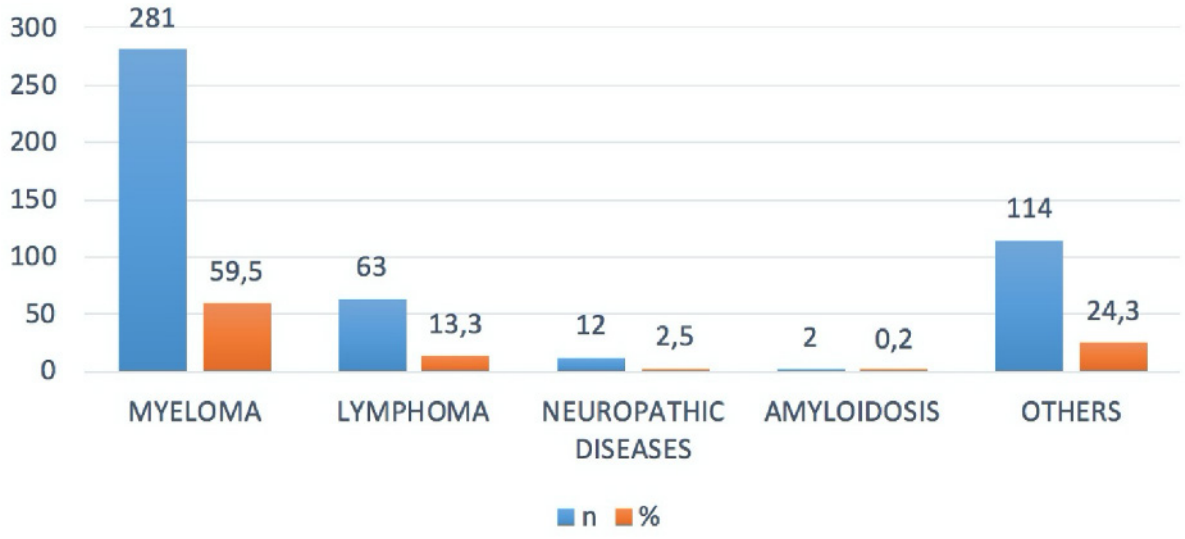

Figure 1. **Distribution of preliminary diagnoses**

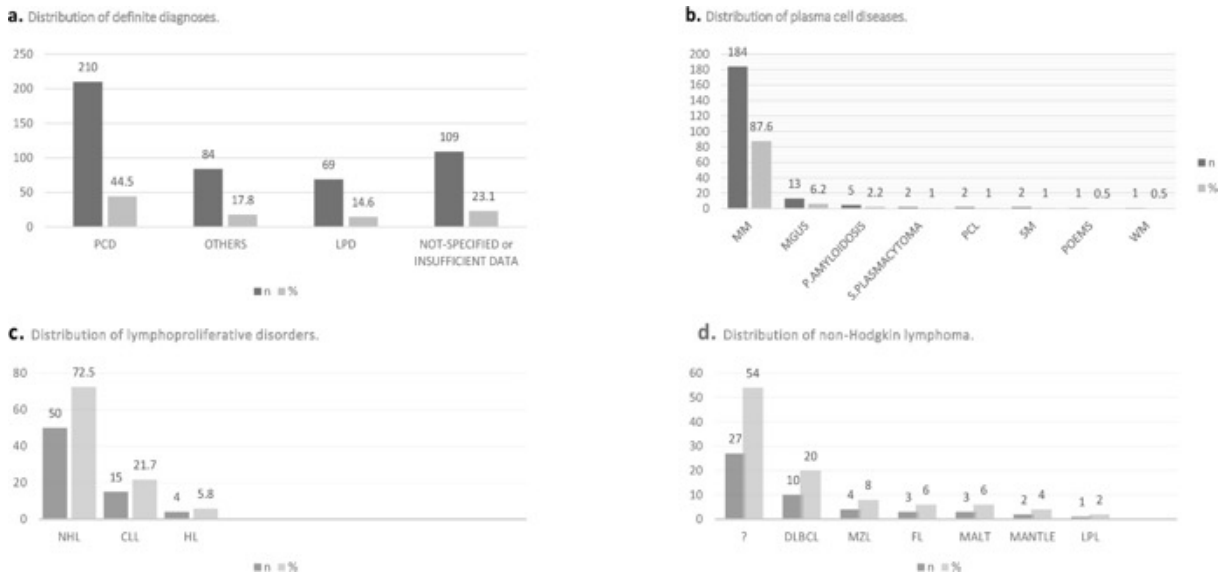

Figure 2. Distribution of diagnoses

myelodysplastic syndrome are given in Table 6.

DISCUSSION

This was a single center study in which IFE results from different medical and surgical departments were screened; 472 patients with monoclonal band positivity were evaluated retrospectively. We aimed to identify the reasons for IFE testing at different clinics, and in this way, evaluate physician awareness. As we know, there is no similar study in the English literature.

In terms of demographic characteristics, the median age and gender characteristics of the patients with monoclonal band positivity were similar to those

Table 2. The distribution of diagnosis for 84 patients in graphic 2 named 'others'

Disorders	n (84)	%
Rheumatic Disorders	30	35.7
Chronic Kidney Disease	11	13.1
Myelodysplastic syndrome	11	13.1
Solid Tumor	8	9.5
Leukemia (ALL/AML)	6	7.2
Myelofibrosis	4	4.7
Organ Transplantation	4	4.7
Renal transplantation	3	3.5
Liver transplantation	4	4.7
MG associated neuropathy	1	1.2
MG associated crystal keratopath	1	1.2
MG associated cryoglobulinemia type 1	1	1.2
HIV infection	2	2.4
Iron Deficiency Anemia	2	2.4
Paroxysmal nocturnal hemoglobinuria	1	1.2
Autoimmune Hemolytic Anemia	1	1.2
Antiphospholipid Antibody Syndrome	1	1.2

Abbreviations; ALL;acute lymphocytic leukemia, AML; acute myeloidleukemia, MG; monoclonal gammopathy, HIV; human immunodeficiency virus

Table 4. Heavy and light chain distribution of plasma cell disorders

Plasma cell disorders	n (210)	%
MM	**184**	**87.6**
IgG (κ / λ)	97 (71/26)	45.4
IgA (κ / λ)	37 (22/15)	17.7
IgM (κ / λ)	5 (3/2)	02.3
Light chain (κ light chain/ λ light chain)	44 (26/18)	21.8
IgD λ	1	0.04
MGUS	**13**	**06.2**
IgG (κ / λ)	9 (5/4)	04.4
IgM (κ / λ)	2 (1/1)	00.9
Light chain (κ light chain/ λ light chain)	2 (1/1)	00.9
Primer Amiloidoz	**5**	**02.2**
IgG (κ / λ)	4 (2/2)	01.8
IgM λ	1	00.4
Solitary plasmacytoma	**2**	**01.0**
IgA κ	1	00.5
IgG κ	1	00.5
Plasma cell leukemia	**2**	**01.0**
κ light chain	1	00.5
IgG λ	1	00.5
Smoldering myeloma	**2**	**01.0**
IgG κ	2	01.0
POEMS	**1**	**00.5**
IgA λ	1	00.5
WM	**1**	**00.5**
IgM κ	1	00.5

Abbreviations; MM; multiple myelom, IgG; immunoglobulin G, κ; kapa, λ; lambda, IgA; immunoglobulin A, IgG; immunoglobulin M, IgD; immunoglobulin D, MGUS; monoclonal gammopathy of undetermined significance, POEMS; Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes syndrome, WM; Waldenström makroglobulinemisi

of two previous studies.[7, 8] Like in other studies, the most commonly observed monoclonal protein isotypes were IgG kappa and kappa MG in serum and urine, respectively. IFE tests were mostly planned by Hematology and General Internal Medicine clinics. Plasma cell disorders and lymphoproliferative disorders were the most frequent, and MM was the most common among the plasma cell disorders. These results were similar to those reported in the Mayo Clinic study by Kyle *et al*.[9]

In 84 patients in the "other disorder with MG" class, the most common disorders were rheumatological diseases; among these, rheumatoid arthritis and ankylosing spondylitis were the most common. In addition, Sjogren's syndrome, systemic lupus erythematosus, scleroderma, and psoriatic arthritis cases were observed. A meta-analysis performed by McShane *et al*.[10] did not show a significant increase in risk between the development of MGUS in rheumatoid arthritis and ankylosing spondylitis patients, but in this study, the number of cases was insufficient and a heterogeneous group was evaluated. In another prospective study of patients with Sjogren's syndrome, MG was detected more prevalently in the patients, and hematological malignancy was later reported in these patients.[11]

One patient presenting with angioedema had IgM lambda MG and C1 inhibitor deficiency in the serum; this patient was diagnosed with splenic mar-

Table 5. Heavy and light chain distribution of lymphoproliferative disorders

Lymphoproliferative disorders Type of M component	n (69)	%
Non-Hodgkin Lymphoma	**49**	**71.0**
IgG (κ / λ)	14 (10/4)	
IgA (κ / λ)	2 (1/1)	
IgM (κ / λ)	16 (10/6)	
Biclonal	5	
κ light chain	9	
λ light chain	2	
Triclonal	1	
CLL	**15**	**27.1**
IgG (κ / λ)	8 (6/2)	
IgA (κ / λ)	2 (1/1)	
IgM (κ / λ)	3 (2/1)	
Biclonal	1	
κ light chain	1	
Hodgkin Lymphoma	**4**	**05.8**
IgG (κ / λ)	2(1/1)	
IgM κ	1	
λ light chain	1	
LPL	**1**	**01.4**
IgM κ	1	

Abbreviations; IgG; immunoglobulin G, κ; kapa, λ; lambda, IgA; immunoglobulin A, IgG; immunoglobulin M, CLL; chronic lymphocytic leukemia, LPL; Lenfoplazmasitik Lenfoma

ginal zone lymphoma. In a study evaluating acquired C1 inhibitor deficiency and MG prevalence at the time of diagnosis of 19 patients with C1 inhibitor deficiency-related angioedema, MG was detected in 12 patients. Eleven of these 12 patients had the same heavy- and light-chain isotype as the C1 inhibitor antibody, and 3 of these patients developed lymphoproliferative disease within 6 years. A possible underlying mechanism for this is the clonal increase of B-cells producing C1 inhibitor antibody; thus, it should be kept in mind that lymphoid malignancies may develop in patients presenting with angioedema and MG.[12] In another study involving 32 patients with acquired C1 inhibitor deficiency, 9 were diagnosed with NHL.[13]

One patient presented with generalized livedo reticularis as the first manifestation of type 1 cryoglobulinemia. There are many skin manifestations associated with MGs. Today, these are classified as MG of cutaneous significance.[14] Type I cryoglobulinemia (CG) is usually asymptomatic. When it is symptomatic, it most commonly causes signs related to hyperviscosity and blood vessel occlusion due to the precipitation of immunoglobulins in response to cold. The Raynaud phenomenon, livedo reticularis, and digital ischemia may occur and are often found on acral areas. Type I CG is usually associated with multiple myeloma, Waldenstrom's macroglobulinemia, chronic lymphocytic leukemia, or MG of unknown significance.

One patient presented with blurred vision as the first manifestation of MG-related crystal keratopathy. IgG kappa and kappa MGs were observed in the patient's serum and urine, respectively. Crystalline keratopathy is a rare result of MG and estimated to occur in up to 1% of cases with MG. Pathological changes leading to visual dysfunction may be observed or corneal deposits may be the only manifestation of MG in patients who are otherwise systemically asymptomatic. In symptomatic patients with paraproteinemic crystalline keratopathy, treatment of the underlying disorder is the mainstay of management. Thus, it is

Table 6. Heavy and light chain distribution of rheumatological disorders, chronic kidney disease and myelodysplastic syndrome.

Rheumatic Diseases		
Type of M component	**n (30)**	**%**
Rheumatoid arthritis	**12**	**14.3**
IgG κ	8	9.5
IgA (κ / λ)	2 (1/1)	2.4
κ light chain	1	1.2
Biclonal	1	1.2
Ankylosing spondylitis	**5**	**6.0**
IgG (κ / λ)	3 (2/1)	3.6
κ light chain	1	1.2
IgM λ	1	1.2
SLE	**4**	**4.7**
IgG (κ / λ)	3(2/1)	3.5
κ light chain	1	1.2
Sjogren's syndrome	**3**	**3.6**
IgG κ	3	3.6
Psoriatic arthritis	2	2.4
IgG κ	2	2.4
Chronic Kidney Disease		
Type of M component	**n (11)**	**%**
IgG (κ / λ)	10 (9/1)	11.9
Biclonal	1	1.2
Myelodysplastic Syndrome		
Type of M component	**n (11)**	%
IgG κ	8	9.5
IgA λ	1	1.2
κ light chain	1	1.2
Biclonal	1	1.2

Abbreviations; IgG; immunoglobulin G, κ; kapa, λ; lambda, IgA; immunoglobulin A, IgG; immunoglobulin M, SLE; Systemic Lupus Erythematosus.

important to keep in mind that MG may be present in patients via awareness of ocular damage, as well as that ocular lesions may heal with treatment of the underlying disease. In addition, patients with known MG should be aware of the possibility of developing associated ocular disease.[15]

One patient with IgM kappa MG in the urine was remarkable in our study. He had been diagnosed with type 2 diabetes and Waldenstrom's macroglobulinemia years before. We described the presence of IgM in the urine with the patient's nephrotic-level proteinuria due to uncontrolled diabetes mellitus. There was another patient presenting with Evans syndrome and the IgG kappa, IgM kappa, M heavy chain triclonal band in his serum; he was diagnosed with splenic marginal zone lymphoma.

In practice, a significant number of patients who present with back pain and have been diagnosed with multiple myeloma are referred to an orthopedist or neurosurgeon before an Internal medicine or Hematology admission. For this reason, it is expected that more IFEs will be studied in Orthopedic and Neurosurgical departments with a multiple myeloma prevalence. Similarly, while many plasma cell diseases

present with skin lesions, far fewer IFE tests were performed by Dermatology in our study than we expected.

Due to the difficulty in accessing patient data and the fact that some of the data obtained were inadequate, which was the limitation of our study, only the patients who were found to be positive for MG were evaluated. MG of undetermined significance is an asymptomatic, premalignant, clonal plasma cell disorder, and there is a life-long risk of progression to MM or lymphoma at a constant rate of 1% per year. No treatment is required for patients with MGUS. The current approach is monitoring these patients. However, for each case, the clinician should question whether the symptoms are associated with MG and exclude "MG-related" conditions before a diagnosis of MGUS is established. This awareness will further clarify the patient's follow up in terms of both primary disease progression and neoplasia development. More research is needed on MG in specific autoimmune diseases, not only in plasma cell disorders and lymphoproliferative diseases. Increasing the awareness of physicians in other medical and surgical branches concerning this issue will enable more patients to be diagnosed correctly and receive treatment at the appropriate time.

Authors' Contribution

Study Conception: YM, UI, HS, TU, OS, SO, LU,; Study Design: YM, UI, HS, TU, OS, SO, LU,; Supervision: OS, SO, LU,; Materials: YM, UI, HS, TU, OS, SO, LU,; Data Collection and/or Processing: YM, UI, HS, TU,; Statistical Analysis and/or Data Interpretation: YM, UI, HS, OS, SO,; Literature Review: YM, UI, HS, TU, OS,; Manuscript Preparation: YM, UI, HS, TU, OS, SO, LU and Critical Review: UI, TU, OS, LU.

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Original Article

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Evaluation of Malnutrition Risk with Malnutrition Universal Screening Tool (MUST) in Inflammatory Bowel Disease Patients

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ABSTRACT

Objectives: Malnutrition can lead to morbidity and mortalityin Inflammatory bowel diseases (IBD). Malnutrition screening tool (MUST) is a simple and easy-to-apply screening questionnaire developed for outpatiets. In this study, we aimed to evaluate the frequency of malnutrition risk with MUST in IBD patients.

Method: Between 01 April 2016 and 01 April 2017, patients diagnosed with IBD in outpatient and inpatient clinics of Gastroenterology were screened for malnutrition risk with MUST. Patients with a MUST score of ≥ 2 were concluded as high-risk for malnutrition.

Results: A total of 216 IBD patients enrolled in this study. The study included a total of 177 (81.9%) patients from outpatient polyclinic and 39 (18.1%) from inpatient clinic. Risk of malnutrition was identified in 24.1% of patients according to MUST. Number of hospitalized patients with malnutrition rsik was significantly higher than the outpatient ones (71.7% vs. 13.5%, $p < 0.001$). The frequency of high malnutrition risk was 21.7% in ulcerative colitis (UC) patients and 29.68% in Crohn's disease (CD) patients. The economic status of patients with malnutrition was significantly lower ($p = 0.010$) and the history of surgery was significantly higher in patients with CD ($p = 0.002$).

Conclusion: A quarters of IBD patients had a high risk of malnutrition in our study. The risk of hospitalized patients was much higher. Care should be taken with low economic status for all patients and in CD patients with a surgical history for malnutrition risk.

Keywords: Inflammatory bowel disease, Malnutrition, Nutritional assessment

Inflammatory bowel diseases (IBD) are a group of chronic and recurrent diseases consisting of ulcerative colitis (UC) and Crohn's disease (CD) in which genetic predispositions, environmental factors and various host factors play a role in the etiology. Increased inflammation, especially in the active stages of the disease, can cause serious damage to the intestinal mucosa and loss of physiological functions of the intestine.[1] Malnutrition is a clinical condition that occurs with the destruction of endogenous energy sources when food consumption cannot compensate the metabolic rate. Inadequate food intake or absorption, increased loss, decreased anabolism and protein synthesis, increased calorie requirement and medications are effective factors in the development of malnutrition.[2]

IBD patients are at risk of malnutrition due to the nature of the disease, the drugs used, and some dietary restrictions. Proinflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha), which play a role in the pathogenesis of the disease, and medications such as metronidazole,

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5-aminosalicylic acid (5 ASA) and sulfasalazine used in the treatment can cause nausea, vomiting and dyspepsia in these patients, and may reduce oral intake. Nutrient absorption may be impaired in patients with surgical bowel resections, bacterial overgrowth, and extensive mucosal involvement.[3] Protein-energy malnutrition in IBD patients has been reported in a wide range of 20-85% in studies.[4,5] The nutritional status of the patients is one of the most important factors affecting the recovery of all diseases in general, including IBD. The quality of life of patients with malnutrition deteriorates, complications related to the disease may increase, and the duration and cost of treatments may increase.[2,6] For these reasons, nutritional evaluation, daily calorie intake and energy expenditure should be evaluated in terms of malnutrition risk in the follow-up of IBD patients. Screening methods such as Subjective Global Assessment (SGA), Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA) and Nutritional Risk Screening 2002 (NRS 2002) can be used in nutritional screening. MUST is a malnutrition screening questionnaire that can be easily calculated and has consistent results compared to other methods. It includes 3 independent components to determine the overall risk for malnutrition; current weight status measured by body mass index (BMI), unintentional weight loss, and acute disease effect resulting in no nutritional intake for 5 days (Table 1).[7, 8]

In this study, we screened the prevalence of malnutrition in IBD patients with MUST method and tried to evaluate the parameters that may be associated with malnutrition. To our knowledge, this is the first study in our country to screen for malnutrition risk in IBD patients using the MUST method.

METHODS

The study included 216 consecutive IBD patients who applied to Antalya Training and Research Hospital Gastroenterology Outpatient and Inpatient Clinics between 01 April 2016 and 01 April 2017. Patients with more than one admission were included in the study only at their first admission. Patients under the age of 18 years old were not included in the study. All resection operations of the patients regarding the small intestine and colon were recorded as surgical history.

The malnutrition risk of the patients was screened by the MUST by a doctor and a trained dietitian. Patients with inconsistent scores were re-evaluated by a third doctor and 2 equal results were considered final score. Patients with a score of 0-1 were classified as normal and those with a score of ≥2 were classified at risk of malnutrition8.

The study protocol was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and was approved by the Antalya Training and Research Hospital Research Ethics Committee (Reference no;76/4).

Statistical analysis

Statistical analysis was made using Statistical Package for the Social Sciences (SPSS) for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Fisher's exact test and Pearson's chi-square analysis were performed for categorical variables. In the normality test, the Shapiro-Wilks test was used when the sample size in the group was less than 50, and the Kolmogorov-Smirnov test was used when it was large. The differences between the two groups were evaluated with Student's t-test for normally distributed data or the Mann–Whitney U test for non-

Table 1. Parameters of malnutrition universal screening tool (MUST)

Parameters Score		
1- BMI (kg/m2)		
	> 20	0
	18.5-20	1
	< 18.5	2
2- Unplanned weight loss in the past 3-6 months (%)		
	< 5	0
	5-10	1
	> 10	2
3- If patient is acutely ill, and there has been or is likely to be no nutritional intake for >5 days		

normally distributed data. Data are expressed as n (%), the mean ± standard deviation (SD), or median (min–max), as appropriate. $p < 0.05$ were considered statistically significant.

RESULTS

The mean age of the 216 patients included in the study was 43.1 ± 13.6 years, and 101 (46.8%) of the patients were female and 115 (53.2%) were male. Of the patients, 64 (29.6%) were diagnosed with CD, and 152 (70.4%) with UC. Mean disease duration of all patients was 5.9 ± 5.8 years. Apart from IBD, 22 (10.2%) patients had diabetes mellitus (DM), 31 (14.4%) hypertension (HT), 32 (14.9%) rheumatic diseases, and 21 (9.7%) cardiovascular diseases. Of the patients, 177 (81.9%) were outpatients and 39 (18.1%) were inpatients. Fifty-two (24.1%) of the patients were at high risk of malnutrition (MUST score; ≥ 2) (Table 2).

Patients with a MUST score ≥ 2 did not differ by gender, disease type and duration, surgical history, education, smoking status and residential area compared with patients with a MUST score of < 2. Median age of patients with a MUST score ≥ 2 was significantly lower than the group with a MUST score < 2 [33.5(18-79) years vs. 45(19-81) years, p < 0.001]. Of the patients with a MUST score < 2, 153 (93.3%) were admitted as outpatients and 11 (6.7%) were inpatients. Of those with a MUST score of ≥ 2, 24 (46.2%) were admitted as outpatients and 28 (53.8%) were receiving inpatient treatment ($p < 0.001$). The group with a MUST score ≥ 2 had significantly lower BMI [26(18.4-39.1)kg/m2 vs. 19.1(15.1-34) kg/m^2, $p < 0.001$]. When the monthly incomes of the patients were compared, it was seen that the number of patients with an income below 1000 Turkish lira (TL) was higher in the high risk group, and those with 3000 TL and above in the low-intermediate risk group, and this was statistically significant ($p = 0.010$) (Table 3).

When the patients with UC and CD with a high risk of malnutrition were compared, no statistically significant difference was found between the 2 groups in terms of gender, age, duration of disease, MUST score, smoking status and residential area. In this comparison, only the patients with CD had more surgical operations than those with UC, and the difference was statistically significant [1(3) vs. 7(36.8), $p = 0.002$] (Table 4).

Table 2. Demographic characteristics of patients, comorbidities, characteristics of IBD and MUST score.

	n = 216
Sex, n (%)	
Female	101(46.8)
Male	115(53.2)
Age(years), mean ± sd	43.1 ± 13.6
Disease type, n(%)	
Ulcerative colitis	152(70.4)
Crohn's disease	64(29.6)
Disease duration (years), mean ± sd	5.9 ± 5.8
Comorbidities, n(%)	
Diabetes mellitus	22(10.2)
Hypertension	31(14.4)
Rheumatic diseases	32(14.9)
Cardiovascular diseases	21(9.7)
Patient status, n(%)	
Outpatients	177(81.9)
Inpatients	39(18.1)
MUST score, n(%)	
< 2	164(75.9)
≥ 2	52(24.1)

IBD: inflammatory bowel disease, MUST: malnutrition universal screening tool

Table 3. Comparison of patients with high malnutrition risk and low-intermediate risk according to MUST score.

	MUST		*p*
	< 2 n: 164	≥ 2 n: 52	
Sex, n (%)			
Female	75(45.7)	26(50)	0.591
Male	89(54.3)	26(50)	
Age, median (min-max)	45(19-81)	33.5(18-79)	**< 0.001**
Disease type, n(%)			
Ulcerative colitis	119(72.6)	33(63,5)	0.211
Crohn's disease	45(27.4)	19(36.5)	
Disease duration, median (min-max)	5(0-38)	4(0-20)	0.519
Patient status, n(%)			
Outpatients	153(93.3)	24(46.2)	**< 0.001**
Inpatients	11(6.7)	28(53.8)	
BMI (kg/m^2), median (min-max)	26(18.4-39.1)	19.1(15.1-34)	**< 0.001**
Sugical history, n (%)	12(7.3)	8(15.4)	0.099
Education, n (%)			
Illiterate	3(1.8)	1(1.9)	0.301
Literate	6(3.7)	1(1.9)	
Primary school	63(38.4)	17(32.7)	
Middle School	19(11.6)	4(7.7)	
High school	56(34.1)	17(32.7)	
University	17(10.4)	12(23.1)	
Monthly income (TL), n(%)			
< 1000 TL	22(13.4)[a]	15(28.8)[b]	**0.010**
1000-2000 TL	77(47)[a]	20(38.5)[a]	
2000-3000 TL	43(26.2)[a]	16(30.8)[a]	
> 3000 TL	22(13.4)[a]	1(1.9)[b]	
Smoking status, n(%)			
Non-smoking	129(78.7)	40(76.9)	0.792
Smoking	35(21.3)	12(23.1)	
Residental area, n(%)			
Urban	133(81.1)	40(76.9)	0.511
Rural	31(18.9)	12(23.1)	

MUST: malnutrition universal screening tool TL: Turkish lira

DISCUSSION

The MUST is a simple and easily applicable malnutrition screening test recommended by European Society for Clinical Nutrition and Metabolism (ESPEN).[9] It is generally a practical method and mostly recommended in the screening of outpatients due to its 3rd item (presence of no food intake for the next 5 days due to acute illness puts the patient directly in the high-risk group with 2 points).[8] MUST has also been validated in various medical fields including medical, surgical, and oncologic patients.[8, 10, 11] In addition, there are publications stating that it can be valid in IBD patients as well.[12, 13] In our study, a high risk of malnutrition was detected in 24.1% of all IBD patients using the MUST method. MUST was used in 173 IBD patients for malnutrition screening in 2017 and a high risk of malnutrition was found in 21.4% of patients at a rate similar to ours.[14] However, in the literature, the prevalence of malnutrition in IBD patients has been reported in a wide range of 20-85% in studies conducted with different methods.[3] The reporting of such different rates is attributed to the heterogeneous nature of the disease and the influence

Table 4. Comparison of Ulcerative colitis and Crohn's disease patients with high malnutrition risk.

	Ulcerative colitis n = 33	Crohn's disease n = 19	*p*
Sex, n (%)			
Female	18(54.5)	8(42.1)	0.388
Male	15(45.5)	11(57.9)	
Age, median(min-max)	33(18-79)	35(20-69)	0.414
Disease duration, median(min-max)	4(0-16)	4(0-20)	0.511
MUST score, median(min-max)	4(2-6)	4(2-6)	0.298
Surgical history, n (%)	1(3)	7(36.8)	**0.002**
Smoking status, n (%)			
Non-smoking	24(72.7)	16(84.2)	0.499
Smoking	9(27.3)	3(15.8)	
Residental area, n (%)			
Urban	27(81.8)	13(68.4)	0.317
Rural	6(18.2)	6(31.6)	

MUST: malnutrition universal screening tool

of environmental factors.

In our study, 46.2% of the patients with malnutrition were outpatients and 53.8% were inpatients. In addition, a high risk of malnutrition was detected in 71.7% of the hospitalized patients with MUST. In a study by Azusa Takaoka *et al.*[15], consisting of 40 patients with active and hospitalized IBD, the risk of malnutrition was found to be 68.9% in patients with CD and 61.1% in patients with UC using the MUST method. Malnutrition in active IBD patients hospitalized in the clinics is an expected finding due to 3rd item of MUST as mentioned above, compatible with our study. There are studies reporting that nutritional status can be adversely affected in IBD at any time of the disease, even at the time of diagnosis.[16] Although a positive relationship was expected between disease duration and malnutrition, there was no difference in disease duration between the risky and non-risk groups in our study. In two studies conducted in 2008 and 2017, a relationship between disease duration and malnutrition was not found, which is consistent with ours.[14, 16] So, IBD patients, both inpatients and outpatients, should be evaluated in terms of malnutrition risk at each visit, starting from the time of diagnosis.

Apart from the main disease, there are many factors that can affect the development of malnutrition; such as low socioeconomic status, co-morbidities, old age, inability to access health services and food due to living in rural areas.[17] In our study, there was no difference in the risk of malnutrition in terms of education, smoking status and residential area, which are the parameters we evaluated. However, the economic status was lower in the high-risk group. Although surgical bowel resections may also cause malnutrition, no difference was found between the high-risk and low-risk groups in terms of surgical histories in our study. However, when we compared patients with high risk of malnutrition with CD and UC, surgery history was more common in patients with CD.

In addition to screening tests, some biochemical tests and anthropometric measurements can be used to determine the nutritional status. The lack of anthropometric measurements and laboratory parameters, and the inability to examine the relationship between malnutrition and disease activity can be considered as limitations of our study.

CONCLUSION

In our study, we found a high risk of malnutrition in about a quarter of IBD patients with the MUST method. The risk of malnutrition was high in both CD and UC patients, especially inpatients. Care should be taken in terms of the risk of malnutrition in IBD patients with low economic status and in CD patients with a surgical history. Considering the effect of malnutrition on the prognosis of the disease, IBD patients should be evaluated in terms of malnutrition risk both during their routine outpatient clinic follow-

ups and hospitalizations and necessary precautions should be taken.

Authors' Contribution

Study Conception: SU,; Study Design: SÇ,; Supervision: AHÇ,; Materials: SÇ,; Data Collection and/or Processing: SÇ,; Statistical Analysis and/or Data Interpretation: SU, AHÇ,; Literature Review: SU,; Manuscript Preparation: SÇ and Critical Review: AHÇ.

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Case Report

Internal Medicine

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Medical Journal

A Two Alkaptonuria Case Diagnosed at Elderly Patient

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ABSTRACT

Alkaptonuria is a rare autosomal recessive metabolic disease due to a deficiency of e the homogentisic acid oxidase enzyme. We report two cases with advanced age. Our aim is to draw attention to the fact that alkaptonuria should suggestions for clarity in every patient who shows clinical features regardless of age. We diagnosed two patients, 61 and 69 years old, with alkaptonuria. Alkaptonuria is a rare disease that presents with multisystemic manifestation. While early detection of the clinical signs of the disease provides early diagnosis, appropriate treatment can significantly increase the quality of life.

Keywords: alkatonuria, elderly, patient

Alkaptonuria is a congenital metabolic disease inherited autosomal recessively.[1] Clinical manifestations due to the accumulation of homogentisic acid (HGA) and its metabolites in collagen rich connective tissue accumulation due to the lack of homogentisic acid oxidase enzyme in the disease tyrosine metabolism.

Characteristic clinical presentation is the observation that urine darkens on standing. This symptom is the seen only in the pediatric age group.[2] In the diagnosis of alkaptonuria; classical triad is important, which is characterized by degenerative arthritis, ochronotic pigmentation and darkening of the urine color. Diagnosis can be made by the measurement of homogentisic acid metabolits in the urine.[3] The incidence of alkaptonuria is 1/250.000-1.000.000. Alkaptonuria is a disease characterized by progressive and systemic involvement. Although there is no significant shortening in the life expectancy, octronotic arthropathy and cardiovascular involvement in the 4th and 6th decades is the most important cause of morbidity.

CASE 1

A 61-year-old male patient was admitted to the internal medicine clinic to receive home care services. He was further investigated for the suspicion of octronos is because of his phenotypic features. The patient's history revealed that there was a darkening of the color in the urine since the younger ages. He has joint pain. He has impaired vision for 20 years. There is no history of medicine or drug use. Physical examination revealed hyperpigmented areas in the body and brown hyperpigmentation in the sclera. Hemogram and complete biochemistry of the patient was normal. There is no abnormality in the fresh urine. Urine developed brown-coke colour after addition of NaOH. HGA was studied in urine. 1885 mmol / mol (normal: 0). Echocardiography of the patient showed stenosis and calcification of the aortic and mitral valves.

CASE 2

A 69-year-old male patient with no disease was admitted to the ophthalmology clinic for the eye spot he has since 20 years. Eye biopsy was planned for biopsy and internal medicine outpatient clinic was consulted. The patient was taken to Internal Medicine Department for further examination. In history; For 20 years he had on his eyes and skin spot

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and stains and knee-back pains. The urine color was dark since his childhood. In physical examination; There were hyperpigmented areas on his face, hands and feet. The sclera had black-brown pigmentation. His biochemistry and complete blood count were normal. Fresh urine was normal. Regarding these findings, ochronosis was considered first in the diagnosis. The patient had no drug use and no heavy metal exposure in terms of exogenous ochronosis. He had dark urine since childhood. HGA was studied in urine. 1577 mmol / mol (normal: 0). When fresh water was dripped with NaOH, the color became black. Thoracolumber and knee radiographs were taken. The graphs revealed degenerative changes in the spinal vertebrae, narrowing of the knee joint space and calcifications. His echocardiography showed left ventricular hypertrophy, biatrial dilatation, mid mitral and tricuspid regurgitation. The conjunctival biopsy was performed. Biopsy revealed homogenous material accumulation except subepithelial yellow-orange colored cells.

DISCUSSION

Alkaptonuria is a rare autosomal recessive disorder characterized by a disorder of tyrosine metabolism.[4] It is generally noticed by the families in the neonatal period that the child's diaper is gray-black. Since the patients remain asymptomatic for a long time in the alkaptonuria, diagnosis can be made in advanced ages.[5]

The accumulation of HGA in alkaptonuria, especially in connective tissue, may cause joint, skin, eye, cardiovascular system, genitourinary system, respiratory system, and rarely central nervous system,

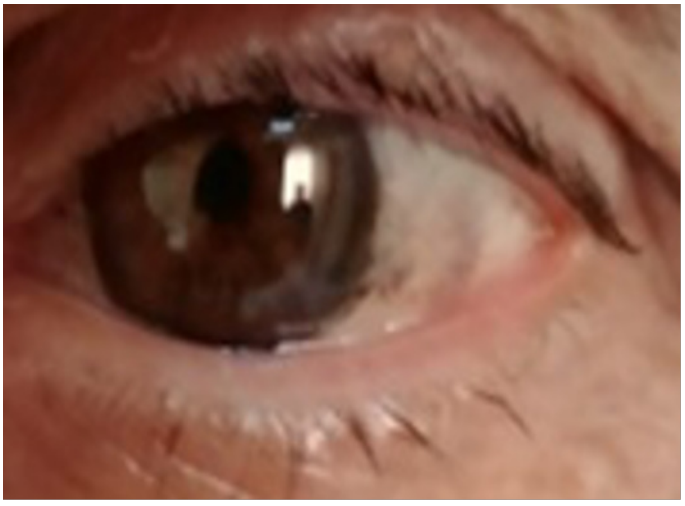

Figure 1. Hyperpigmented areas in conjunctival of the case 1

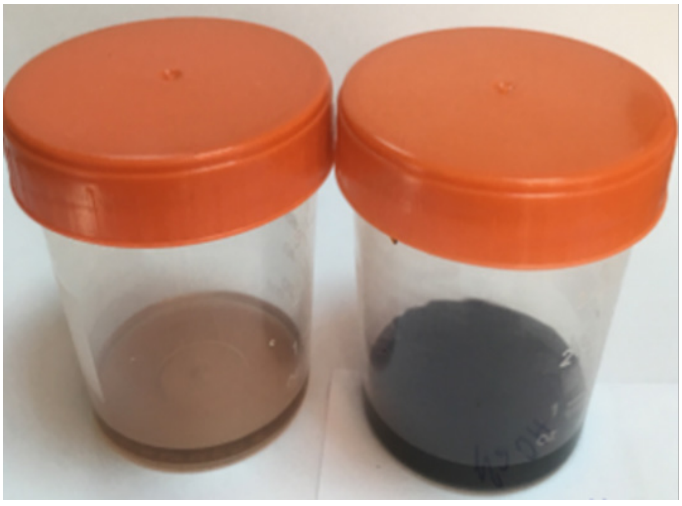

Figure 3. Case 1, Fresh urine of the case and its urine after instillation of NAOH

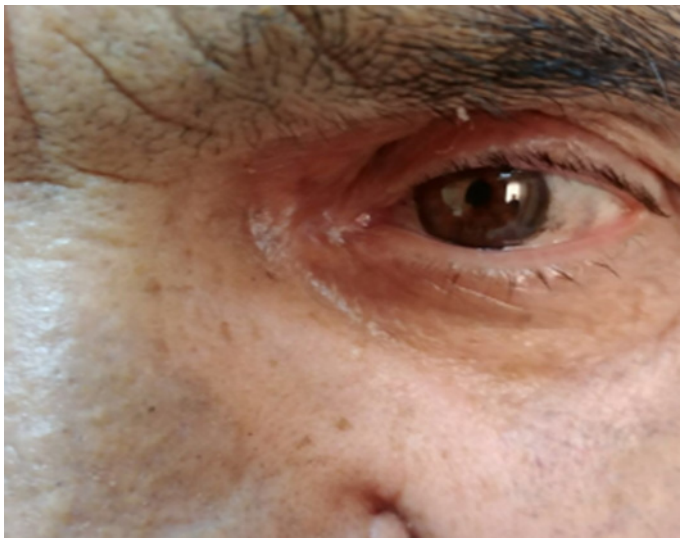

Figure 2. Hyperpigmented areas in conjunctival of the case 1

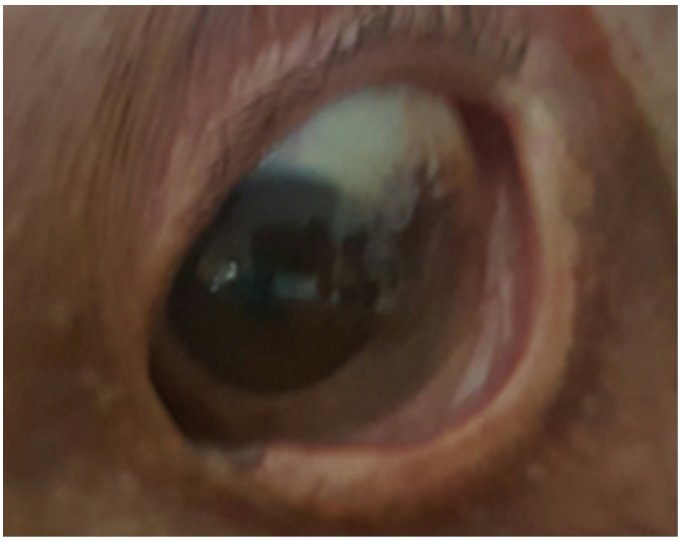

Figure 4. Hyperpigmented areas in conjunctival of the case 1

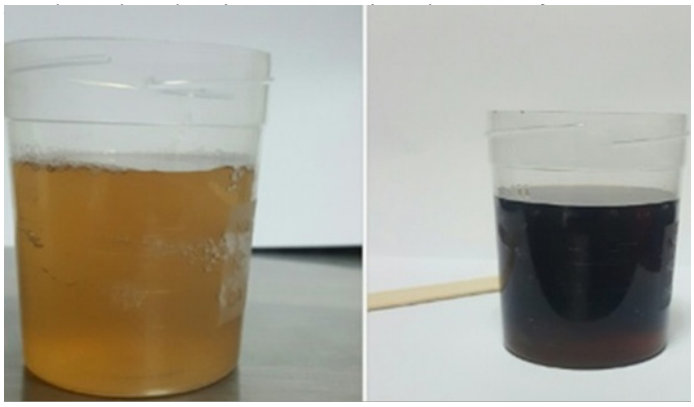

Figure 5. Case 1, Fresh urine of the case and its urine after instillation of NAOH

in cross-linking. The ochronotic pigments accumulate in the cartilage. This results in ochronotic arthropathy. Symptoms of ocronotic arthropathy in men in the fourth and fifth decades; women in the sixth decade. Large joints and intervertebral discs are affected at an earlier stage. Degenerative osteophytic changes at all levels seen on thoracolumbar graphies and extensive calcification in intervertebral discs are typical for alkaptonuria and have been found in both cases.[7] Histopathologically, in skin biopsies, the ochronotic pigment stained with hematoxylin and eosin yellowish brown can be observed in free tissue in the tissue, in the vascular wall endothelium, in the basement membrane, in ecrine sweat gland secretory cells and in the macrophage as fine granule. It is typical that the pigment deposited in collagen bands causes homogenization and swelling and fragmentation in collagen.[8] Conjunctival biopsy in our second case also showed a yellowish-orange extracellular homogenous accumulation in the subepithelial area. There is no definitive treatment for alkaptonuria, but it is intended to reduce the rate of pigment deposition by medical treatment. High-dose vitamin C is recommended in older children and adults.[9] We did not give vitamin C treatment because our patients were older and could not benefit.

CONCLUSION

The causes of serious morbidity in these patients are ochronotic arthropathy and cardiovascular involvement, especially in the 4th to 6th decade. Therefore, it is very important to know the diagnosis and to inform the patient. In addition, family screening of patients diagnosed with alkaptonuria should be recommended. Thus, early diagnosis and treatment can prevent or delay the development of complications. In cases diagnosed at a late age, follow-up should be in the form of follow-up complications.

Authors' Contribution

Study Conception: HBP,; Study Design: HBP,; Supervision: TA,; Funding: TA,; Materials: HBP,; Data Collection and/or Processing: HBP,; Statistical Analysis and/or Data Interpretation: HBP; Literature Review: TA,; Manuscript Preparation: HBP and Critical Review: TA.

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Case Report

Internal Medicine

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G6PD deficiency resulting in massive hemolysis and acute renal failure

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ABSTRACT

Objectives: Glucose 6 phosphate dehydrogenase (G6PD) is an intracellular enzyme that protects cells from oxidative stress by catalyzing the first step of the pentose phosphate pathway. Since erythrocytes do not have mitochondria, the pentose phosphate pathway is the only resource for NADPH production. Decreased NADPH production in G6PD deficient erythrocytes, results in susceptibility to oxidative damage and hemolysis eventually. G6PD deficiency is an X-linked hereditary disorder and the most common enzyme deficiency in the world.1 Since the patients who have G6PD deficiency may be asymptomatic the actual incidence cannot be estimated. Usually, hemolytic episodes resolve themselves, however, in some cases, it may end up with severe complications such as acute renal failure.

A 43-year-old male patient was admitted to our emergency department with jaundice. His complete blood count and biochemical test results were consistent with acute hemolysis; further diagnostic tests evaluating hemolytic anemia, low G6PD levels indicated that G6PD deficiency is the most probable etiology. When a more detailed anamnesis was obtained, it is learned that the patient had eaten fava beans for the first time in his life. Since the patient was anuric and his renal function tests were worsening, we planned hemodialysis, several transfusions, and therapeutic plasma exchange (TPE). Our case is a rare one in which severe hemolysis and acute renal failure developed following fava ingestion due to G6PD deficiency and TPE and hemolysis were successful.

Keywords: G6PD, plasmapheresis, therapeutic plasma exchange (TPE) severe hemolysis, acute renal failure

Glucose 6 phosphate dehydrogenase (G6PD) is an intracellular enzyme that protects cells from oxidative stress by catalyzing the first step of the pentose phosphate pathway. Since erythrocytes do not have mitochondria, the pentose phosphate pathway is the only resource for NADPH production. Decreased NADPH production in G6PD deficient erythrocytes, results in susceptibility to oxidative damage and hemolysis.[1] Various medications, infections, and food may trigger hemolytic episodes by generating an oxidative environment.[2] Peripheral blood smear obtained at an acute hemolytic episode reveal microspherocytes, eccentrocytes, or "bite" cells, and "blister cells" with hemoglobin puddled to one side. Special stains can document the production of Heinz bodies, which are collections of denatured globin chains often attached to the RBC membrane.[3] Quantitative tests should be performed in suspected cases. G6PD deficiency is an X-linked hereditary disorder and the most common enzyme deficiency in the world.[1] The National Organization for Rare Disorders estimates that 400 million people worldwide are living with G6PD deficiency. The prevalence of the disorder is highest in Africa, Asia, the Middle East, Latin America, and the Mediterranean.[4] Due to its X-linked inheritance, it is more common in males

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however heterozygous females can also be affected.

Since the patients who have G6PD deficiency may be asymptomatic the actual incidence can not be estimated. Usually, hemolytic episodes resolve themselves, however, in some cases it may end up with severe complications such as acute renal failure.[5, 6] Here, we report our case of a G6PD deficient patient presenting with severe hemolysis and acute renal failure, treated successfully with therapeutic plasma exchange (TPE) and hemodialysis.

CASE REPORT

A 43-year-old male patient was admitted to our emergency department with yellow discoloration of his eyes and skin that became evident three days ago. He also mentioned dark urine discoloration. Nausea, vomiting, loss of appetite, and fever were accompanying his complaints. His medical history was unremarkable. His vital signs were a temperature of 36.5°C, heart rate 105 bpm, blood pressure 117/63 mmHg, respiratory rate 25 breaths per minute, and oxygen saturation 79%. He was tachypneic, also his skin was icteric and he had tenderness on the right upper quadrant on abdominal examination. His laboratory values on admission are included in Table 1. There was no pathology observed in abdominal ultrasonography. Both kidneys were normal in size and echotexture. The patient was admitted to our intensive care unit for further evaluation and treatment since he was tachypneic and hypoxic. As the patient was evaluated for severe hemolysis, his reticulocyte index was 5% (N:1- 3.5%), peripheral blood smear revealed, normocytic normochromic red blood cells (RBCs) with anisopoikilocytosis, several blister cells, and bite cells, no schistocytes were observed. Indirect and direct Coombs tests were negative and CD55, CD58 and CD59 levels were all in normal ranges. Also, several tests were performed to exclude Weil's disease and ceftriaxone treatment was initiated. A more detailed history showed that he had eaten fava beans for the first time in his life before the onset of his symptoms. As result hemolysis secondary to G6PD deficiency was considered. Keeping in mind that test results may come out normal in acute episodes because during the acute hemolytic episodes RBCs with the lowest G6PD activity undergo hemolysis and circulating RBCs may have relatively higher enzyme activity, G6PD enzyme activity test was performed before RBC transfusion. Enzyme level was 3.023 U/g Hb (N: 6.97-20.5 U/g Hb). Despite aggressive fluid resuscitation, the patient was anuric and his renal function tests were deteriorating progressively. As renal biopsy is done, it was consistent with acute tubulointerstitial nephritis, hemodialysis was planned by that time. Also, therapeutic plasma exchange (TPE) was done for three days considering severe hemolysis with Haemonetics MCS+ cell separator. Fresh frozen plasma is used as a replacement fluid. One plasma volume is replaced in each procedure. Blood volumes processed were 5799 mL, 6123 mL, 5881 mL, and

Table 1. Patients laboratory results on admission, before and after TPE

	Reference Range	On Admission	Before first TPE*	After first TPE*
Hemoglobin	13.6-17.2 g/dl	8.1	7.6	8.3
Platelet count	156 - 373 10^3/mm^3	297	225	174
Leukocyte count	4.5 - 10.3 10^3/mm^3	24.6	23.5	19.7
Total bilirubin	0.3-1.2 mg/dl	7.49	8.3	3.5
Indirect bilirubin	0.1-1 mg/dl	6.4	4.07	1.82
LDH*	0-248 U/L	1403	2979	912
AST*	0-50 U/L	77	210	86
ALT*	0-50 U/L	47	154	119
CK*	< 172 U/L	989	1578	211
Creatinine	0.66-1.09 mg/dl	1.6	6.11	4.28
Coombs Tests (direct/indirect)		negative		
INR*	0.8-1.2	1.14	1.2	1.1

*TPE: Therapeutic plasma exchange, LDH: Lactate dehydrogenase, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, CK: Creatinine kinase, INR: International Normalized Ratio

plasma volumes processed were 3636 mL, 4014 mL, 3954 ml for each day respectively. Each session lasted approximately two hours. The color of filtered plasma following TPE was black. (Figure 1) Following these interventions, patients' clinical condition and laboratory findings improved. (Table 1) The patient underwent hemodialysis ten times and TPE for three days during his stay for twenty-three days. Eventually, as the renal functions improved, diuresis began. The patient was discharged with a scheduled follow-up plan from the outpatient clinic.

RESULTS

G6PD deficiency is one of the most common hereditary disorders. G6PD is responsible for producing reduced glutathione by catalyzing the first step of the pentose phosphate pathway which is the only antioxidant defense mechanism in RBCs.[7] RBCs lacking G6PD, consumes available reduced glutathione rapidly and becomes more vulnerable to oxidative damage as they expose to oxidative substances. Consequently, ongoing oxidative stress ends up with hemolysis.[8] RBCs that are most severely damaged undergo hemolysis intravascularly, nevertheless, hemolysis is mostly extravascular.[9]

G6PD deficient subjects generally don't have any symptoms unless they expose to certain medications, infections, and/or food. Rarely severe hemolysis may occur. As seen in our patient, detailed anamnesis revealing ingestion of fava beans was the cause of hemolysis; emphasizing the importance of careful medical history taking in daily practice.

"Vicine, convincing, ascorbate, and L-dopa" are substances that are present in high amounts in fava beans are thought to be toxic. These substances oxidate reduced glutathione by generating free oxygen radicals and cause hemolysis in G6PD deficient people.[10]

Favism is defined as acute hemolysis that occurs 24-48 hours after ingestion of fava beans. All subjects with favism show G6PD deficiency to the contrary, all subjects with G6PD deficiency may not experience acute hemolytic episodes following ingestion of fava beans. Despite its low incidence, few cases of severe hemolysis accompanied by renal failure are present in the current literature.[11]

Acute renal failure secondary to acute tubular necrosis and tubulointerstitial nephritis due to hemoglobinuria is a complication of severe hemolysis that is observed following severe hemolytic episodes in patients with G6PD deficiency.[12, 13]

The underlying mechanism that results in kidney injury secondary to hemoglobinuria is not fully understood. Studies are pointing that various factors may take part in renal injuries, like exposure to ferrihemate which is nephrotoxic (which is converted from hemoglobin in pH < 6.5), obstruction of renal tubules by hemolyzed red cells which is nephrotoxic. intravascular coagulation

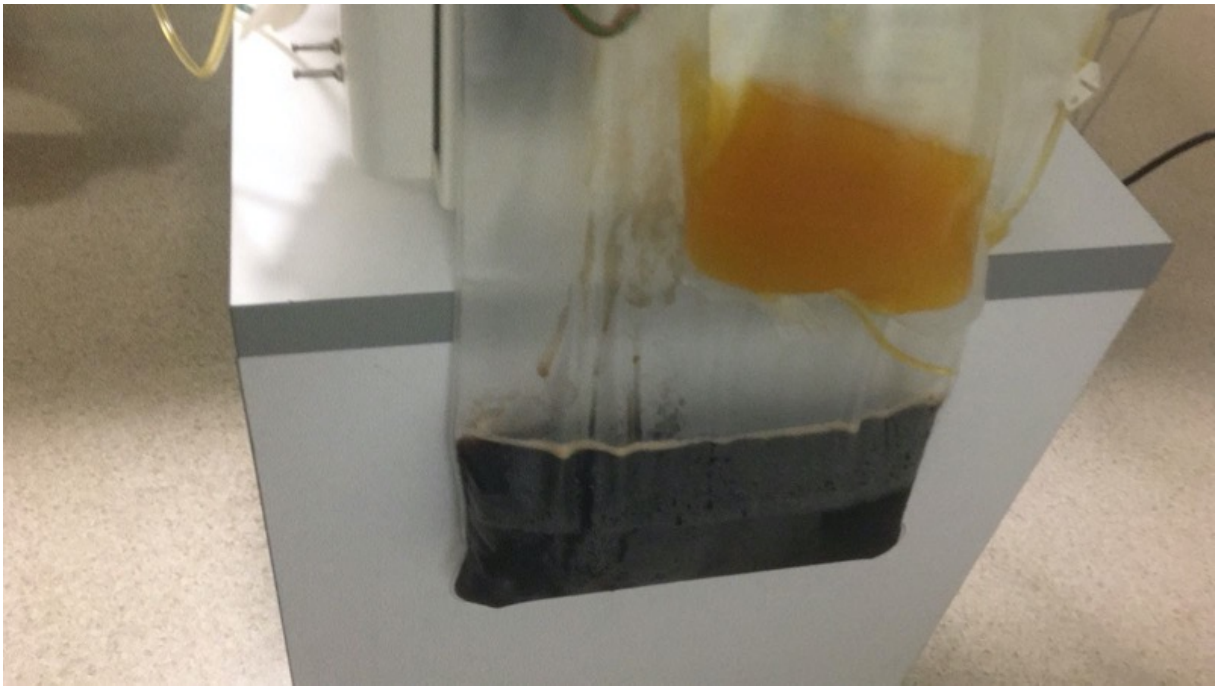

Figure 1. Image of filtered plasma following plasmapheresis

causing a release of thromboplastin factors, altered renal blood flow, and decreased glomerular filtration rate, or by a combination of the above.[1, 14, 15] Renal biopsies obtained reveal acute tubular necrosis and tubulointerstitial nephritis histopathologically. Rare cases of acute cortical necrosis due to hemolysis have also been reported.[16] Acute kidney failure secondary to hemoglobinuria cannot be predicted. Patients with accompanying volume defect, sepsis, acidosis, and/or taking nephrotoxic medications are at higher risk for developing renal failure.[11] Since our patient was not taking any nephrotoxic medication, we thought hemoglobinuria resulting in acute tubular necrosis and tubulointerstitial nephritis was the reason for his condition. Another possible cause of acute renal failure may be tissue hypoxia due to severe anemia in the patient with metabolic acidosis as well. Nevertheless lacking additional findings of other organ dysfunction made this explanation less possible.

The most effective management strategy in hemolysis is to prevent it by avoiding triggers.

Cases that result in severe anemia may require transfusions. Splenectomy is indicated in patients who need transfusions repeatedly.[17] In massive intravascular hemolysis, Hemoglobin clearance mechanisms become saturated and excess plasma free-hemoglobin easily moves into the renal parenchyma causing damage to the kidneys. Acute renal failure secondary to hemolysis can be prevented and treated as well with efficacious hydration and forced alkaline diuresis (keeping pH of urine > 6.5).[18] Furosemide or mannitol may be beneficial in patients with oliguria, renal replacement therapies may be needed in more severe cases.[9]

TPE is the procedure that macromolecules are eliminated from plasma for therapeutic purposes. The clinical benefits are based on removal of pathologic substances or on the replacement of abnormal components of plasma if necessary.

Even though TPE is not mentioned in management strategies of severe hemolysis in patients with G6PD deficiency; TPE can accelerate resolution in cases of acute tubular necrosis and tubulointerstitial nephritis by preventing continuous hemolysis and hemoglobinuria as in our case.[20]

CONCLUSION

Favism is a more common condition than estimated and rarely may result in severe hemolysis associated with renal failure. Currently, there is no approved treatment algorithm in the literature for such cases. Plasmapheresis may be an important treatment option in these patients by breaking the vicious cycle of hemolysis and reversing renal failure.

Authors' Contribution

Study Conception: MED, YŞ,; Study Design: MED, YŞ,; Supervision: MED, YŞ,; Materials: İŞY; Data Collection and/or Processing: İŞY,; Statistical Analysis and/or Data Interpretation: MED, YŞ,; Literature Review: MED,; Manuscript Preparation: MED and Critical Review: YŞ.

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Conflict Of Interest

None.

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Case Report

Internal Medicine & Endocrinology

DAHUDER Medical Journal

Successful treatment of thyroid storm with therapeutic plasmapheresis in a geriatric patient

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ABSTRACT

Thyroid storm is a rare and fatal condition characterized by severe clinical manifestations of thyrotoxicosis. In geriatric patients, care should be taken in the follow-up of thyrotoxicosis due to comorbid diseases. Therapeutic plasmapheresis is an apheresis method that separates plasma from the components and removes the harmfull substances from the blood. This method may clear thyroid hormones from the blood and is recommended as an alternative option in the treatment of thyroid storm. In this case, we aimed to present an old patient with known alzheimer's disease and multinodular goiter induced thyrotoxicosis. The patient who could not get the first line treatments completely due to complications and were finally diagnosed with thyroid storm, recovered with therapeutic plasmapheresis treatment without any problem and was discharged.

Keywords: Lithium, Thyroid storm, Plasmapheresis

A thyroid storm is a rare and life-threatening condition characterized by severe clinical manifestations of thyrotoxicosis. It can be seen in 2-16% of patients with thyrotoxicosis and mortality may be up to 30%.[1] Thyroid storm is diagnosed clinically, as there are no specific diagnostic laboratory findings. Although not widely used in clinical practice, the scoring system developed by Burch and Wartofsky in 1993 can be used for an objective diagnosis. In this system, scoring is made based on body temperature, neurological findings, gastrointestinal-hepatic findings, tachycardia-atrial fibrillation, heart failure, and the presence of a precipitating factor, and the possibility of thyroid crisis diagnosis is tried to be determined (Table 1).[2] After the hemodynamic stabilization, improvement of the underlying causes that may trigger the storm, and antithyroid drugs are the management methods of the thyroid storm.

Therapeutic plasmapheresis (TP) is an effective treatment option that removes cytokines, antibodies, and thyroid hormones from plasma when the first-line treatments are not successful or cannot be used.[3] TP was first used in the treatment of hyperthyroidism by Ashkar *et al*.[4] in 1970 and continues to be an effective and safe alternative treatment option with technological advances. In this case report, we wanted to present a geriatric patient with Alzheimer's disease who was diagnosed with thyroid storm during the course of hyperthyroidism treatment and her clinic recovered successfully with TP treatment.

CASE REPORT

An 88-year-old female patient with known Alzheimer's disease who could not use any medication was diagnosed with multinodular goiter-related hyperthyroidism 1 month ago. Her thyroid ultrasonography (USG) showed bilateral multiple nodules with the largest of which was 16 mm.

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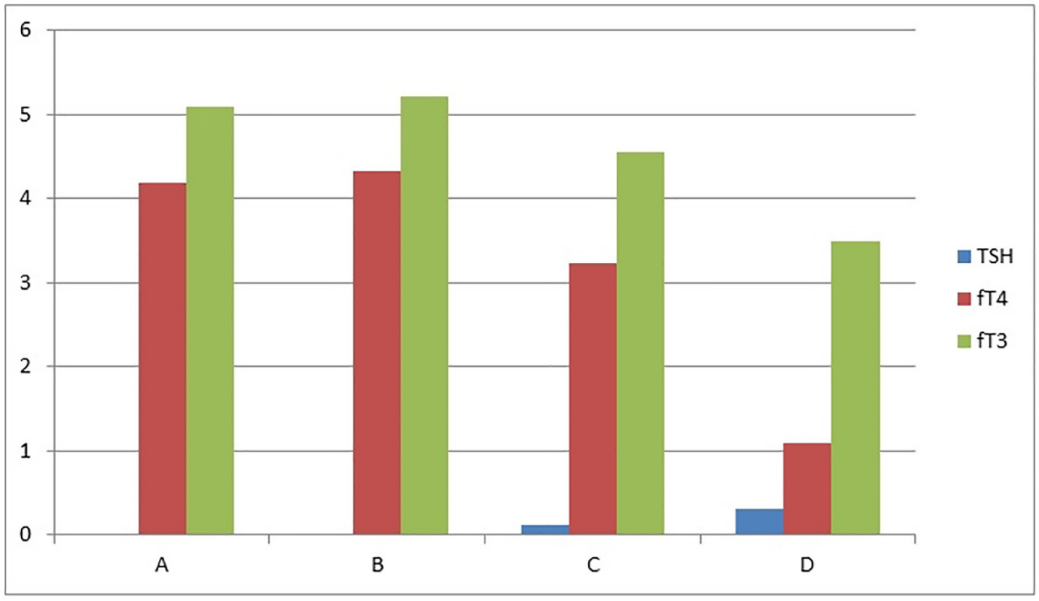

A: First thyroid function tests levels B: Before plasmaphresis
C: After the 2nd session of plasmapheresis D: After the 4th session of plasmapheresis
TSH: thyroid stimulating hormone (normal range; 0.34-5.8 µIU/mL)
fT4: free T4 (normal range; 0.61-1.12 ng/dl)
fT3: free T3 (normal range; 2.5-3.9 ng/L)

Figure 1. Change of patient's thyroid hormones levels during the clinical course

Thyroid-stimulating hormone (TSH) has been found < 0.01 µIU/mL (normal range = 0.34-5.86), free T4 has been found 4.18 ng/dL (normal range = 0.61-1.12) and free T3 has been found 5.1 ng/L (normal range = 2.5-3.9) at the laboratory tests (Figure 1, column A). The patient was prescribed methimazole at first, but it was changed to propylthiouracil (PTU) due to agranulocytosis. Because agranulocytosis did not improve, the patient was referred to our hospital's endocrinology department. The patient's antithyroid medications were stopped and radioactive iodine (RAI) treatment was planned. Lithium 2x300 mg was prescribed until the RAI treatment. On the 8th day of lithium treatment, the patient was admitted to the emergency service with complaints of unconsciousness, fever, and palpitation. Her peripheral pulses were filiformic and 120/minute, her fever was 38.9 °C and her blood pressure was 105/75 mmHg. In electrocardiography (ECG), the pulse was 110/minute and the rhythm was atrial fibrillation (AF). In laboratory tests, hemogram, electrolytes, and liver function tests were normal. But, serum BUN [89 mg/dL (normal range= 8-20)], creatinine [1.7 mg/dL (normal range = 0.66-1.09)], and C-reactive protein (CRP) [38 mg/L (normal range = 0-5)] were measured abnormal. No pathology was detected in computed tomography (CT) and magnetic resonance (MR) of the brain. The patient was consulted by neurology as the electroencephalography (EEG) in the emergency room was compatible with mildly diffuse cerebral dysfunction and valproic acid treatment was started with the preliminary diagnosis of epilepsy. Since the serum lithium level was 1.9 mmol/L (normal range = 1-1.2), she was admitted to the intensive care unit (ICU) with the diagnosis of lithium intoxication, and hemodialysis (HD) was performed. On the 2nd day of ICU hospitalization, the patient was transferred to the internal medicine clinic.

When she was admitted to the internal medicine clinic, the patient was conscious but had meaningless speech, and her orientation and cooperation were still incomplete. Her blood pressure was 115/74 mmHg, pulse was 105/minute, AF rhythm, and fever was 37.9 °C.

The TSH measured in our clinic was < 0.01 µIU/mL, free T4 was 4.32 ng/dl and free T3 was 5.22 ng/L (Graphic 1, column B). Since there was no additional infectious and neurological pathology to explain the current clinical status and Burch&Wartofsky score was 45 points (fever; 10 points, agitation; 10 points, pulse; 5 points, AF; 10 points, precipitating condition; 10 points), the patient was diagnosed as thyroid storm and TP treatment was initiated. TSH (0.12 µIU/mL), free T4 (3.23 ng/dl), and free T3 (4.56 ng/L) were

Table 1. Burch and Wartsofsky scoring system for the identification of thyroid storm.

Thermoregulatory dysfunction [Temperature (°C)]	
37.2 to 37.7	5
37.8 to 38.2	10
38.3 to 38.8	15
38.9 to 39.4	20
39.4 to 39.9	25
> 40.0	30
Central nervous system effects	
Mild (Agitation)	10
Moderate (Delirium, Psychosis, Extreme lethargy)	20
Severe (Seizure, Coma)	30
Gastrointestinal-hepatic dysfunction	
Moderate (Diarrhea, Nausea/vomiting, Abdominal pain)	10
Severe (Unexplained jaundice)	20
Cardiovascular dysfunction (Tachycardia)	
99 to 109	5
110 to 119	10
120 to 129	15
130 to 139	20
≥ 140	25
Atrial fibrillation	10
Heart failure	
Mild (Pedal edema)	5
Moderate (Bibasilar rales)	10
Severe (Pulmonary edema)	15
Precipitant history	
Negative	0
Positive	10

A score of ≥ 45; highly suggestive of thyroid storm, 25-44; supports the diagnosis, < 25 makes thyroid storm unlikely.

improved after 2 sessions of TP (Graphic 1, column C). She was orientated and cooperated, and vital signs were normal after TP. Valproic acid was gradually decreased and discontinued. The patient received a single dose of RAI therapy for hyperthyroidism and was discharged for polyclinic follow-up.

DISCUSSION

A thyroid storm is an advanced and more severe form of thyrotoxicosis, and fever, nausea, vomiting, and unconsciousness can be observed. Acute events such as thyroid or non-thyroid surgery, trauma, infections, myocardial infarction, acute iodine load, or birth may trigger thyroid storm.[5] Since a fully formed thyroid storm is very rare, it should be considered in patients with severe hyperthyroidism findings, and treatment should be started immediately. Thionamides, beta-blockers, iodine solutions, glucocorticoids, and bile acid sequestrants are the first-line drugs used in the treatment of hyperthyroidism and thyroid storm.[6] Lithium is a drug used primarily in the treatment of mood disorders and may lead to hypothyroidism with effects such as blocking the intake of iodine into the thyroid gland, reducing the release of thyroid hormones into the periphery, and preventing the conversion of T4 to T3 in the blood.[7] Lithium can be used as an alternative treatment option in the treatment of hyperthyroidism when there is a lack of response or side effects to primary treatments. However, its use is

Table 2. Category definitions for therapeutic apheresis.

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

IRB = Institutional Review Board

limited due to its renal and neurological toxic effects and should be monitored very closely, especially in geriatric patients.

Apheresis is the general name of the procedure that has been used safely since 1944, where the blood is separated into one or more components by passing it through a medical device, and the remainder is returned to the patient with or without extracorporeal treatment.[4] TP, on the other hand, is an apheresis subtype in which plasma is separated from its components, and some unwanted substances are selectively purified with the help of different techniques and then returned to the patient by adding albumin or plasma.[4] Since the substances bound to the proteins cannot be purified from the blood by HD, they can be cleaned from the blood by TP. Antibodies, immunocomplexes, monoclonal proteins, cryoglobulins, complement components, lipoproteins, and protein-bound toxins are some of the substances that can be removed from the body by this method. TP has become one of the first-line treatments in the treatment of some neurological, hematological, autoimmune, and rheumatological diseases in recent years.[4] The American Apheresis Association periodically updates the indications and techniques for apheresis and published the last report (8th report) in 2019.[8] Diseases are divided into 4 categories (Table 2) according to the effectiveness of apheresis in this report and thyroid storm is classified as category II (disorders in which apheresis alone or combined with other options are considered a second-line treatment) with 2C level of evidence.[8]

In the thyroid storm, TP can be used if the patient's symptoms are severe and there is no adequate response within 24-48 hours with primary treatments or if side effects have developed.[8] In addition to reducing hormone concentrations, TP also reduces the severity of thyrotoxicosis by removing catecholamines and cytokines from the blood. However, the effectiveness of TP is temporary and hormone levels increase again the next day. Therefore, the TP procedure can be applied according to the patient's clinic, either daily or 2 or 3 days apart. The procedure is repeated until the patient's symptoms improve, and a clinical response can be obtained with an average of 3-6 sessions.[8] Colloidal solutions (plasma or albumin) or combinations of colloids and crystalloids can be used in the TP process as replacement fluids. Since plasma contains coagulation factors, it should be preferred in patients with coagulation disorder or before surgery.[9]

CONCLUSION

Authors' Contribution

Study Conception: MK, SU,; Study Design: IKS,; Supervision: EK,; Materials: EK,; Data Collection and/or Processing: FPE, MS,; Statistical Analysis and/or Data Interpretation: MK,; Literature Review: SU,; Manuscript Preparation: MK and Critical Review: IKS.

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