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Original Articles

Case Reports

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Case Reports

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Original Article

Determining Frailty Status in Patients Who Apply for Home Health Care Services Frailty and Home Health Care

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ABSTRACT

Background To examine the relationship between an institutionally prepared standardized patient evaluation form and the Edmonton Frail Scale (EFS) in patients receiving home health care.

Material and Methods Our prospective, observational study included 200 patients over the age of 18 who requested home health care, regardless of gender. The EFS and institutional data collection forms were applied consecutively on the same day to all patients included in the study.

Results Among the 200 individuals recruited for the study, 59% were female and 41% were male; the overall average age was 80 years. According to the EFS results, 4.5% of the patients were classified as non-frail, 6% were vulnerable, and 89.5% had varying degrees of frailty (mild, moderate and severe). There was a significant positive correlation between EFS score and age ($p<0.001$). There was no significant relationship between EFS score and confinement to bed; however, EFS scores were higher in bedridden patients ($p=0.017$). The EFS score was higher in those with chronic disease ($p<0.001$). A >9 threshold for EFS score could identify those in need of home health care services, with a sensitivity of 80.34% and a specificity of 90.91%.

Conclusion Age is an important risk factor for frailty, and the presence of chronic illness and confinement to bed may potentiate its effects. On the contrary, the level of personal care, pain conditions and pressure sores/ulcers were unassociated with frailty. It was determined that the EFS score could be supportive in distinguishing patients in need of home health care services.

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Introduction

Aging can be described as a gradual decrease in physiological reserves that inevitably leads to the emergence of physical limitations. In fragile individuals, the reduction is much more severe, increasing their susceptibility to serious health problems, even when they are exposed to the slightest physical stress. A 10-year cohort study involving elderly individuals identified the most common causes of death as frailty (27.9%), organ failure (21.4%), cancer (19.3%), dementia (13.8%) and other conditions (14.9%).[1] Frailty increases with age[2,3] and is more frequent in women.[4,5]

Pressure injury is the damage that occurs in the skin due to continuous or repeating pressure, usually localized in areas where the bone structure is close to the skin.[6] The frequency of pressure ulcers increases with increased life expectancy and poor performance in daily life. The development of a pressure ulcer after an injury is a common geriatric syndrome that reflects the common pathogenetic process of aging and frailty.[7]

A significant proportion of the vulnerable elderly population consists of people with various medical and geriatric needs who must be tended to at their homes. The most economical and targeted solution for such needs in society is the establishment of home health care services (also known as in-home care or domiciliary care) and ensuring their effectiveness. Today, the need for home health care services and the annual number of applications for these services is increasing. The approach to home health care and the types of assistance provided by caregivers vary from country to country and region to region; however, according to the Regulation on the Provision of Home Health Care Services put forth by the Turkish Ministry of Health and its affiliates, home health care services in Turkey include examination, medical workup, analysis, treatment, medical care, follow-up, rehabilitation and social and psychological counseling services at the residence of the individual.[8] Bedridden patients and dependent individuals fall naturally into the definition of home health care recipients. However, patients other than these are evaluated by the home health care commission, which decides whether they need home health care.

In this study, patients requesting home health care were evaluated using the "home health care patient evaluation form" created by our institution. Applicants were also evaluated using the Edmonton Frail Scale (EFS). Our purpose was to examine the relationships between EFS and the evaluation form to ascertain whether it would be possible to develop the patient evaluation form with input from EFS, thereby increasing the objectivity of the evaluation of home health care requests.

Material and Methods

After obtaining approval from the Clinical Research Ethical Committee of the Health Sciences University, Bursa Yuksek Ihtisas Training and Research Hospital (BYIH) (protocol number 2011-KAEK-25 2019/03-27, dated 13.03.2019), our study was conducted from March 1, 2019 to June 30, 2019 as a prospective observational study among patients who applied, for the first time, to the Home Health Care Unit of Bursa Yuksek Ihtisas Training and Research Hospital.

Two hundred patients aged 18 years and older were recruited into the study, regardless of sociodemographic characteristics. Within the scope of the Home Health Care Evaluation Form (used for the evaluation of patients whose applications were accepted), the following patient data were recorded: identity and contact information, application characteristics, personal care, income status, assistance/social support status, residency and safety information, social security status, dependency status (whether bedridden or not), appropriateness of personal hygiene and nutrition, habits, presence of chronic diseases (hypertension, diabetes mellitus, chronic obstructive pulmonary disease and asthma, coronary artery disease, cancer, chronic renal disease, gastritis/peptic ulcer, depression, neurological diseases, etc.), allergies and prescribed medications. Detailed information about the study was given to the patients and the consent form was signed. Detailed physical examinations and psychological assessments were performed, and the presence and degree of pain and pressure sores/ulcer was recorded.

Finally, the need for home health care was ascertained, and eligibility for registration for services was determined.

The frailty of the patients was evaluated using the EFS. Those "non-frail" (0-4 points) and "seemingly frail" (5-6 points) patients were grouped as "non-frail patients," and patients that were "mildly frail" (7-8 points), "moderately frail" (9-10 points) and "severely frail" (11 points and above) were grouped as "frail patients." The clock-drawing test was used to evaluate cognitive status in which patients were asked to draw a clock without providing any visual cues and were graded according to the accuracy of the final image. General health conditions and a history of hospitalization in the last year were questioned. Patients were asked about their functional independence and the number of daily activities that they required assistance in performing. Validity and reliability studies for the EFS were conducted by Aygör et al.[9] in our country.

Statistical Analysis

The compatibility of the variables with normal distribution was examined using the Shapiro-Wilk test. Continuous variables are expressed as median (minimum–maximum) values. Categorical variables are expressed as frequencies and percentages. The Mann-Whitney U and Kruskal-Wallis tests were used for the comparison of EFS scores between groups. The relationship of the EFS score with age was analyzed by calculating the Spearman correlation coefficient. ROC (Receiver Operating Characteristics) analysis was performed to examine whether EFS scores could be used to determine the need for confinement to bed and home health care. The relevant cut-off point was determined by applying the Youden J. Index to values obtained from the area under curve (AUC) graph, and the resultant sensitivity, specificity and positive/negative predictive values were reported. The internal consistency of the EFS was examined with the Cronbach's alpha coefficient. The SPSS software (IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY, USA) was used for statistical analysis, and p-values of <0.05 were considered statistically significant.

Results

The median age was 80 (range: 23-102); 59% (n: 118) were females and 41% (n: 82) were males. The EFS score distribution is shown in Figure 1. Accordingly, 4.5% of the cases were classified as non-frail, 6% were classified as vulnerable, and 89.5% had different degrees of frailty (mild, moderate and severe).

It was determined that the EFS score could be used to identify the requirements for home health care services in our subjects. According to the ROC analysis results, the AUC for EFS was 0.932. It was determined that an EFS threshold of >9 points would be able to distinguish those requiring home health care services from those that did not, with a sensitivity of 80.34% and a specificity of 90.91% (*Table 1*). There was a significant positive correlation between EFS score and age (r=0.280, p<0.001). The EFS score was not associated with gender, social security status or income.

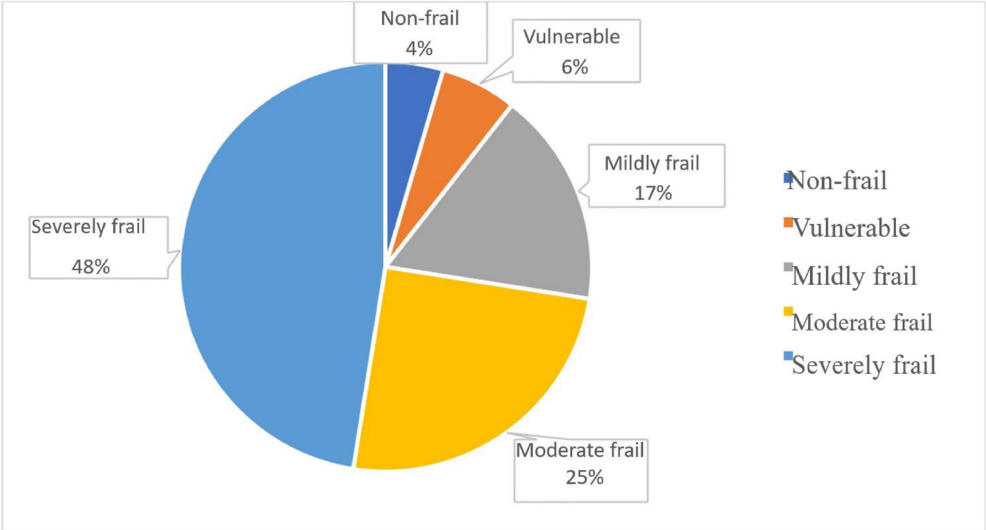

Figure 1. Edmonton Frail Scale score.

Table 1. Edmonton Frail Scale score distribution and ROC analysis.

Total score	11 (3–16); 10.85±2.83
Non-frail	9 (4.50%)
Vulnerable	12 (6%)
Mildly frail	34 (17%)
Moderate frail	50 (25%)
Severely frail	95 (47.50%)
Cronbach alpha	0.650
Criterion Value	>9
Sensitivity (95% CI)	80.34 (73.70-85.90)
Specificity (95% CI)	90.91 (70.80-98.90)
Youden J Index	0.71
AUC	0.932
PPV (95% CI)	98.60 (95-99.60)
NPV (95% CI)	36.40 (29.20-44.20)

EFS: Edmonton Frail Scale, CI: confidence interval, AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value.

There was no difference between those with pressure sores/ulcers and those without in terms of EFS scores; however, EFS scores differed among those with and without bed confinement, and significantly higher scores were observed in bedridden individuals. Interestingly, the EFS score was not associated with the use of auxiliary devices. There was no difference in EFS scores between individuals who were able to tend to their personal care and those who could not. Finally, it was also observed that the EFS scores were higher in the group with chronic disease (*Table 2*).

Discussion

As expected, age was associated with frailty, and we found a significant relationship between frailty and the presence of chronic illness and confinement to bed. However, we did not find a significant relationship between frailty and gender, social security status, income, personal care, pressure sores/ulcers and pain levels. The results of our ROC analysis showed that an EFS cut-off value of >9 could identify patients in need of home health care services-even though the negative predictive value was rather low.

In a study assessing the frequency of frailty in the United States, Bandeen et al.[10] found that, among the 7,439 people between the ages of 65 and 90 years, 15.3% were identified as frail, 45.5% were prefrail and 39.2% were non-frail. In terms of gender, they found that 17.2% of women were frail and 47.2% were prefrail, whereas 12.9% of men were frail and 43.3% were prefrail. When the participants were evaluated in terms of age groups, they detected that the frequency of frailty was 8.9% in the 65-69 age group and 33.3% in the 8-89 age group. They reported that frailty increased with increasing age.[10] In a Turkish study, Akin et al.[11] included 906 individuals aged 60 and above in their cross-sectional study based on two different frailty scales. In this study, frailty frequency was identified as 10% to 27.8% while the frequency of prefrail individuals was 34.8% to 45.6%.[11] The present study reports that 4.5% of the cases were in the non-frail group, 6% were in the prefrail(vulnerable) group, and 89.5% were in the frail group. The higher frailty frequency in our study compared to other similar studies may be because the study was conducted among patients who applied for home health care, meaning that these individuals were drawn from a sub-population that was already in need. We also determined a significant positive correlation between EFS score and age; however, various other factors, including gender, social security status and income levels, were not associated with EFS scores.

In one study, the effect of frailty on adverse health outcomes was investigated using the fragility index, and it was determined that 42 out of the 1,418 patients (3.2%) included developed pressure ulcers during their hospitalization. The study reported that each 0.1-point increase in frailty index increased the risk of pressure ulcer development by 1.51-fold.[12] Unlike similar studies, in our study, no significant difference was found between those with and without pressure ulcers in terms of EFS scores. This situation may arise from various factors, including the characteristics of the population studied. However, as per the sociocultural structure in Turkey, the care of the elderly is almost always undertaken by a close-

Table 2. EFS score distribution according to clinical and demographic variables.

		EFS score	P-value
Age	r	0.280	
	p	<0.001	
Gender	Female (n: 118)	11 (4-16)	0.609[a]
	Male (n: 82)	11 (3-16)	
Social security status	GHI (n: 154)	11 (3-16)	
	Others (n: 33)	12 (7-14)	0.593[a]
	Green card (n: 13)	11 (3-15)	
Income status	Salaried (n: 174)	11 (3-16)	0.736[a]
	Non-salaried (n: 26)	12 (4-14)	
Pressure ulcer	Exist (n: 28)	11.50 (9-16)	0.226[a]
	Non-exist (n: 172)	11 (3-16)	
Confinement to bed	Full (n: 103)	12 (4-16)	0.017[a]
	Partial (n: 97)	11 (3-15)	
Personal care	Self (n: 11)	11 (5-14)	0.907[a]
	Others (n: 189)	11 (3-16)	
Auxiliary tool	Exist (n: 96)	11 (3-15)	0.108[a]
	Non-exist (n: 104)	12 (4-16)	
Chronic disease	Exist (n: 187)	12 (4-16)	<0.001[a]
	Non-exist (n: 13)	7 (3-12)	

EFS: Edmonton Frail Scale. GHI: General Health Insurance, Green card: Health card for uninsured people in Turkey.
[a] Mann-Whitney U test.
Data were given as median (minimum: maximum).

often a first-degree relative. Therefore, it can be thought that the caregiver of the patients in our study was mostly a first-degree relative, which may have reduced the prevalence of pressure ulcers due to effective care provided by caregivers.

When we evaluated patients who applied for home health care services in terms of bed confinement, 51.5% of the patients were found to be bedridden and 48% were semi-bedridden. Although there was no significant relationship between confinement to bed and the EFS score, it was determined that the EFS score was higher among bedridden patients. In a study conducted with patients who applied to the health board recently, it was reported that the frailty score was higher in the group with severe disabilities (completely dependent disabled individuals).[13]

With aging, the number of chronic diseases increases and the quality of life decreases at a similar rate. Symptoms and findings that occur with a decrease in physiological reserve, which are also affected by chronic diseases, are important in terms of frailty. In our study, it was observed that frailty score was higher in the group with chronic disease, similar to previous studies.[5,14]

In our study, physical examinations were performed on the patients in accordance with the home health care patient evaluation form, and the resultant examination findings were compared with the EFS score. The EFS score was found to vary due to the presence of an abnormal gastrointestinal system (dyspepsia gastroesophageal reflux, diarrhea and constipation) and nervous system findings (abnormal neurological examination

and/or abnormal findings on neuroimaging), whereas there were no differences in other analyses. Our literature review did not reveal any studies evaluating these relationships.

Epidemiological studies have shown that pain caused by activity, especially in old age, increases with advancing age. Generally, it is known that the prevalence of some type of pain is in the range of 45-80% in elderly patients.[15] Studies have reported that chronic pain is associated with frailty and that patients with chronic pain are more likely to develop frailty.[16-18] In a study of 2,736 male patients between the ages of 40 and 79, it was found that chronic widespread pain was associated with frailty.[19] Similarly, Coelho et al.[20] examined the relationship between pain and frailty in 252 elderly patients and reported that frailty was associated with pain; additionally, pain treatment contributed to reducing frailty and mortality. Unlike other studies, our study found no significant correlation between pain and EFS scores.[8]

The reasons for this may be the patients' level of consciousness or inability to express their pain. In addition, since these patients often used analgesics, they may have had less pain.

Our study is single-centered, and the power of studies to represent all patients is weak. The obtained results cannot be generalized. As can be seen from our findings, most of our participants were elderly. Therefore, there were difficulties in cooperation and the negative attitudes of the individuals they receive care at home have caused some difficulties.

Conclusions

As a result, with the increase in the elderly population all over the world, the need and number of applications for home health services are increasing. In our country, home care services are typically carried out jointly by family medicine practitioners, hospitals and municipalities, and its scope has not been clearly revealed. Patients may request that daily injections and simple dressings be made by home care services. Some patients may also keep their home care workers busy with the renewal of their chronic disease reports. In addition, bedridden patients who have had a stroke or cancer patients in their terminal period expect to be cared for through the same system. We think that frailty may be an important indicator for the evaluation of priority patients in service planning for home care service practice, whose job definition lines are not yet clear. Our study revealed that an EFS score of >9 can be a rational indication criterion for home care service. Although many studies have examined the effects of frailty on the health of the elderly, few studies have evaluated frailty in patients receiving home health services. The cut-off point we determined is an additional contribution to the literature.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding Sources

There are no funding sources to declare.

Ethical Approval

For this study, approval was obtained local ethics committee.

Authors' Contribution

Study Conception, Literature Review, Critical Review, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Manuscript preparing held by all authors.

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Original Article

Sulfasalazine-associated Nephrolithiasis in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis

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ABSTRACT

Background Sulfasalazine (SSZ) is an anti-inflammatory and immunomodulatory drug used to treat many inflammatory diseases. Bacteria in the gut metabolize SSZ to active 5-aminosalicylic acid and inactive sulfapyridine. Sulfapyridine can crystallize in the kidney. We aimed to investigate the frequency of nephrolithiasis in patients who were diagnosed with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and who received SSZ treatment retrospectively.

Material and Methods We retrospectively analyzed the files of AS and RA patients in the rheumatology outpatient clinic between 2009 and 2018. We identified patients who underwent kidney ultrasonography at least six months after initiation of SSZ. One hundred six patients and 50 healthy adults were included in the study.

Results Only eight patients (6 AS, 2 RA) had nephrolithiasis on ultrasonography, but none in the control group (p=0.046). In logistic regression analysis, no correlation was found between gender, age, vitamin D, parathyroid hormone, and urinary calcium excretion with SSZ use (p>0.05).

Conclusion Although, it is noteworthy that these patients are prone to stone formation for various reasons. Therefore, paying attention to the patient's hydration while using these drugs may prevent such side effects.

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Introduction

Sulfasalazine (SSZ) is an anti-inflammatory and immunomodulatory drug used in the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and inflammatory bowel diseases (IBD). The anti-inflammatory effects of SSZ are mediated by 5- aminosalicylic acid (5-ASA).[1] The anti-inflammatory effect of 5- ASA in IBD is enhanced by its concentration in the intestinal lumen. Therefore, 5-ASA is combined with substances such as sulfapyridine to reduce intestinal absorption to inhibit metabolism. Bacteria metabolize SSZ in the gut to active 5-ASA and inactive sulfapyridine. Following degradation, sulfapyridine passes into the bloodstream while a large amount of 5-ASA remains in the intestine. Approximately 90% of sulfapyridine and its metabolites are excreted in the kidneys and can crystallize. The best-known side effects of SSZ are nausea-vomiting, skin rashes and fever.[2-4] SSZ's renal adverse effects are less than mesalazine, another drug commonly used in IBD.[5,6] In this study, we aimed to investigate the frequency of nephrolithiasis in patients with the diagnosis of RA and AS and who received SSZ treatment retrospectively.

Material and Methods

The files of patients with AS and RA who were followed in the rheumatology outpatient clinic between 2009-2018 were reviewed. Those who had renal ultrasonography (USG) for reasons other than the suspicion of nephrolithiasis (such as hepatosteatosis and choledocholithiasis) at least six months after SSZ was initiated were planned to be included in the study.

Demographic characteristics of the patients, such as age, gender, comorbidity, and medications, were recorded from the files. Laboratory values such as calcium, phosphorus, uric acid, vitamin D, parathyroid hormone (PTH) and urinary calcium excretion (routinely requested when evaluating osteoporosis in our clinic) were recorded from the electronic database. Those with a history of nephrolithiasis, a family history of kidney stones, kidney disease, metabolic disease, chronic diarrhoea, vitamin C, vitamin D, diuretic users, and sickle cell anaemia were excluded from the study. It was given to SSZ at a dose adjusted for body surface area. The control group consisted of healthy individuals who underwent abdominal USG except for the suspicion of nephrolithiasis and who did not use any medication. Permission was obtained from the local ethics committee for the study. Consent of the patients was obtained.

Statistical Analysis

Data were evaluated with SPSS (version 25.0, SPSS Inc, Chicago, IL). The control and study groups were compared in terms of factors that may pose a risk for nephrolithiasis. Chi-square for categorical data and t-test or Mann-Witney U test for continuous data were chosen related to the data distribution. Spearman correlation analysis was performed to detect factors associated with nephrolithiasis. Regression analysis was performed to determine the factors affecting the occurrence of nephrolithiasis. If the p-value was less than 0.05, it was considered significant.

Results

One hundred and six patients and 50 healthy adults were included in the study. The characteristics of the patients and the control group were shown in Table 1. Nephrolithiasis was seen in 8 patients (6 AS, 2 RA), although it was not detected in any patient in the control group (p=0.046).

In correlation analysis, no relationship was found between the presence of nephrolithiasis and gender, age, calcium, phosphorus, uric acid, vitamin D, PTH, urinary calcium excretion and time of SSZ use (p>0.005). The time between SSZ usage and USG was 50.85±76.54 months. There was no correlation between the duration of SSZ usage and the detection of nephrolithiasis (p=0.213). There was no correlation between nephrolithiasis and related factors in the logistic regression analysis performed with the model created with gender, age, vitamin D, PTH, urinary calcium excretion, and SSZ usage (p>0.05) (*Table 2*).

Table 2. Comparison of demographic and laboratory data of patient and control groups.

Variables	Patients (n: 106)	Control (n:50)	P-value
Age (year)	55.2±12.2	52.4±6.8	0.073
Gender (Male/Female)	30/76	16/34	0.636
Diabetes mellitus	14 (13.2%)	6 (12%)	0.833
Hypertension	30 (28.3%)	9 (18%)	0.430
Urea (mg/dL)	28.7±10.2	27.2±7.9	0.699
Creatinine (mg/dL)	0.79±0.22	0.68±0.07	0.000
Calcium (mg/dL)	9.6±0.4	9.5±0.3	0.063
Phosphorus (mg/dL)	3.7±2.3	4.8±6.4	0.438
Uric acid (mg/dL)	4.0±1.0	4.3±1.2	0.588
Parathyroid hormone (mg/dL)	56.5±20.8	62.1±30.6	0.431
25-OH-D (ng/mL)	19.7±9.5	21.5±8.6	0.053
Spot urine calcium/creatinine ratio	0.10±0.06	0.08±0.05	0.270
Nephrolithiasis	8 (7.5%)	0 (0%)	0.046

Data were given as mean±SD (standard deviation) or n (%).

Table 2. Multivariate regression analysis to identify the relationship between nephrolithiasis and SSZ usage after adjusted for gender, age, vitamin D, parathyroid hormone and urinary calcium excretion.

	Presence of nephrolithiasis		
	Beta	P-value	95% Confidence interval
SSZ-usage	–0.928	0.360	–0.002 to 0.001

Discussion

SSZ is an agent frequently used in patients with AS and RA. SSZ-related nephrolithiasis is reported as case reports. Our study included 106 patients, and we found increased kidney stone formation. However, in the regression analysis, we could not show the relationship between nephrolithiasis and SSZ. This may be due to the limited number of patients and the limited follow-up period.

Of all kidney stones, 1-2% are medication-related. SSZ is one of the drugs that can rarely cause kidney stones. Compared to mesalazine, SSZ rarely causes kidney adverse effects. Sulfa drugs possess low water solubility and can precipitate in renal tubules.[7] Dehydration and low urinary pH pose a risk for sulfonamide stones.[8] It has been reported that kidney stones consisting of sulfadiazine are detected in low density on computed tomography and cannot be visualized in USG.[9] USG is insufficient to exclude this disease because of failure to demonstrate sulfa-drug-related renal stones radiologically in patients treated with SSZ. However, USG was used in our study since there were no other signs and symptoms related to stones, such as flank pain,

hematuria, and impaired renal function.

Studies have found that the frequency of urolithiasis increases in patients with AS compared to the normal population. In the study by Fallahi et al.[10] in 2012, the frequency of urolithiasis among patients with AS was 11.7%, while this rate was 5.7% in the normal population. In Sweden, Jakobsen et al.[11] studied a large patient cohort, which included 8,572 AS patients and 39,639 healthy individuals. They found the unadjusted hazard ratio of urolithiasis for AS compared to the healthy population of 2.4 (95% CI 2.1-2.9).[11] In Turkey in 2015, Resorlu et al.[12] detected urolithiasis in 18.4% of AS patients and 10.4% of controls. Eliah et al.[13] claimed that limited spinal mobility and pyelo-pelvic position in AS patients might be an underlying predisposing factor for urolithiasis. Korkmaz et al.[14] suggested that one of the mechanisms responsible for the development of urolithiasis in AS may be intestinal inflammation as a result of enteric hyperoxaluria. Bone turnover and bone resorption activated by inflammatory cytokines can also cause hypercalciuria.[15,16] Korkmaz et al.[17] found that urinary calcium levels increased in AS patients with urolithiasis, but the difference was not statistically significant.

In our patient group, 6 of 8 patients with stones had AS, and 2 had RA. None of our patients had signs of IBD. In addition, we could not find a relationship between the duration of SSZ use and the detection of nephrolithiasis (p=0.213).

Conclusions

No information was found in the literature regarding the relationship between SSZ and the occurrence of nephrolithiasis. The advantage of our study was that we had vitamin D, PTH, and urinary calcium excretion values, as they were routinely requested in our clinic when evaluating osteoporosis. However, our study had some limitations. The follow-up period of the patients was short, and the stones were not assessed with computed tomography. Since kidney stone analyzes were not performed in our study, the content of the stones could not be determined. However, it is noteworthy that these patients are prone to stone formation for various reasons. Therefore, paying attention to the patient's hydration while using these drugs can prevent such side effects. More extensive, controlled studies, including stone analysis, are needed on this subject.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical Approval

For this study, approval was obtained local ethics committee with the decision number 2018/017.

Authors' Contribution

Study Conception, Literature Review, Critical Review, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Manuscript preparing held by all authors.

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Original Article

Time Elapsed for Switching from Oral Antidiabetic Therapy to Insulin Therapy in Type 2 Diabetic Patients and Evaluation of the Factors Affecting This Period

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ABSTRACT

Background We aimed to determine the time elapsed for switching from oral antidiabetic therapy to insulin therapy in patients with type 2 diabetes mellitus and the factors that affect this period.

Material and Methods Three hundred fifteen patients with type 2 diabetes mellitus who were followed up in the diabetes outpatient clinic were included in the study. The gender, education level, age of onset of diabetes, presence of hypertension, smoking and body mass index of the patients were examined, and the effects of these variables on time elapsed for switching to insulin therapy were analyzed in three phases.

Results Three hundred fifteen patients (117 males, 198 females) were enrolled in the study. The mean time elapsed for switching from oral antidiabetic therapy to insulin therapy was 9.93±6.67 years. The effects of education level, age at the onset of diabetes, presence of hypertension, and body mass index on time elapsed for switching to insulin therapy were found to be statistically significant ($p<0.05$); whereas the effects of gender and smoking were not significant ($p>0.05$). The time elapsed for switching to insulin therapy shortened as the education level, the age at the onset of diabetes, and body mass index level increased. It was found that hypertension in patients with type 2 diabetes mellitus prolongs the time elapsed for switching to insulin therapy.

Conclusion The body mass index level, presence of hypertension, education level and age at the onset of diabetes were the significant factors affecting the time elapsed for switching to insulin therapy.

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Introduction

Type 2 diabetes mellitus (DM) has reached a pandemic worldwide, and the extent of the problem has been gradually increasing. The global diabetes prevalence in 2019 was 9.3% (463 million people). It is estimated to be rising to 10.2% (578 million) by 2030, and 10.9% (700 million) by 2045.[1] DM is characterized by chronic hyperglycemia developed due to the impairment in carbohydrate, lipid, and protein metabolism resulting from the impairment in insulin secretion or insulin effect or both.[2] Progressive loss of ß-cells is the typical characteristic of type 2 DM; at the time of clinical diagnosis, the patients have lost approximately half of the insulin secretion capacity of ß-cells.[3,4]

The initial treatment for type 2 DM generally does not include insulin therapy. Diet, exercise, weight loss, and oral antidiabetic agents are adequate initial treatments for achieving glycemic control. Insulin is indicated for patients who cannot gain glycemic control despite oral antidiabetic drugs, diet and exercise.[5] Insulin therapy is a well-known and most commonly used treatment in which physicians have high clinical experience. Insulin is also the most effective treatment option to reduce glycemia. Any level of elevated haemoglobin A1c (HbA1c, glycosylated haemoglobin) to, or close to, the therapeutic goal may be decreased by using insulin.[6] Some of the goals of insulin therapy in patients with type 2 DM are to eliminate symptoms of hyperglycemia, prevent diabetic ketoacidosis, and reduce the incidence of infections.[1] Maintaining glycemic control reduces the risk of microvascular and macrovascular complications.[7] Insulin therapy also positively affects triacylglycerol and high-density lipoprotein cholesterol levels.[8] Insulin therapy is an effective treatment method in patients with type 2 DM, but there is an inconsistency between the guidelines and clinical practice about the time to start insulin therapy.[9]

The present study aimed to determine the time elapsed for switching from oral antidiabetic therapy to insulin therapy in patients with type 2 DM and the factors that affect this period.

Material and Methods

This study was conducted on patients with type 2 DM in the diabetes outpatient clinic. Despite the optimal combination and dose of oral antidiabetic drugs being determined, insulin therapy was started in accordance with current diabetes guidelines for patients whose blood sugar could not be regulated. Written informed consent was obtained from the patients included in the study, and the ethics committee approved the study.

Three hundred and fifteen patients (117 men and 198 women) were included in the study. Patients with pregnancy, malignancy, severe endocrine, nephrological, haematological, psychiatric and neurological diseases were excluded from the study. Gender, age, education level, medical history, age of onset of diabetes, presence of hypertension, smoking status and body mass index (BMI) in the patients were recorded. The time to transition from oral antidiabetic therapy to insulin therapy (in addition to or in place of oral treatment) was calculated for each patient.

Statistical Analysis

Statistical analyzes were made with the obtained data. The effects of the recorded variables on the time elapsed for switching to insulin therapy were analyzed in three phases. Since one of the primary goals of the present study was to identify the factors affecting the time elapsed for switching to insulin therapy, correlation analysis was performed in the first phase of the analysis. In the second phase, associations were analyzed using a regression model including these factors. The third phase examined whether there was a statistically significant difference between the determined groups in terms of variables. IBM Corporation SPSS (Statistical Package for Social Sciences), version 23.0, New York, US was used for statistical analyses. Jarque-Bera normality test was performed for the data to identify which method would be used for the analyses; a p-value <0.05 indicated that the data were not normally distributed. Therefore, non-parametric tests (which do not require normal distribution) were used. Mann-Whitney U test, a non-parametric test, was also used to analyze the differences between the groups. Kendall's tau-b correlation coefficient, one of the non-parametric measures

of association, was used to determine the correlation of the dependent variable (the time elapsed for switching to insulin therapy) with the independent variables (gender, education level, age at the onset of diabetes, hypertension status, smoking status, and BMI), and to evaluate the effects of these independent variables on the dependent variable, which were the main goals of the study. A significant but weak correlation was found in terms of defined variables. Therefore, associations needed to be tested via a regression model. Independent variables were analyzed by the method of Least Squares.

Results

A total of 315 patients with type 2 DM were evaluated in the present study. 117 (37.1%) of the patients were male, and 198 (62.9%) were female. The mean age of the patients was 60.29±9.04 years. Regarding the education level, 110 patients (34.9%) were illiterate, 40 patients (12.7%) were literate, 151 patients (47.9%) were primary school graduates, and 14 patients (4.5%) were high school or university graduates. Two hundred forty-seven patients (78.4%) were non-smokers, and 68 patients (21.6%) were smokers. Two hundred thirty-six patients (74.9%) had hypertension with type 2 DM, and 79 patients (25.1%) did not have hypertension. The mean age at the onset of diabetes was 46.58±10.54 years. The mean BMI value was 29.14±4.60 kg/m^2. The mean time elapsed for switching from oral antidiabetic therapy to insulin therapy was 9.93±6.67 years (*Table 1*).

Table 1. General characteristics of the study group.

Characteristics	Study group (n: 315)
Gender	
Male	117 (37.1%)
Female	198 (62.9%)
Age ranges (years)	
35-49	77 (24.4%)
50-59	171 (54.3%)
≥60	67 (21.3%)
Mean age (years)	60.29±9.04
BMI ranges (kg/m^2)	
<25	43 (13.6%)
25.0-29.9	151 (47.9%)
≥30	121 (38.5%)
Mean body mass index (kg/m^2)	29.14±4.60
Smoking	
Smoker	68 (21.6%)
Non-smoker	247 (78.4%)
Hypertension	
Present	236 (74.9%)
No	79 (25.1%)
Education level	
Illiterate	110 (34.9%)
Literate	40 (12.7%)
Primary school	151 (47.9%)
High school-University	14 (4.5%)
Age at the onset of diabetes mellitus (years)	46.85±10.54
Time elapsed for switching to insulin therapy (years)	9.93±6.67

Data were given as mean±SD (standard deviation) or n (%).

Education level, age of onset of diabetes, BMI and presence of hypertension significantly affected the time elapsed to switch to insulin therapy ($p<0.05$), while gender and smoking status did not (*Table 2*). We found that as the education level, age of onset of diabetes and BMI level increased, the time elapsed for switching to insulin therapy shortened. However, we found that the presence of hypertension in patients with type 2 DM prolonged the time elapsed for switching to insulin therapy. The standardized (beta) coefficients, which indicate the degree of effect size, for the individual variables, were as follows: 4.606 for BMI, 4.415 for the presence of hypertension, 1.647 for education level, and 0.230 for age at the onset of diabetes. The model we used was statistically significant and the results obtained were reliable ($p<0.05$) (*Table 3*). The independent variables affected the time elapsed for switching to insulin therapy by 89% (*Table 4*).

Discussion

Type 2 DM is a progressive disease in which pancreatic ß cell functions are constantly decreased. As a result, most patients need insulin therapy. There is evidence that early glycemic control reduces long-term vascular complications and may increase pancreatic ß-cell lifespan. The importance of glycemic control in reducing the risk of vascular complications of diabetes is well known.[10,11] Long-term hyperglycemia leads to glucotoxicity and oxidative stress, which may cause microvascular and macrovascular complications.[12,13] Therefore, the primary goal in treating type 2 DM is to achieve glycemic control. Evidence suggests that good glycemic control prevents the occurrence of macrovascular events

Table 2. The regression analysis.

Model	Coefficients[1] Unstandardized coefficients		t	Significance
	B	Standard error		
(Constant)	24.485	4.823	5.077	0.000
Gender	–1.079	1.378	–0.783	0.435
Education	–1.647	0.593	–2.775	0.006
Age at the onset of DM	–0.231	0.056	–4.098	0.000
Hypertension	4.415	1.256	3.517	0.001
Smoking	2.071	1.365	1.517	0.132
Body mass index	–4.606	1.255	–3.673	0.000

[1]Dependent variable, the time elapsed for switching to insulin therapy, DM: diabetes mellitus.

Table 3. The results obtained from analysis of variance.

	ANOVA[b]				
Model	Sum of squares	df	Mean square	F	Significance
Regression	1128.733	6	188.122	5.450	0.000[a]
Residual	4590.838	133	34.518	-	-
Total	5719.571	139	-	-	-

ANOVA, analysis of variance, [a]Predictors: (Constant), body mass index, hypertension, smoking, age at the onset of diabetes, education, gender; [b]Dependent variable: the time elapsed for switching to insulin therapy.

Table 4. Model summary.

	Model Summary[b]			
Model	R	R square	Adjusted R square	Durbin-Watson
1	0.844[a]	0.897	0.861	1.763

[a]Predictors: (Constant), body mass index; hypertension, smoking, age at the onset of diabetes, education, gender, [b]Dependent variable: the time elapsed for switching to insulin therapy.

in diabetic patients.[10,11] In the UK Prospective Diabetes Study (UKPDS), it has been reported that good glycemic control with sulphonylurea or insulin reduces the risk of microvascular disease in patients diagnosed with new type 2 DM compared to conventional therapy.[14]

The initiation of insulin therapy at the appropriate time helps improve glycemic control and protect pancreatic ß cells from functional impairment caused by hyperglycemia.[15] Some studies have found that early insulin therapy can change the progression of diabetes.[16,17] Using insulin in combination with oral diabetic drugs at the appropriate time can prevent the progression of diabetes.[17] Despite the positive effects of insulin therapy in patients with type 2 DM, guidelines and clinical practice are not compatible with the timing of insulin therapy initiation.[9] In general, the mean time elapsed for switching to insulin therapy has been reported to be 8 to 9 years in the literature; however, the number of studies reporting a definite number is limited. In one arm of the UKPDS study, it was found that 53% of patients receiving sulfonylureas required insulin therapy within six years.[18] In our research, the mean time elapsed for switching from oral antidiabetic therapy to insulin therapy was 9.93±6.67 years.

The initiation of insulin therapy leads to many therapeutic barriers for physicians and patients. Insulin is still considered a "last resort" or an "end-stage" therapy. Fear of injections, hypoglycemia and weight gain anxiety are reasons for delayed insulin therapy.[19,20] We considered that there might be different factors that could affect switching to insulin therapy other than these factors, which are of psychological origin in general, and thereby investigated the documentable characteristics of the patients, including gender, education level, age at the onset of diabetes, hypertension status, smoking, and BMI. In contrast to our general expectation, gender and smoking were not significantly effective in the time elapsed for switching to insulin therapy, which may be attributed to the country's characteristics and tendency towards complication. However, education level, age at the onset of diabetes, BMI and presence of hypertension were significantly effective in the time elapsed for switching to insulin therapy ($p<0.05$). Patients with higher levels of education more easily adapt the insulin therapy. The patients diagnosed with diabetes at an advanced age require insulin therapy earlier, likely because of early complications. BMI was determined as the most influential factor in the present study; insulin requirement appears earlier in obese patients. We found that the presence of hypertension in patients with type 2 DM prolonged the time elapsed for switching to insulin therapy. We cannot provide a complete explanation for this observation. However, patients with hypertension as comorbidity may have better compliance with diet and treatment and a higher awareness of the disease.

Various insulin analogues are now available that can reduce the risk of hypoglycemia and cause less weight gain, thus reducing the anxiety associated with insulin therapy. Early initiation of insulin therapy can be made attractive by clinical data demonstrating the benefits of insulin therapy and the use of insulin analogues with proven safety. Additionally, educating patients on insulin therapy, blood sugar monitoring, diet and lifestyle changes can reduce anxiety about insulin and provide more successful treatment.

Conclusions

The BMI level, presence of hypertension, education level and age at the onset of diabetes were the significant factors affecting the time elapsed for switching to insulin therapy. As the education level, diabetes onset age or BMI level increases, the time elapsed for switching to insulin therapy may shorten. Hypertension accompanying type 2 diabetes mellitus may increase the time elapsed for switching to insulin therapy.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical Approval

For this study, approval was obtained local ethics committee with the decision number 2018/017.

Authors' Contribution

Study Conception, Literature Review, Critical Review, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Manuscript preparing held by all authors.

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Assessment of Relation between JAK2 Gene and Thrombosis in Myeloproliferative Neoplasms

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ABSTRACT

Background Thrombotic complications are the most considerable etiology causing morbidity and mortality in patients with philadelphia (Ph) negative myeloproliferative neoplasms (MPN). There are many studies evaluating the association of JAK2 mutation and risk of thrombosis in MPN with inconclusive results. We also investigated the relation between JAK2 mutation in all Ph negative MPN and thrombosis.

Material and Methods Thrombotic events and demographic features of 177 patients with Ph negative MPN were evaluated retrospectively.

Results JAK2 V617 F mutation was detected in 57% of patients with essential thrombocythemia (ET), %90.3 of pateints with polycythemia vera (PV), 100% of pateints with primary myelofibrosis (PMF). Thrombotic complications occured more frequently with JAK2 mutation in all MPN patients than without (p=0.014). In JAK 2 mutation positive groups, the median age, thrombosis risk scores and leucocyte values are higher, splenomegaly and arterial and/or venous thrombosis are detected more frequently (p<0.05). In subgroup analysis, there is a significant difference found in JAK 2 positive ET patients and negative group in case of thrombosis (p=0.023).

Conclusions JAK2 mutation and monitoring for thrombotic events should be performed in all MPN patients.

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Introduction

Myeloproliferative neoplasms (MPN) include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF).[1] These diseases have common clinical features, such as the high risk of vascular complications (especially in PV), progression to secondary myelofibrosis (especially in PV), and clonal evolution to the blast phase (especially in PMF).[2] From a biological point of view, 95% of patients with PV and 50-60% of patients with ET and PMF carried a common mutation of the JAK2 gene, the JAK2 (V617F).

The patients with PV and ET are currently stratified per thrombotic risk, and treatments are prescribed accordingly.[3] Patients older than 60 years old or with prior thrombosis attacks should be considered in a high-risk group, whereas those younger than 60 years old or with no history of thrombosis should be considered in a low-risk group. High-risk patients should be treated with cytoreductive agents, for example, hydroxyurea. Although this indication is valid for current practice, other parameters may be considered for patients with PV and ET in determining risk stratification, such as leukocyte count, the JAK2 (V617F) mutation, and bone marrow fibrosis grading. A higher leukocyte count has been shown to correlate with thrombosis in both PV and ET.[4,5] However, not all retrospective analyses accept a direct correlation between the leukocyte count and thrombosis.[6,7] Investigators supporting leukocytosis's role in predicting thrombosis in ET showed convincing data on patients with low-risk ET left untreated. In this setting, other investigators did not obtain the same results.[8]

The incidence of thrombosis detected in PV and ET are 12-39% and 11-25%, respectively.[9] Thrombosis is a critical prognostic criterion in MPN. Age over 60 and a history of thrombosis are two factors that increase thrombosis risk in MPN.[10] Cardiovascular risk factors promoting arterial thromboses like smoking, hypertension, diabetes and dyslipidemia are still controversial as a prognostic value.[11] In this group of diseases, thrombosis is usually identified in veins and/or large arteries.[12] By discovering clonal JAK2 mutation in PV patients, the definition and treatment of myeloproliferative neoplasms data is upgraded in 2020. JAK2 mutation forms by the switch between valine and phenylalanine in the 617th codon, the JAK2 pseudokinase piece. JAK2 mutation plays a fundamental role in the genetic description of myeloproliferative disease pathogenesis.[13-26] It is suggested that JAK2 differs the position and stability of thrombopoietin receptor MPL to affect thrombocyte activation.[14] As a result of a mutation in JAK2, the coagulation cascade is indirectly activated by alterations in apoptosis and transcription factors expressed in the activated JAK/STAT pathway.[15-29] Many studies evaluated the association of JAK2 mutation and risk of thrombosis in MPN with inconclusive results.[16] We also investigated the relation between JAK2 mutation in all Ph negative MPN and thrombosis and want to contribute Turkish data about the frequency of thrombosis in JAK2 positive, Ph negative patients.

Material and Methods

This study evaluated the clinical and demographic characteristics of 177 Ph negative chronic MPN patients according to classic and updated diagnostic criteria from 1994 to 2011 in Dokuz Eylul Hematology Clinic. All thrombotic events were recorded in MPN patients before and/or after diagnosis. Thrombotic events proven with clinic, laboratory and/or imaging were accepted for assessment. Thrombotic events were evaluated under two titles: 1. Thrombosis related to venous system: Events with venous thromboembolism (VTE) (deep venous thrombosis [DVT], pulmonary embolism [PE], portal venous thrombosis, and splenic venous thrombosis); 2. Thrombosis related to arterial system: Proceeds with atherosclerosis and/or arterial thrombosis (atherothrombotic vessel disease-related myocardial infarction, coronary artery disease, cerebrovascular disease, peripheral arterial disease). The thrombosis risk scores for every patient were calculated.

Statistical Analysis

The retrospective study was evaluated by SPSS 15.0 for Windows Software Program. The odds ratio and Chi-square test determined the relation between JAK2 mutation and thrombosis. The odds ratio was 95%. Thrombosis risk factors other than JAK2 mutation in JAK2 (+) and (-) groups

were established by the Student t-test and Mann-Whitney U test. The statistically significant difference was p<0.05 for the Student-t-test, Mann-Whitey U and Chi-square test.

Results

The mean age of the MPN patients was 60 years (range: 18-90), and the male/female ratio was 1.1 (53.7% of the patients were male and 46.3% female). Most patients were diagnosed with ET (63.3%, 62 patients). Of the others, 62 had PV (35%), and 3 had PMF (1.7%). JAK2 mutation was positive in 107 patients (60.5%) and negative in 70 patients (39.5%). JAK2 V617 F mutation was detected in 57% of patients with ET, 90.3% of patients with PV, and 100% of patients with PMF. Thromboembolic events were detected in 71 patients (41%). Venous thrombosis was detected in 22 patients (12.4%) and arterial thrombosis in 49 patients (27.7%). The region of thromboembolisms was summarized in Table 1.

When we evaluated the patient's history, there were hypertension in 60 patients (33.9%), diabetes mellitus in 25 patients (14.1%), dyslipidemia in 27 patients (15.3%), and smoking in 27 patients (15.3%). Forty patients (22.6%) were considered high, 55 (31.1%) moderate, and 82 (46.3%) low risk for thrombosis. The characteristics of 177 MPN patients (with PV, ET, and MF) were showed in Table 2. At diagnosis, haemoglobin value was 14.83±2.61 g/dL hematocrit value was 44.25±8.08%, leucocyte count was 10,300 mm^3 (880-38,000), thrombocyte count was 702,000 mm^3 (57,000-2,285,000). Splenomegaly existed in 32.8% (n: 58) patients however 119 patients did not have splenomegaly (67.2%). Assessment of thrombosis risk score of PV, ET and PMF patients according to age at diagnosis, sex, JAK 2 mutation, laboratory values, splenomegaly, other diseases, arterial and venous thrombosis was presented in Table 2. There were significant differences detected in sex, age, haemoglobin, hematocrit and thrombocyte values between PV and ET (p<0.05) (*Table 2*). The effect of JAK2 mutation in venous and/or arterial thrombotic events was investigated in all MPN groups and PV, ET and PMF subgroups. All statistical analysis of the retrospective study was done by odds ratio (*Table 3*). In JAK 2 mutation-positive groups, the median age, thrombosis risk scores, and leucocyte values were higher, and splenomegaly and arterial and/or venous thrombosis were detected more frequently (p<0.05). Venous thromboembolic events in JAK (+) MPN patients were detected higher than JAK2 (-) patients (odds ratio: 4.82, p=0.014). In subgroup analysis, a significant difference was found in JAK 2 positive ET patients (p=0.023). No significant difference was detected between JAK 2 positive PV patients and VTE (p=0.562).

Arterial thromboembolic events were evaluated higher in JAK2 (+) MPN patients (odds ratio: 2.954, p=0.005). It was confirmed that there was a statistically significant increase in arterial thrombotic events in JAK 2 positive patients rather than JAK2 negative patients with ET (p=0.011). On the other hand, there was no relation between JAK2 mutation and arterial thrombosis development in PV patients (p=0.277). If all vascular diseases were included, JAK 2 positive MPN patients had a higher probability of thromboembolic events than JAK2 negative patients detected in our study (odds ratio: 3.376, p=0.001). In the subgroup analysis of all vascular diseases, JAK2-positive ET patients had a significantly higher affinity to thrombosis (p=0.001). On the other hand, there was no statistically significant relation between affinity to thrombosis in JAK2 positive PV patients (p=0.359).

Venous thrombosis was statistically significant with a high-risk score, presence of splenomegaly, hypertension and JAK2 mutation in simple variable regression analysis (p values <0.034-0.062-0.014). Venous thrombosis was increased in patients with JAK2 mutation, splenomegaly and hypertension (p values as follows <0.030-0.065-0.041, according to multiple variable regression analysis) (*Table 4*).

In simple variable regression analysis, arterial thrombosis was detected more frequent in old, hypertensive, dyslipidemic patients and with the presence of high leucocyte count, smoking and JAK2 positiveness (p<0.05) (*Table 5*). According to arterial thrombosis predictors in multiple variable regression analysis, smoking, leucocyte value, and JAK2 positiveness increased arterial thrombosis development (*Table 5*).

Table 1. Frequency of venous and arterial thromboembolic events and distribution.

Venous thromboembolism 12.4% (n: 22)		Arterial thromboembolism 27.7% (n: 49)	
Region	Number of patients	Region	Number of patients
Deep venous thrombosis	17	Myocardial infarction	12
Pulmonary embolism	4	Coronary artery disease	25
Portal venous thrombosis	4	Cerebrovascular disease	23
Splenic venous thrombosis	2	Periferic arterial disease	4

*In 22 patients only venous, in 49 patients only arterial; in 15 patients both venous and arterial thromboembolic event are existed.

Table 2. Patients characteristics due to diagnostic groups.

	PV (n: 62)	ET (n: 122)	MF (n: 3)	p value†
Age	67 (18-85)	61 (27-90)	61 (53-63)	0.018
Sex (female/male)	21/41	60/52	1/2	0.013
JAK 2 mutatation	56/6 (90.3%)	66/46 (58.9%)	3/3 (100%)	0.042
Hypertension	25/37 (40.3%)	34/78 (30.4%)	1/3 (33.3%)	0.184
Dsylipidemia	8/54 (12.9%)	19/93 (17%)	0/3 (0%)	0.479
Smoking	12/50 (19.4%)	14/98 (12.5%)	0/3 (0%)	0.224
Diabetes mellitus	8/54 (12.9%)	17/95 (15.2%)	0/3 (0%)	0.682
Thrombosis risk score	L: 24 (38.7%) I: 24 (38.7%) H: 14 (22.6%)	L: 57 (50.9%) I: 30 (26.8%) H: 25 (22.3%)	L: 1 (33.3%) I: 1 (33.3%) H: 1 (33.3%)	0.212
Hemoglobine (g/dL)	17.14±2.03	13.68±1.91	10.30±1.41	<0.001*
Hematocrit (%)	51.08±6.23	40.81±6.30	31.77±3.96	<0.001*
Leucocyte (/10^3 mm^3)	10.4 (3.9-26.4)	10.2 (0.88-38)	16.4 (15.4-19.5)	0.492
Thrombocyte (/10^3 mm^3)	359 (127-1,143)	814 (162-2,285)	370 (57-2,027)	<0.001*
Splenomegaly	21/41 (33.9%)	34/78 (30.4%)	3/3 (100%)	0.633
Venous thrombosis	7/55 (11.3%)	14/98 (12.5%)	1/3 (33.3%)	0.815
Arterial thromboembolism	15/47 (24.2%)	32/80 (28.6%)	2/3 (66.7%)	0.533
Venous or arterial thromboembolism	17/45 (27.4%)	37/75 (33%)	2/3 (66.7%)	0.443

† Evaluation between difference in PV and ET groups.
*p<0.05.
EV: essential thrombocythemia, PV: polycythemia vera, PMF: primary myelofibrosis, L: low risk, I: intermediate risk, H: high risk.

Table 3. Patient characteristics due to JAK 2 mutation.

	Positive (n: 125)	Negative (n: 52)	p value†
Age	65 (27-90)	57 (18-84)	0.003*
Sex (female/male)	65/60	30/27	0.895
Diagnosis	PV: 56 ET: 66 MF: 3	PV: 6 ET: 46	0.761
Hypertension	40/85	17/35	0.813
Dsylipidemia	16/109	6/46	0.252
Smoking	20/105	7/45	0.772
Diabetes mellitus	33/92	6/46	0.695
Thrombosis risk score	L: 37 I: 42 H: 46	L: 32 I: 14 H: 6	0.002*
Hemoglobine (g/dL)	14.84±2.41	14.83±2.92	0.976
Hematocrit (%)	44.81±8.01	43.41±8.18	0.264
Leucocyte (/10^3 mm^3)	11.1 (3.9-34.2)	9.55 (0.88-38)	0.002*
Thrombocyte (/10^3 mm^3)	702 (57-2,285)	695.5 (139-2,175)	0.739
Splenomegaly	51/74	10/42	0.003*
Venous thrombosis	22/103	2/50	0.008*
Arterial thromboembolism	42/83	7/45	0.004*
Venous or arterial thromboembolism	50/75	6/46	0.001*

† Evalutation of differance in PV and ET groups
*p<0.05
PV: polycythemia vera, ET: essential thrombocytosis, MF: myelofibrosis.

Table 4. Venous thrombosis predictors (simple-multiple variable logistic regression analysis, n: 177)

Venous thromboembolic events	OR	p value	OR*	p value*
JAK2 mutation	4.82 (1.34-16.97)	0.014	4.17 (1.15-15.14)	0.030
Age	1.02 (0.99-1.06)	0.195		
Sex (male/female)	0.85 (0.35-2.07)	0.712		
Diagnosis (PV/ET)	1.22 (0.43-2.95)	0.815		
Splenomegaly	2.73 (1.08-6.87)	0.034	2.50 (0.94-6.59)	0.065
Leucocyte (/10^3 mm^3)	1.00 (1.01-1.11)	0.524		
Hemoglobine (g/dL)	0.88 (0.74-1.06)	0.880		
Thrombocyte (/10^3 mm^3)	1.00 (0.99-1.01)	0.840		
Smoking	0.94 (0.26-3.48)	0.930		
Dyslipidemia	2.51 (0.88-7.21)	0.086		
Diabetes mellitus	0.99 (0.27-3.65)	0.991		
Hypertension	2.41 (0.96-6.05)	0.062	2.75 (1.04-7.25)	0.041

*OR (CI), was defined as p value.
Multiple variable regression analysis (R^2=0.152, p=0.002).

Table 5. Arterial thrombosis predictors (simple-multiple variable logistic regression analysis n: 177)†

Arterial thromboembolic events	OR	p value	OR *	p value*
JAK2 mutation	2.84 (1.33-6.07)	0.007	2.54 (1.06-6.08)	0.037
Age	1.03 (1.01-1.06)	0.009	1.01 (0.98-1.04)	0.465
Sex (male/female)	1.10 (0.57-2.17)	0.763		
Diagnosis (PV/ET)	1.25 (0.62-2.55)	0.534		
Splenomegaly	1.72 (0.85-3.45)	0.130		
Leucocyte (/10^3 mm^3)	1.01 (0.99-1.10)	0.006	1.00 (0.99-1.02)	0.049
Hemoglobine (g/dL)	0.97 (0.85-1.11)	0.689		
Thrombocyte (/10^3 mm^3)	1.00 (0.99-1.01)	0.057	0.99 (0.97-1.03)	0.063
Smoking	4.94 (2.07-11.81)	0.001	3.86 (1.33-11.22)	0.013
Dyslipidemia	5.44 (2.29-12.91)	0.001	2.15 (0.72-6.44)	0.173
Diabetes mellitus	1.64 (0.67-4.03)	0.277		
Hypertension	4.01 (1.98-8.10)	0.001	2.24 (0.72-6.44)	0.079

*OR (CI), was defined as p value.

Discussion

Thrombosis is the most considerable aetiology causing morbidity and mortality in myeloproliferative diseases.[17] The thrombosis is declared mostly in veins and/or large arteries.[18] In 2005, clonal JAK2 mutation was defined in PV patients, upgrading the data on diagnosis and treatment of myeloproliferative diseases. JAK2 mutations are detected in 90-95% of PV patients and 50-60% of ET and PMF patients.[19-27] In our study, the frequency of JAK2 mutations was 90.3%, 57% and 100% in PV, ET and PMF patients, respectively. The major problem in our study was numerical inhomogeneity in our patients.[28] There is a consideration about the relation between JAK2 mutation and the development of thrombosis due to increased thrombotic vascular events detected in JAK2 positive MPN patients or thrombotic diseases such as Budd-Chiari syndrome without MPN.[20,30,31]

The incidence of thrombosis in MPN is 10% to 30%.[19] We included all atherosclerotic vascular changes in our study. Thus, isolated venous thromboembolic events were detected in 12.4% of all MPN patients, isolated arterial events in 27.7%, and both arterial and venous events in 8.47%. The higher frequency in our study may be due to the inhomogeneity of our patient population.

The relation between JAK2 mutation in MPN and thrombosis was first mentioned in a 2005 publication. Kralovic et al.[20] investigated a total of 244 patients (128 PV, 93 ET and 23 PMF) in the study and found the frequency of the JAK2 positivity as 48%. Among 177 follow-up patients in our study, 60.5% of the patients had JAK2 mutation. Campbell et al.[21] mentioned the statistically significant increment of frequency in venous thromboembolism in JAK2 positive ET patients (n: 776). However, there was no difference in arterial thrombosis in 2005. Evaluation of ET patients in Wolanskyj et al.[13] studies showed no relation between thrombosis and JAK2 mutation. Cheung (n: 60) and FInazzi (n: 179) analyzed patients with ET, and they declared the increased thrombosis risk in the JAK2 positive group (62% vs. 26% and 46% vs. 4%, respectively), similar to our study.[22] In our study, totally thrombosis risk in JAK2 positive patients was significantly higher than in JAK2 negative patients, and arterial thrombosis frequency was 21.46%, venous thrombosis frequency 10.73%, venous and/or arterial thrombosis frequency is 24.85%. In subgroup analysis, JAK2 mutation-positive PV

patients had 5% of arterial thrombosis and 17.7% of venous thrombosis, which was not statistically significant between the JAK2 negative group. The arterial thrombosis frequency was 22.3%, and venous thrombosis frequency was 11.6% in JAK2 mutation-positive ET patients, significantly higher than in JAK 2 negative ET patients.

As a result, there is a positive correlation between arterial and venous thrombosis and JAK2 positiveness in ET patients rather than PV patients. Smoking, advanced age, and splenomegaly were significantly associated with an increased risk of thrombosis in the JAK2 positive and negative MPN groups. In general, it is possible to prove that JAK2 mutation increases the risk of thrombosis in MPN patients. This condition is due to patient population heterogeneity and various factors contributing to thrombosis. On the other hand, no proven data shows simultaneous different thrombophilic mutations in JAK2 positive patients. Although JAK 2 mutations are correlated with thrombosis in MPN patients, JAK2 positivity is not detected in arterial and venous thrombosis rather than in MPN. There aren't enough appropriate data to include routine JAK2 mutation investigation in idiopathic venous thrombosis or early age and/or unexpected areas with venous/arterial thrombosis. The only exclusion of this can be splanchnic venous thrombosis.[23] Proven in several trials, isolated splanchnic thrombosis at diagnosis is related to increased JAK2 positiveness (17-58%). Further studies have discovered that almost all patients have MPN. In a retrospective study, Bayraktar et al.[24] found JAK2 positivity in 24% of 25 patients with chronic isolated non-cirrhotic portal vein thrombosis and found the frequency of MPN to be 44% in JAK2 positive and negative patients. They also showed at least one thrombophilic factor positivity in 19 of 25 patients. However, 3 out of 5 JAK2-negative MPN patients had no other clinically thrombophilic risk factors. The other two patients were diagnosed with protein C and antithrombin deficiency. 3 of 6 JAK2-positive patients had a homozygous methylene tetrahydrofolic acid reductase (MTHFR) C677T mutation.[24] Kahraman et al.[32] evaluated 143 JAK2-positive patients diagnosed with PV, PMF and ET. There was no significant relationship between JAK2 mutation burden and vascular complications such as thrombosis and bleeding.[32] After splenic vein thrombosis was first detected in our patient group, two patients were diagnosed with MPN in further evaluation. Both patients were JAK2 positive. However, this does not reflect the current prevalence of JAK2 positivity in splanchnic venous thrombosis because patients are referred to the haematology clinic after diagnosing MPN. Until recent data, it has been suggested that JAK2 mutation analysis is sufficient to screen for thrombophilia in splanchnic vein thrombosis. In the study of Fouassier et al.[25], none of the 11 paroxysmal nocturnal hemoglobinuria patients had a JAK2 mutation. The increased frequency of JAK2 mutations in other thrombotic diseases is controversial, but a direct relationship has not yet been proven. We found an association between arterial and venous thrombosis in JAK2 positive and negative ET patients. However, the exclusion of patients with insufficient data and progress in evaluating our study should be considered.

Conclusions

In conclusion, in the subgroup analysis of MPN patients, we proved the statistically significant relation between JAK2 mutation and arterial and/or venous thrombosis frequency in ET patients. However, there is no significant relation in PV patients. Multicenter prospective studies with long-term follow-up should be designed to determine the link between the JAK2 gene and thrombosis in MPN.

Conflict of interest

The authors declare that they have no conflict of interest.

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There is no financial or other relationship that might lead to a conflict of interest.

Ethical Approval

For this study, approval was obtained local ethics committee.

Authors' Contribution

Study Conception, Literature Review, Critical Review, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Manuscript preparing held by all authors.

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Original Article

C-Reactive Protein Lymphocyte Ratio in the Diagnosis of Pulmonary Tuberculosis

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ABSTRACT

Background Tuberculosis (TB) is still a severe problem in underdeveloped and developing countries. Diagnostic tests are unavailable in every health institution, and TB culture can take up to 45 days. Therefore, there is a need for cheaper, faster, and easily accessible diagnostic methods that can guide the diagnosis. This study aimed to determine whether red blood cell distribution width (RDW), C-reactive protein (CRP)-lymphocyte ratio (CLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) can be used as biomarkers in the diagnosis of pulmonary TB in patients with no comorbidities.

Material and Methods Files of microbiologically confirmed 122 patients with pulmonary TB and 153 patients in whom pulmonary TB was excluded were retrospectively reviewed. Out of them, patients with comorbidities were excluded from the study. Eighty-one patients with TB and 100 controls were included in the study.

Results The lymphocyte, eosinophil, and LMR levels remained significantly lower in the TB group, while neutrophil, monocyte, RDW, platelet, and PLR levels were higher in the same group.

Conclusion In those patients suspicious of pulmonary TB, higher levels of RDW, PLR, and CLR, whereas lower levels of eosinophil, PDW, and LMR may predict the diagnosis of pulmonary TB in previously healthy individuals.

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Introduction

Tuberculosis (TB) is an infectious disease that is a significant public health problem transmitted via aerosols. A definitive diagnosis of pulmonary TB is put bacteriologically; in some cases, histopathology can make the diagnosis. But in both cases, usually, the diagnosis is delayed and, in some patients, leads to the progress and transmission of the disease. In the light of developing science, the fight against infectious diseases has gained momentum with new treatment methods and vaccinations. Although TB poses a lesser risk for the western world, it is still a severe problem in underdeveloped and developing countries. The acid-fast bacillus (AFB) tests used to diagnose the disease are not available in every health institution, and the result of the TB culture can take up to 45 days. Therefore, there is a need for cheaper and easily accessible diagnostic methods that can guide physicians in the diagnosis phase. The biomarkers of inflammation that are derived from the peripheral blood and hemogram parameters such as white blood cell (WBC) count, red blood cell distribution width (RDW), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) have been used as independent predictors of the prognosis of systematic inflammatory diseases.[1,2] In a previous study, high platelet distribution width (PDW) levels have been associated with COVID-19 mortality.[3] All parameters mentioned above are studied by routine complete blood count tests that clinicians might overlook. The physician's primary difficulty is translating the recommended guidelines into clinical practice. There is a need for tests that help physicians diagnose and give information about which patients should have an anti-TB treatment. This study aimed to investigate laboratory-based differences between the patients with microbiologically confirmed pulmonary TB and controls those proven not to have and to determine whether RDW, C-reactive protein (CRP)-lymphocyte ratio (CLR), NLR, PLR and lymphocyte monocyte ratio (LMR) can be used as biomarkers in the early diagnosis of pulmonary TB.

Material and Methods

Data on patients admitted to a tertiary city hospital in Turkey between January 2021 and October 2021 with complaints compatible with pulmonary TB were retrospectively investigated. We retrospectively reviewed files of microbiologically confirmed 122 patients with pulmonary TB and 153 patients in whom pulmonary TB was excluded. Patients with comorbid diseases (such as malignancy, chronic kidney disease, immunosuppressive diseases, diabetes mellitus, and hypertension) were excluded from both groups. Out of reviewed files, 81 patients with microbiologically confirmed pulmonary TB and 100 controls were included in the study. All laboratory parameters belong to the first admission before treatment, including anti-TB therapy. The NLR, PLR and CLR were obtained by dividing neutrophil, platelet, and CRP levels by lymphocyte count. LMR, lymphocyte-eosinophil ratio (LER), and platelet-neutrophil ratio (PNR) values were obtained by dividing lymphocyte levels by monocyte, eosinophil, and neutrophil levels, respectively. CRP-neutrophil ratio (CNR) and CLR were obtained by dividing CRP levels by neutrophil and lymphocyte levels, respectively. The ethical committee approval was obtained from a tertiary city hospital Clinical Research Ethical Committee (Ethics Committee Approval No: 2021-24/6).

Statistical Analysis

All statistical analyses were carried out using SPSS 25.0 software. The Kolmogorov-Smirnov test was performed to examine the normality of the data. Continuous variables were given as mean±standard deviation and median values (interquartile range %25-%75), while the categorical variables were presented as frequency and percentage. The independent groups were compared to the Student's t-test for parametric assumptions and Mann Whitney U test for nonparametric hypotheses. The ROC analysis was performed to determine the optimal cut-off values for predicting the TB. The Youden index values were used to identify the optimal cut-off values. In addition, a p-value less than 0.05 was set as the statistical significance level. Spearman's correlation coefficient (p) was used to analyze associations between investigated parameters. In all instances, p values <0.05 were taken to indicate statistical significance.

Results

The mean age was determined to be 51.6±20.7 years in the TB group and 43.9±11.2 years in the control group (*Table 1*), with the TB group having a significantly greater mean age (p<0.03). The gender distribution in the control group was 32% women and 68% men, while it was 28.4% (n: 23) women and 71.6% (n: 58) men in the TB group.

The levels of lymphocyte, eosinophil, mean platelet volume (MPV), PDW, LMR, LER, and PNR remained significantly lower in the TB group. In contrast, the WBC, neutrophil, monocyte, basophil, RDW, platelet, CRP, NLR, PLR, CNR, and CLR levels were higher in the same group. The ROC analysis calculated optimal cut-off values for RDW, NLR, PLR, CNR, CLR (*Figure 1*) and lymphocyte, eosinophil, PDW, LMR, and PNR (*Figure 2*).

When TB group compared to controls the areas under the curve (AUC) of RDW, NLR, PLR, CNR, CLR, lymphocyte, eosinophil, PDW, LMR, and PNR were found as 0.93, 0.88, 0.89, 0.94, 0.96, 0.84, 0.70, 0.65, 0.87 and 0.61

Table 1. Demographic data and laboratory findings of patients with pulmonary tuberculosis and controls*.

Parameters	Controls (n: 100)	Pulmonary TB (n: 81)	P-value
Age (years)	43.9±11.2	51.6±20.7	0.030
Number of females	32 (32%)	23 (28.39%)	0.600
WBC	8.6 (4.6-24)	9.2 (3-35)	0.035
Neutrophil	4.9 (0.65-19)	6.8 (2-32)	0.001
Lymphocyte	2.5 (0.69-11.5)	1.37 (0.07-4.04)	0.001
Monocyte	0.68±0.24	0.88±0.5	0.003
Eosinophil	0.15 (0.01-0.63)	0.08 (0.01-1.2)	0.001
Basophils	0.04 (0.01-0.4)	0.05 (0-0.29)	0.005
RDW	13(11.5-46.2)	42.6 (32-75)	0.001
Platelet	279.7±67.5	334.5±132	0.001
MPV	10.1±0.87	9.7±0.8	0.008
PDW	11.5±1.7	10.6±1.7	0.001
CRP	1.5 (0.2-98)	90.7 (1.7-386)	0.001
NLR	1.89 (0.16-13.16)	5.06 (1.2-234)	0.001
PLR	114.9 (30.8-345.7)	260.5 (24-1742)	0.001
LMR	4.09 (0.22-12.3)	1.6 (0.1-5.5)	0.001
LER	17.2 (0.22-287)	16.7 (0.28-218)	0.001
CNR	0.34 (0.04-14.4)	10.8 (0.3-43.6)	0.001
CLR	0.66 (0.08-59.2)	70 (0.87-1831)	0.001
PNR	55.4 (12.8-615.3)	48.4 (1.2-109.9)	0.010

*p<0.05, statistically significant.
WBC: white blood count, RDW: red blood cell distribution width, MPV: mean platelet volume, PDW: platelet distribution width, CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, LER: lymphocyte-eosinophil ratio, CNR: CRP-neutrophil ratio, CLR: CRP-lymphocyte ratio, PNR: platelet-neutrophil ratio.

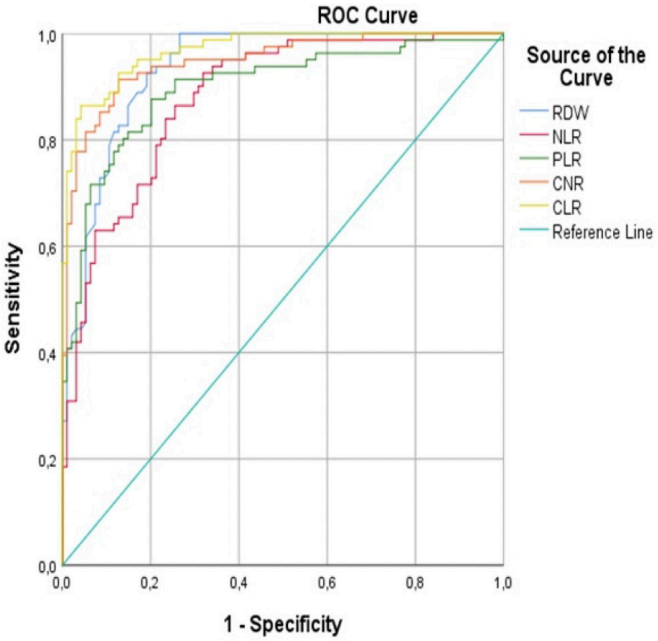

Figure 1. ROC curves comparing the prediction of pulmonary tuberculosis. Variables for RDW: red blood cell distribution width, NLR: neutrophil-lymphocyte ratio, PLR: platelet lymphocyte ratio, CNR: C-reactive protein (CRP)-neutrophil ratio, CLR: CRP-lymphocyte ratio.

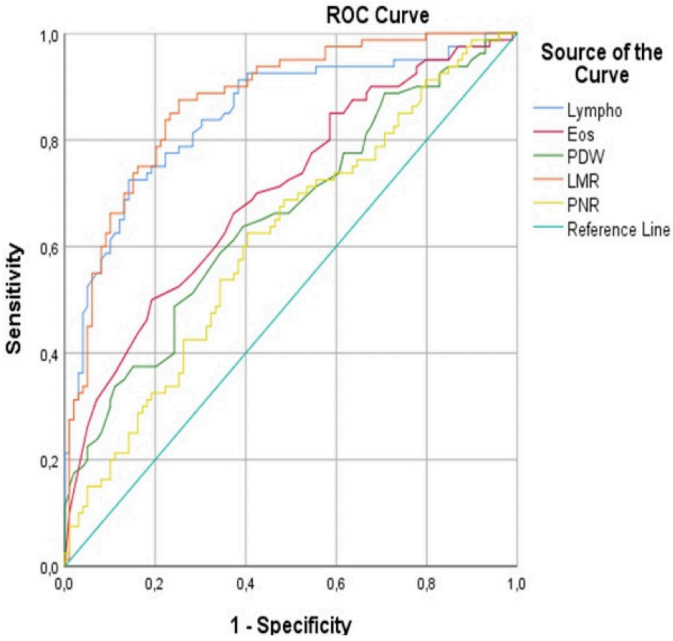

Figure 2. ROC curves comparing the prediction of pulmonary tuberculosis.
*p<0.05 statistically significant. Variables for Lymph: lymphocyte, Eos: eosinophil, PDW: platelet distribution width, LMR: lymphocyte monocyte ratio, PNR: platelet neutrophil ratio.

Table 2. ROC analysis of patients with pulmonary tuberculosis and controls*.

Variable	AUC	Cut-off	Sensitivity (%)	Specificity (%)	P-value
RDW	0.934	37.7	86	85	0.001
NLR	0.880	3.26	79	78	0.001
PLR	0.898	167	82	82	0.001
CNR	0.948	2.9	88	87	0.001
CLR	0.968	8.5	88	87	0.001
Lymph	0.847	1.84	77	77	0.001
Eos	0.702	0.11	66	62	0.001
PDW	0.657	11.1	63	60	0.001
LMR	0.871	2.5	80	79	0.001
PNR	0.613	52.3	60	59	0.009

*p<0.05 statistically significant.
AUC: area under the ROC curve, RDW: red blood cell distribution width, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, CNR: C-reactive protein (CRP)-neutrophil ratio, CLR: CRP-lymphocyte ratio, Lymph: lymphocyte, Eos: eosinophil, PDW: platelet distribution width, LMR: lymphocyte-monocyte ratio, PNR: platelet-neutrophil ratio.

Table 3. Spearman correlations between laboratory findings of patients with pulmonary TB and healthy controls.

		Age	Lymph	RDW	PLT	MPV	CRP	NLR	PLR	PDW	CNR	CLR
Age	r	1	-0.354	0.449	0.040	-0.099	0.429	0.339	0.369	-0.138	0.416	0.447
	p		0.001	0.001	0.59	0.18	0.001	0.001	0.001	0.06	0.001	0.001
Lymph	r	-0.3	1	-0.48	-0.06	0.20	-0.60	-0.81	-0.88	0.30	-0.60	-0.74
	p	0.001		0.001	0.41	0.006	0.001	0.001	0.001	0.001	0.001	0.001
RDW	r	0.44	-0.48	1	0.25	-0.09	0.58	0.53	0.56	-0.19	0.56	0.61
	p	0.001	0.001		0.001	0.205	0.001	0.001	0.001	0.009	0.001	0.001
PLT	r	0.040	-0.061	0.252	1	-0.409	0.257	0.224	0.458	-0.395	0.186	0.227
	p	0.594	0.413	0.001		0.001	0.001	0.002	0.001	0.001	0.014	0.002
MPV	r	-0.099	0.205	-0.095	-0.409	1	-0.189	-0.254	-0.342	0.919	-0.163	-0.200
	p	0.188	0.006	0.205	0.001		0.013	0.001	0.001	0.001	0.033	0.008
CRP	r	0.42	-0.60	0.58	0.25	-0.18	1	0.72	0.65	-0.29	0.95	0.96
	p	0.001	0.001	0.001	0.001	0.013		0.001	0.001	0.001	0.001	0.001
NLR	r	0.33	-0.81	0.53	0.22	-0.25	0.72	1	0.8	-0.3	0.58	0.8
	p	0.001	0.001	0.001	0.002	0.001	0.001		0.001	0.001	0.001	0.001
PLR	r	0.36	-0.88	0.56	0.45	-0.34	0.65	0.8	1	-0.42	0.62	0.76
	p	0.001	0.001	0.001	0.001	0.001	0.001	0.001		0.001	0.001	0.001
PDW	r	-0.13	0.3	-0.19	-0.39	0.9	-0.29	-0.3	-0.4	1	-0.29	-0.31
	p	0.065	0.001	0.009	0.001	0.001	0.001	0.001	0.001		0.001	0.001
CNR	r	0.41	-0.6	0.56	0.18	-0.16	0.95	0.58	0.62	-0.29	1	0.9
	p	0.001	0.000	0.001	0.014	0.033	0.001	0.001	0.001	0.001		0.001
CLR	r	0.44	-0.74	0.61	0.22	-0.2	0.96	0.8	0.76	-0.3	0.93	1
	p	0.001	0.001	0.001	0.002	0.008	0.001	0.001	0.001	0.001	0.001	

Lymph: lymphocyte, RDW: red blood cell distribution width, PLT: platelet, MPV: mean platelet volume, CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, PDW: platelet distribution width, CNR: CRP-neutrophil ratio, CLR: CRP-lymphocyte ratio.

(*Table 2*). The correlation analysis was carried out to explore the correlation between laboratory parameters. A positive correlation was observed between age and RDW, CNR, CLR, RDW and PLR, MPV and PDW, CRP, and CLR. In contrast, a negative correlation was detected between age and lymphocyte levels, lymphocyte and RDW, NLR, and CLR (*Table 3*).

Discussion

Despite the developing science, there are still no tests that make a rapid diagnosis of TB at the first admission. Hemogram parameters are inexpensive, easily accessible, and have fast results. RDW is the variation coefficient which is a simple test with low cost. Previously high levels of RDW have been associated with the severity and prognosis of community-acquired pneumonia.[4]

In a study, Henry et al. found a progressive increase of RDW with advancing COVID-19 severity.[5] But data about TB is minimal. In the present study, the TB group had higher RDW levels with an AUC of 0.93 alongside 86% sensitivity and 85% specificities. RDW levels had a positive correlation with CRP levels. High RDW values may be associated with infection and inflammation derived from *Mycobacterium tuberculosis*. In light of the present study results, RDW might be a valuable parameter in predicting pulmonary TB.

Researchers have investigated the usefulness of some ratios in the diagnosis and prognosis of many inflammatory conditions in recent years. These are neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratio. The NLR is easily calculated from the WBC of routine complete blood count, not introducing additional cost or workload to the laboratory or the clinician. In the pandemic of our time, high NLR was reported in patients who tested positive for SARS-CoV-2 compared to controls.[6] Iliaz et al.[7] have demonstrated NLR of patients with TB was higher than those with sarcoidosis. High levels of NLR helped diagnose TB among HIV-infected individuals.[8] In the present study, NLR levels were higher in the TB group with an AUC of 0.88 (79% sensitivity and 78% specificities), and also had a positive correlation with RDW and a strongly negative correlation with lymphocyte levels. PLR was reported to help identify TB infection in chronic obstructive pulmonary disease patients and predict sepsis mortality.[9,10] According to the results of the present study, patients with pulmonary TB had a higher PLR than controls. AUC was 0.89 with an 82% sensitivity and specificity. PLR was positively correlated with CRP (r=0.65) and negatively with lymphocyte levels (r=–0.88).

CRP is a biomarker that increases in many inflammatory and infectious conditions. High levels have been associated with a need for mechanical ventilation and a poor prognosis in patients with COVID-19.[11] Serum CRP levels are reported to be high in the human immunodeficiency virus (HIV) infected individuals.[12] As CRP is elevated in many other inflammatory and infectious diseases, it is not specific for diagnosing TB. In this study, we hypothesized that the ratio of this vital marker to neutrophil and lymphocyte values might guide the diagnosis of TB. When the results were analyzed, it was found that CNR and CLR were both significantly higher in the TB group. On ROC analysis CNR and CLR had AUC of 0.95 and 0.96, respectively (both 88% sensitivity and 87% specificities). To our knowledge, no previous studies investigated the diagnostic value of NLR, PLR, CNR, and CLR in pre-TB healthy individuals. The results of our study suggest that these parameters, which are inexpensive, easily accessible, and result quickly, may guide the diagnosis of TB.

After the pandemic of COVID-19, investigations on monocyte cells increased, and a preeminent role for monocyte-macrophage activation in the development of immunopathology of COVID-19 patients was reported.[13] Other studies pointed to morphological and inflammation-related phenotypic changes in peripheral blood monocytes in patients with COVID-19.[14] In the present study, monocyte levels were higher in the TB group. Kos et al.[15] reported a reduced rate of activated monocytes in a study mainly observed in patients with severe COVID-19. TB and COVID-19 may affect the lungs, but they are distinct diseases and may affect cells differently. The present study investigated if LMR could help physicians diagnose previously healthy patients with pulmonary TB. According to the current study results, LMR remained lower in the TB group and had an AUC of 0.87 (80% sensitivity and 79% specificity).

Studies have shown that platelets have essential roles in the immune system.[16] But there are few studies about changes in platelet levels and platelet indices, including MPV and PDW in pulmonary TB. MPV is a helpful index of platelet activation, which has been reported to be a marker to determine the disease activity in TB patients.[17] In the present study, PDW and MPV levels remained lower in the TB group. Xu et al.[18] have demonstrated that MPV might be a good clinical laboratory marker in distinguishing patients with TB and diabetes mellitus (DM) from those without DM. PDW is a direct measure of the variation of platelet size and a marker of platelet activation, which may be affected in many inflammatory and infectious conditions. In the present study, platelet levels of patients with TB were significantly higher, suggesting that thrombocytes may have a role in the fight against TB.

Limitations

This study has limitations since we included healthy individuals in both groups; this study does not provide information about TB patients with comorbid diseases. The present study investigated the diagnostic value of the parameters mentioned above and did not provide post-treatment status or prognosis information.

Conclusions

In conclusion, in those patients suspicious of pulmonary TB, higher CRP, PLR, CNR, and CLR levels, whereas low PDW, LMR, LER, and PNR may predict the diagnosis of pulmonary TB.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical Approval

For this study, approval was obtained local ethics committee.

Authors' Contribution

Study Conception: IK; Literature Review: IK, YTG; Data Collection and/or Processing: IK; Statistical Analysis and/or Data Interpretation: IK, YTG; Manuscript preparing: IK, YTG.

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Case Report

Rosai-Dorfman Disease and Concomitant Hodgkin Lymphoma and Tuberculosis Activation: A Rare Case Report

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ABSTRACT

Rosai-Dorfman disease (RDD) is a rare, benign disease with extensive lymphadenopathy. In this case, an 81-year-old gentleman with previous pulmonary tuberculosis presented painless cervical lymphadenopathy associated with generalized weakness, loss of appetite, and cough. The causes of cervical lymphadenopathy in the elderly are comprehensive; thorough history, examination, and appropriate investigations are vital in diagnosing diseases. A lymph node biopsy is recommended if blood investigations and imaging are inconclusive. He was later diagnosed with RDD associated with Hodgkin's lymphoma, and dexamethasone treatment was initiated. Concomitant diagnoses are rare but should not be disregarded. This case report is a reminder that RDD remains a differential diagnosis of cervical lymphadenopathy. Regular monitoring is required as immune dysregulation from the treatment of RDD may exacerbate quiescently treated pulmonary tuberculosis.

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Keywords: *Lymphadenopathy, Rosai-Dorfman disease, sinus histiocytosis.*

Introduction

Rosai-Dorfman Disease (RDD) is an uncommon disorder first described by Destombes in 1965. Rosai and Dorfman published more data on RDD in 1972.[1] The condition presents commonly in males in the first and second decades, although any age could be affected. RDD is also known as sinus histiocytosis with massive lymphadenopathy (SHML), characterized by benign proliferation of histiocytes within lymph node sinuses and lymphatics in extranodal sites. We presented a unique case of cervical lymphadenopathy in the elderly, later diagnosed as RDD associated with Hodgkin's lymphoma below. This case report serves as a reminder that RDD remains a differential diagnosis of cervical lymphadenopathy.

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Case Report

An 81-year-old male patient with a background history of dementia, seizures, and previously treated pulmonary tuberculosis, presented to the hospital with a week of generalized body weakness and loss of appetite. He denied any fever but complained of a cough with white sputum. His pre-admission medications include levetiracetam 500 mg BD, rivastigmine 1.5 mg BD, and amlodipine 5 mg OD. On examination, he had a palpable pea-sized, painless, enlarged left submandibular lymph nodes and inguinal lymph nodes bilaterally. His abdomen was soft and non-tender, but hepatomegaly was present. Other examination findings were unremarkable.

Significant laboratory results included a raised c reactive protein of 5.0 mg/dL and raised erythrocyte sediment rate of 113 mm/h. Bicytopenia with white blood cells of 3.6 x 10^9/L and haemoglobin of 10.3 g/dL. Total protein was raised at 122 g/L. Sodium was 123 mmol/L; his urea, electrolytes, and liver function tests were unremarkable. A neck ultrasound scan showed multiple enlarged lymph nodes in bilateral submandibular, anterior and posterior cervical triangles. Computed tomography (CT) thorax, abdomen and pelvis was done and showed multiple nodes measuring 5.7 mm to 9.2 mm in right paratracheal and subcarinal regions, 7.0 mm to 28.4 mm in both axillae, abdominopelvic adenopathies noted at left paraaortic (largest measuring 2.1x1.5 cm), interaortocaval (1.4x1 cm), retrocaval (1.7x1 cm), portal (2.6x2.1 cm) (*Figure 1*), coeliac (2.7x1.9 cm) (*Figure 1*), mesenteric (3.2x1.8 cm), bilateral external iliac (largest 2.3x1.5 cm on right and 1.5x1.4 cm on left) (*Figure 2*), bilateral inguinal (largest 2.3x1.4 cm on right and 2.2x1.4 cm on left) (*Figure 3*).

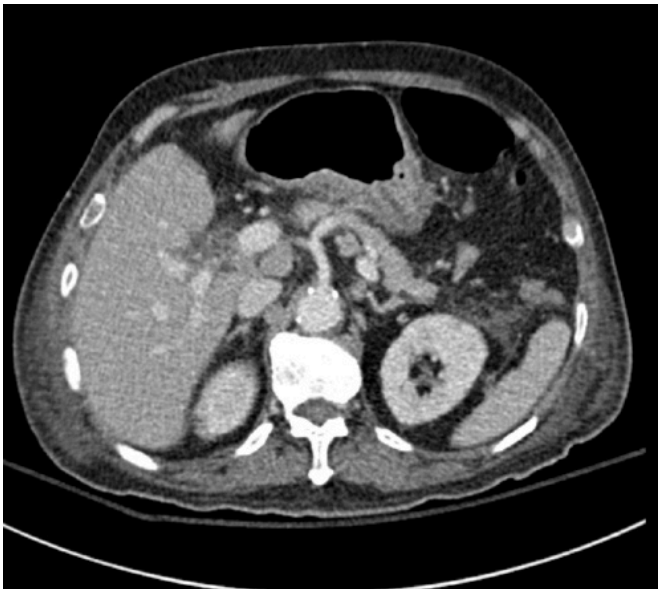

Figure 1. Radiological images

Further work-up for possible diagnoses and immunocompromised status were done, which include human immunodeficiency virus (HIV) serology, hepatitis B and C serologies, triple tuberculosis acid-fast bacteria (AFB) smear, antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) for autoimmune screening, and HbA1c for diabetes mellitus; which were all negative. His total protein was raised with anaemia, and work-up for multiple myeloma was done; lactate dehydrogenase was mildly increased at 267 U/L, but urine Bence-Jones protein and serum paraprotein at electrophoresis were both not detected. An excision biopsy of the right neck node was then performed, and the specimen was sent for a frozen section, showing dilated sinuses filled with histiocytes and lymphocytes. Histiocytes showed emperipolesis (*Figure 4*). The surrounding tissue showed a nodular arrangement with lymphocytic, plasma cell, and Reed-Sternberg (R-S) like cell infiltrate along with a few eosinophils (*Figure 5*). The histiocytes within the sinuses showed a positive reaction with S-100 (*Figure 6*), while the R-S-like cells showed a positive reaction with CD30 and CD15. The overall picture was RDD, associated with Hodgkin's lymphoma. Since Mr N was not a good candidate for chemotherapy, oral dexamethasone 4 mg BD was started with allopurinol for the risk of tumour lysis syndrome after steroid treatment.

He was re-admitted to the hospital three weeks later as his sputum cultures grew *Mycobacterium tuberculosis complex*. Two months of intensive therapy consisting of isoniazid, rifampicin, ethambutol and pyridoxine were initiated, followed by seven months of isoniazid and rifampicin. His dexamethasone dose was subsequently reduced to 2 mg BD.

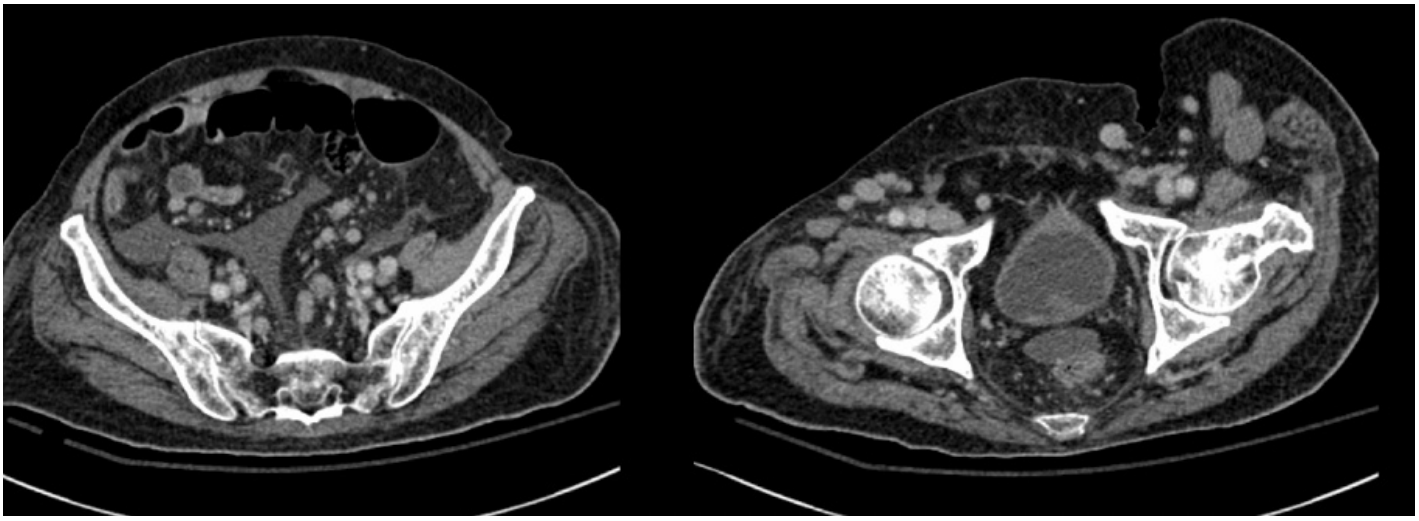

Figure 2 and 3. Radiological images

Discussion

Patients with RDD usually present with nonspecific findings such as low-grade fever, cervical lymphadenopathy, normochromic anaemia, elevated ESR, leukocytosis (mainly neutrophilia), and hyperglobulinemia.[1] These were consistent with his initial presentation, although he did not report any fever and had leukopenia. Cervical lymphadenopathy in the elderly is a common presenting complaint but could be caused by a vast array of diseases, including bacterial infections, e.g. cat scratch disease; viral infections, e.g. hepatitis B, HIV; *Mycobacterium tuberculosis*; cancers, e.g. leukaemia and lymphoma, lymphoproliferative disorders, e.g. RDD, hemophagocytic lymphohistiocytosis; autoimmune disorders, e.g. systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, or medications, e.g. atenolol, captopril, carbamazepine, lamotrigine, and phenytoin.[2] Most patients with RDD present with chronic bilateral, painless cervical lymphadenopathy. Notably, if only one lymph node group was enlarged, this was commonly the submandibular region,[1,3] similar to our case. Our case also had inguinal and axillary lymph nodes, usually less prominent than cervical involvement in RDD.

Evaluation of lymphadenopathy causes should be based on history and physical findings, followed by routine blood investigations, HIV testing, and chest X-ray. If unremarkable, further assessments such as tuberculosis, ANA, syphilis, and heterophile tests should be considered.[2,4] He had most of the research done, except for syphilis and the heterophile test. None of his drugs was found to cause lymphadenopathy. For an uncertain diagnosis, a lymph node biopsy was recommended first.

In SMHL, histological findings of lymph nodes include capsular and pericapsular fibrosis, with numerous histiocytes containing lymphocytes in their cytoplasm (emperipolesis). Emperipolesis, the presence of an intact cell within the cytoplasm of another cell, is of great diagnostic significance for RDD, despite not being pathognomonic. In the initial phase of the disease, prominent dilatation of sinuses was reported. Both emperipolesis and dilated sinuses were seen in our case too. These sinuses would later be occupied by mainly histiocytes and other cells such as lymphocytes, plasma cells and occasional neutrophils, resulting in effacement of nodal structure.[1,3,5] Histiocytes characteristically demonstrate reactivity to CD11c, CD14, CD33, CD68 antigens and S100 protein. They are usually CD1 negative. Differential diagnoses for SHML include reactive sinus histiocytosis, Langerhans cell histiocytosis, malignant histiocytosis, hemophagocytic syndrome, tuberculosis, and lymphoma. Each of the differentials has characteristics to distinguish them from SHML. For instance, reactive sinus histiocytosis expresses CD68 but lacks S100 and CD1a. On the contrary, Langerhans cells

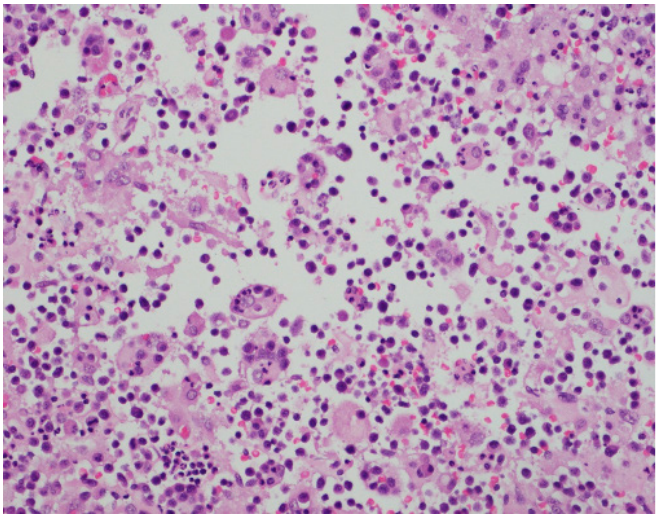

Figure 4

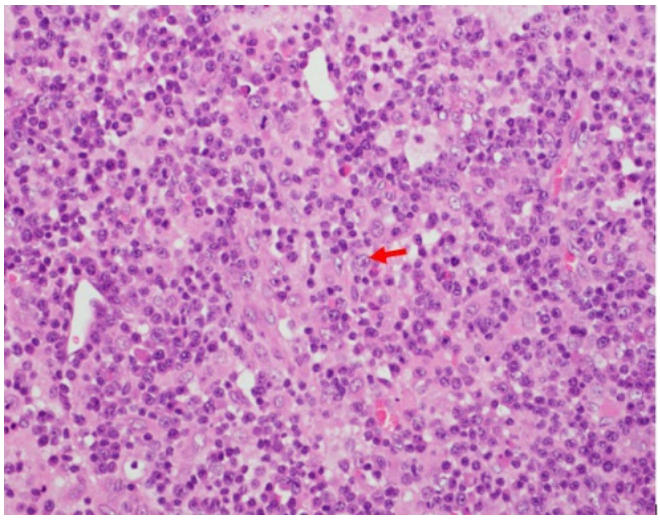

Figure 5

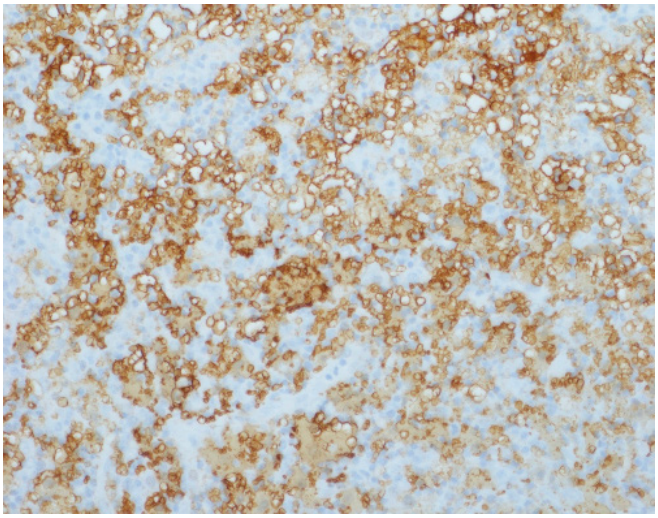

Figure 6

are reactive to S100 and CD1a. They also show Birbeck's granules on electron microscopy. Malignant histiocytosis demonstrates prominent cellular atypia and mitosis, which is rare in SHML. Hemophagocytic syndrome is associated with pancytopenia and hepatosplenomegaly, which are generally absent in SHML. SHML can be differentiated from tuberculous lymphadenitis as tuberculosis would show epithelioid cell granuloma with or without caseous necrosis. Lastly, non-Hodgkin's lymphoma consists of lymphoid cells that show positivity for CD3 (T-cell), CD20 (B-cell), or bcl-2 (anti-apoptotic) marker, while Hodgkin lymphoma contains RS cells reactive to CD15, CD30 or CD20; these are usually negative in SHML.[3,5]

His biopsy showed a positive reaction to S-100, CD30 and CD15, which concluded he has a dual pathology of RDD with Hodgkin's lymphoma and thus warranted treatment as recommended by haematology colleagues. A literature review done by Edelman et al.[6] showed 25 cases of RDD associated with Hodgkin and non-Hodgkin lymphoma, in which 70% of the dual pathologies were diagnosed simultaneously. Sporadic RDD is the most common form of RDD, which include classic nodal, extranodal, neoplastic related, and immune disease-related RDD. Classic RDD is the most prevalent type affecting children and young adults in the first two decades. Extranodal disease is more common in older patients and involves skin, nasal cavity, bone, orbital tissue, and central nervous system. As RDD can co-exist with neoplasia, pathological findings of RDD should be present in more than 10% of the tissue to establish neoplasia-associated RDD.[7]

In addition, our case was later diagnosed with tuberculosis through sputum cultures and received treatment. His tuberculosis was likely a reactivation of the disease, as he was treated for it many years back. The Hodgkin's lymphoma and dexamethasone may suppress the cell-mediated response, which facilitated the mycobacterial infection.[8,9] There has also been documented literature on tuberculosis preceding the onset of RDD with no known causative link; however, this could be attributed to the high prevalence rate in Asian countries.[10] Several reports recorded patients

presenting with symptoms mimicking tuberculosis but were later diagnosed as RDD.[11-13] A study done in Pakistan also showed that the most common causes of lymphadenopathy include tuberculosis (70.45%), followed by reactive lymphadenitis (13.63%), metastases (11.36%), lymphoma (4.54%), and chronic nonspecific lymphadenitis (2.27%).[4] There is potential for misdiagnosis as RDD, tuberculosis and Hodgkin's lymphoma as they present similar signs and symptoms such as fever, cough, loss of appetite, and adenopathy.[8] It is essential to diagnose patients to ensure they receive the proper treatment correctly.

Lymphadenopathy in RDD will eventually regress without treatment, despite waxing and waning over months to years. Therapy with corticosteroids usually shows an excellent clinical response. Other treatments include alkylating agents, vinca alkaloids, and low-dose interferon. Radiation therapy and surgical treatment can be used for life-threatening obstructions due to pressure exerted by lymph nodes. Patients generally have a good prognosis unless they have associated immunological pathologies, extranodal involvement, especially of kidney and liver, or younger age group.[3,5] Long-term follow-up is essential to monitor the course of the disease and reactivation of tuberculosis

Conclusions

RDD is usually diagnosed clinically and confirmed by laboratory investigations. Albeit rare, it should remain a differential diagnosis for cervical lymphadenopathy. Patients may present with concomitant pathologies; hence, it is crucial to do a full work-up for patients to ensure proper treatments can be delivered. Regular surveillance for tuberculosis reactivation should always be considered, especially in highly endemic countries.

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Conflict of Interests

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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Case Report

HIV-associated Opportunistic Pneumonia Case Mimicking COVID-19 Pneumonia

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ABSTRACT

Cytomegalovirus (CMV) pneumonia is a rare opportunistic infection in the progression of human immunodeficiency virus (HIV) infection. Also, COVID-19 has been named a pandemic since the beginning of 2020. During this period, physicians were exposed to many COVID-19 cases, and it was challenged to consider different diagnoses in patients who applied to the emergency room with lung complaints and bilateral pneumonia. Here we reported a 30-year-old man diagnosed with HIV-associated opportunistic CMV pneumonia mimicking COVID-19. The diagnosis of CMV pneumonia was obtained through consistent clinical, radiological, microbiological and cytologic examinations. The patient made a complete clinical recovery after being initialized on anti-CMV treatment.

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Keywords: *COVID-19, CMV, HIV, opportunistic infection.*

Introduction

COVID-19, an accepted pandemic from March 2020 to date, infected 456 million people and led to the extinction of six million.[1] Typical symptom are fever, chill, cough and dyspnea in COVID-19. Even if some cases have mild illnesses, some patients have a severe acute respiratory deficiency. In diagnosing SARS-CoV-2, PCR, serological tests and thoracic computed tomography (CT) findings are used. Thoracic CT findings of COVID-19 pneumonia have been reported in a wide range of different recent studies. However, thoracic CT findings in all studies are bilateral, subpleural, and peripheral ground-glass opacities, among the early-stage findings of the disease. Ground glass densities are the earliest findings seen in 34-98% of patients in various studies.[2,3]

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Human immunodeficiency virus (HIV)-infected patients' number is approximately 34 million in 2020, according to WHO. Also, 680 thousand people died of HIV-related causes in 2020. Opportunistic pneumonia is the major cause of morbidity and mortality among the pulmonary complications associated with HIV infection. HIV-associated opportunistic pneumonia includes bacterial, mycobacterial, fungal, viral, and parasitic pneumonia. Bacterial pneumonia is frequently seen among opportunistic pneumonia in the United States and Europe. On the other hand, tuberculosis is the predominant pathogen in Africa. Pneumocystis pneumonia (PCP) has lowered associated with the combination of antiretroviral therapy and prophylaxis. Nonetheless, PCP continues to occur in people unaware of their HIV infection, those who fail to access medical care, and those who fail to adhere to antiretroviral therapy or prophylaxis. Even though pneumonia caused by cytomegalovirus (CMV), *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum,* and *Toxoplasma gondii* are seen less frequently, they cause disseminated disease in the pulmonary system and are related to the higher mortality rate.[4] In HIV infection, clinical and radiographic findings of HIV-related opportunistic pneumonia may overlap, and more than one concurrent pneumonia may be seen in these individuals.[5] This situation makes the diagnosis of CMV pneumonia difficult.[6] We had reached the diagnosis of CMV opportunistic pneumonia for this process. The importance of differential diagnosis of likely opportunistic pneumonia during the pandemic was emphasized.

Case Report

A 30-year-old single Turkish male patient had applied to the COVID-19 unit of the emergency room with symptoms of dyspnea and cough for a week. He seemed tachypneic and uncomfortable. In his first examination, his blood pressure was 110/70 mmHg, his pulse was 102 beats/minute, and his temperature was 36.6 °C. His oxygen saturation was 87% in the room air. In blood tests, only CRP was 22 mg/L (range: 0-10). Complete blood count and biochemistry tests were within normal ranges *(Table 1)*. There was no obvious feature in the chest X-ray. Thoracic CT demonstrated bilateral peripheral ground glass lesions (*Figure 1*). The findings were consistent with viral pneumonia.

Table 1. Biochemistry parameters

Parameters	Results (Day 1)	Results (Day 10)	Results (First Discharge)	Results (Second Arrival)	Range
Urea (mg/dL)	29	20	16	23	16-48
Creatinine (mg/dL)	0.9	0.83	0.85	0.89	0.7-1.2
Sodium (mmol/L)	139	145	142	138	135-145
Potassium (mmol/L)	4.47	5.03	4.95	4.57	3.5-5.1
CRP (mg/L)	22.11	10.03	1.75	8.98	0-10
Ferritin (ng/mL)	588	591	539	349	21-274
D-dimer (mg/L)	0.66	0.73	0.44	-	0-0.5
AST (U/L)	28	32	36	12	2-40
ALT (U/L)	34	32	42	16	2-41
Leukocyte (10^3/mL)	5.54	4.08	3.71	5.54	
Hemoglobin (g/dL)	12	11.07	12.21	12.01	
Platelet (10^3/mL)	323	384	341	323	

CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

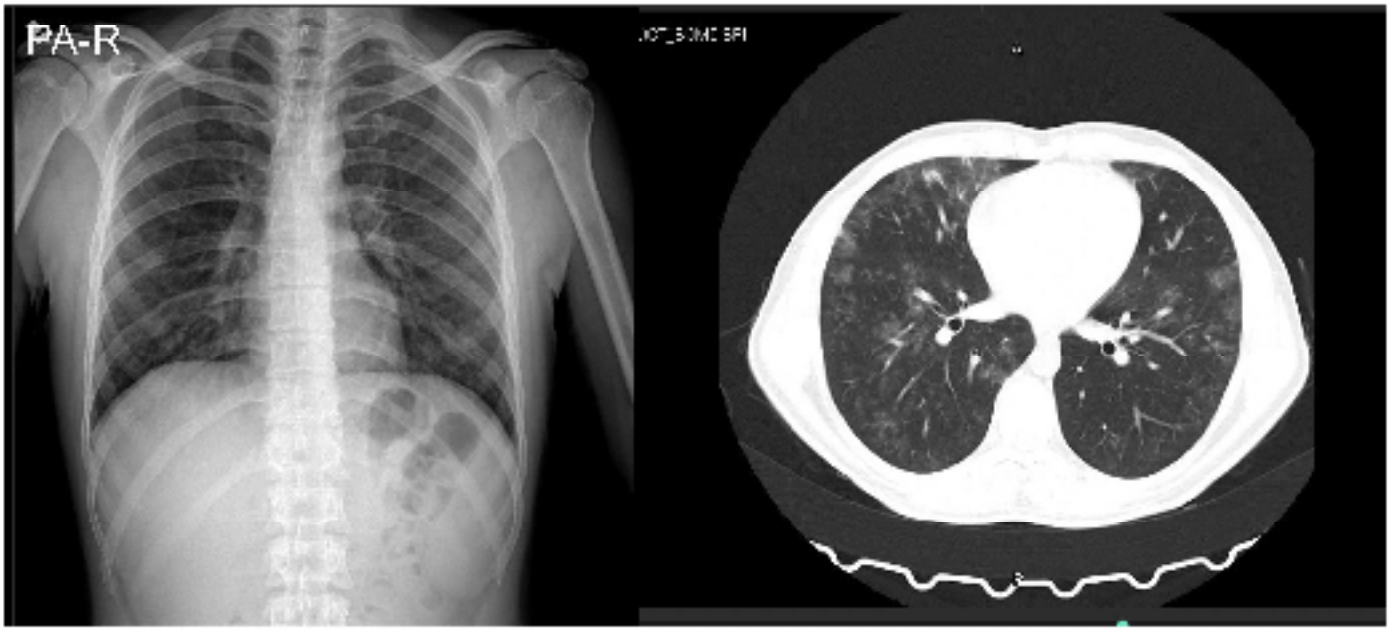

Figure 1. Radiological images

The patient was first diagnosed as having COVID-19 pneumonia due to the pandemic. Combined PCR brush sampling was taken from the oropharynx and nasopharynx for SARS-CoV-2. Then, hydroxychloroquine 400 mg/day and azithromycin 500 mg/day treatments were started for suspected COVID-19 pneumonia. On the second day, the SARS-CoV-2 PCR test resulted as negative. Thus a second PCR test was examined for the patient. At that time, the patient expressed flu-like symptoms; therefore, oseltamivir 150 mg/day was added to the treatment protocol. After the SARS-CoV-2 PCR test was negative on the fourth day, the coronavirus antibody test (IgM+IgG) was performed and it was negative. On the 10th day of hydroxychloroquine treatment, when the CRP value was measured at 25 mg/L, azithromycin was discontinued and moxifloxacin 400 mg/day i.v. was started. Meanwhile, the patient's oxygen saturation was measured at nearly 90% in the room air. We had expected to see decreased CRP and increased oxygen saturation; however, the patient's laboratory findings and physical examination were the same as at the beginning of the treatment period. Although the patient said he felt better, no improvement was observed in the control thorax CT findings. Since our hospital has no microbiology laboratory, we could not perform bacteriological or viral serological tests for non-COVID-19 pneumonia causes. The patient's cardiological examination was unremarkable. Electrocardiogram was in sinus rhythm, and there were no pathological changes. The patient had no history of drugs, alcohol or smoking. When the patient's oxygen saturation lowered to 86-88% in room air, we gave oxygen support with a nasal cannula. Hydroxychloroquine treatment was discontinued. We added favipiravir at a loading dose of 3,200 mg/day and a maintenance dose of 1,200 mg/day to the moxifloxacin treatment. Five days later, the patient's oxygen saturation increased to 94%, dyspnea regressed, and CRP decreased to 1.75 mg/L (*Figure 2*). Afterwards, respiratory symptoms improved and all medications were discontinued on the 15th day, and the patient was discharged.

Fifteen days later, he complained of a dry cough and shortness of breath at the follow-up examination. His vital signs were stable (blood pressure 120/80 mmHg, heart rate 85 beats/minute, body temperature 37 °C). On respiratory system auscultation, rales were found in his lungs. There was no abnormal finding in other system examinations. CRP level was increased. Previous findings on repeated thorax CT persisted. The patient said that he had been treated for oral candidiasis two months ago and that these lesions had recurred. Meanwhile, the patient confessed that he had been using drugs six months ago and had sexual contact with women with suspected HIV, expressing that he could not tell because he hesitated. The anti-HIV test was positive. Given

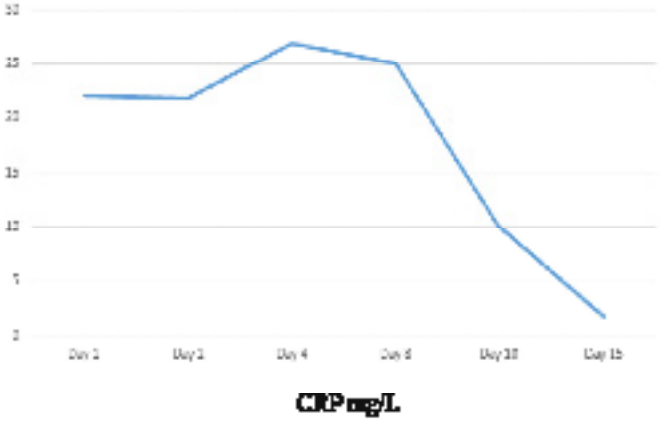

Figure 2. CRP progression

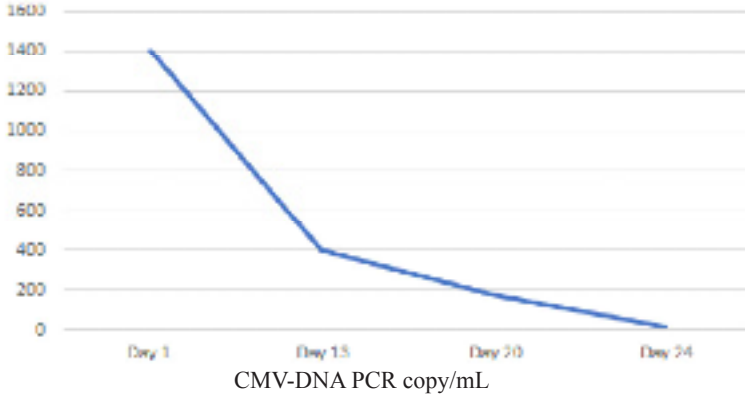

Figure 3. CMV-DNA PCR progression in treatment

the possibility of opportunistic pneumonia in HIV infection, the patient underwent a series of tests in the infectious diseases department. The initial HIV-RNA (PCR) result was 959,336 IU/mL. Serological tests (Toxoplasma IgG, CMV IgG, syphilis IHA and hepatitis) were performed. Sputum culture and microscopy were examined, and normal respiratory tract flora was determined.

In addition, hepatitis markers and syphilis IHA, and toxoplasma IgG-IgM were negative. However, the CMV IgG test was positive. After this positive result, the CMV PCR test was 1,405 copies/mL. The CD4 percentage was 5%, and the absolute CD4 count was 49 cells/µl. Therefore, with the diagnosis of HIV-associated CMV pneumonia, the patient was given antiretroviral therapy and ganciclovir 2x5 mg/kg i.v. started. CMV-DNA results were shown in Figure 3. After starting anti-CMV treatment, the patient's clinical findings improved completely. Thus, he was discharged to come back for control.

Discussion

Burkitt's lymphoma is one of the most ag HIV is a chronic infectious disease that is widespread worldwide and characterized by the suppression of the immune system. The world has been suffering from the 'COVID-19' pandemic since 2020. Because they encountered many COVID-19 patients and almost all pneumonia cases were seen as COVID-19, physicians could not easily consider other pneumonia causes in the differential diagnosis. We started treatment in our patient with the diagnosis of COVID-19 pneumonia, and we insisted on this diagnosis. Unfortunately, the case did not contain any clues for differential diagnosis and withheld critical medical information from us. Even if the patient did not have a coronavirus infection, he responded well to our medical treatment. While coronavirus is an RNA virus, CMV is a DNA virus. Therefore, the mechanisms of medical agents have different stages and targets. We did not consider any effect of antiviral agents such as oseltamivir and favipiravir in this patient on CMV. The patient might have had a secondary bacterial infection at the basement of the CMV infection. At the beginning of the treatment process, we tried to cure the patient with antiviral agents, and no response was obtained in the first week. CRP levels were still high. After adding moxifloxacin, CRP levels dropped, and the patient felt better. This situation indicates that the patient may have some overlapping atypical pneumonia. Such pneumonia can be treated with quinolone antibiotics. It can be thought that the patient has been infected with HIV and has transformed into AIDS. Following these steps, he became infected with CMV, and immunosuppression occurred. Thus, a suitable environment for secondary bacterial infections was created. We treated the secondary bacterial infection with quinolones. In principle, a blood culture could be done, and the microbiological organism could be identified. We selected empiric therapy for pneumonia because he responded well to our treatment.

Conclusions

Eventually, CMV infection is a viral infection that can cause severe clinical events in immunocompromised individuals. Initial suspicion is required for early diagnosis and appropriate treatment in immunocompromised patients. In addition, it should not be forgotten that immunosuppressive conditions such as HIV should be investigated in patients presenting with opportunistic infections.

Conflict of Interests

Authors declare that there is no conflict of interest with regard to this manuscript.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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Teaching Case Series

Challenges in the Management of the Patients With COVID-19 Infected Cushing's Syndrome: Two Cases and Literature Review

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ABSTRACT

Coronavirus disease-2019 (COVID-19) has become a serious health problem in Turkey and the world. The diagnosis stage of many chronic diseases, the treatment process and the status of being affected by COVID-19 have become the focus of attention in the medical community during the pandemic, which has been continuing for nine months. We will discuss the course of COVID-19 infection over a 32-year-old and 76-year-old female patient with Cushing syndrome who applied to our clinic as a tertiary referral centre.

HIGHLIGHTS

In the PUBMED database, we searched the keywords of COVID-19 and Cushing's syndrome, hypercortisolism. We discussed Cushing's disease in the COVID period over our cases and the publications that have the quality of recommendation.

We recommend being more careful when evaluating this group of patients who are considered at high risk for COVID infection, with comorbid diseases such as hypertension and diabetes-referring to relevant centres in case of high suspicion of Cushing syndrome, controlling hypercortisolism during the epidemic process and keeping patients away from hospital environments as much as possible.

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Introduction

COVID-19 infection, which started in China and affected the whole world, is a major pandemic that has become a global problem. In addition to more than 4,000,000 deaths since the disease started in December 2019, the increasing prevalence of COVID-19 in endocrine disorders constitutes a severe health problem.[1]

Since it is a newly identified virus, the effect of the disease on the endocrine system is still unknown. Although there are not many cases in the literature, the possible impacts of COVID-19 on the endocrine system are predicted as postviral hypocortisolemia, hypothyroidism, hypokalemia, hypernatremia, hyperprolactinemia, hypogonadism, hypo-hyperglycemia.[2] Cushing syndrome (CS) is one of the essential endocrine diseases. The presence of long-term and high concentrations of glucocorticoids causes a decrease in B lymphocytes, T lymphocytes and helper T cells. This therapy affects the natural and adaptive immune response to infections.[3] Increased incidence of opportunistic infection, frequently encountered in immunosuppression due to CS, creates a particularly severe bacterial and fungal infection.[4] These factors may cause severe COVID-19-related pneumonia in CS.[2] On the other hand, comorbidities such as hypertension, diabetes mellitus (DM), and obesity are common in CS. These comorbidities may contribute to a more severe course of COVID-19.[2,5,6] However, as far as we know, there is not enough data about managing patients with CS infected with COVID-19. Here, we presented two patients with mild and severe forms of CS infected with COVID-19 and reviewed the available literature.

Case Report 1

A 76-year-old female patient presented with complaints of weakness, fatigue, hair loss, easy bruising and headache for two years. She had been diagnosed with hypertension (metoprolol 50 mg/day) and hypothyroidism (levothyroxine 50 mcg/day) 5 years prior. The patient's serum potassium level was 2.9 mmol/L (3.5-5.19 mmol/L), morning and night cortisol levels were 27.7 mcg/dL and 24.2 mcg/dL, respectively. Plasma ACTH level was 184 pg/mL, 24-hour free urine cortisol (UFC) level was 1657.5 mcg/24 h (reference range: 58-405 mcg/24 h). Salivary cortisol level was not measured due to possible COVID-19 positivity. After two days of the 2 mg dexamethasone suppression test, her cortisol level was 6.42 mcg/dL. Pituitary magnetic resonance imaging (MRI) demonstrated a 15x20 mm mass in the pituitary gland. Visual field examination of the patient was normal.

We needed a differential diagnosis so that 76 years old female patient was presented with hypopotassemia suggesting ectopic hypercortisolemia and pituitary adenomas caused by CS were generally small. Therefore, it was planned to be hospitalized the patient. Due to the COVID-19 pandemic, nasal swabs were taken on the first day of the patient's hospitalization in line with the management's decision. SARS-CoV2 PCR result was positive for this patient without any symptoms. After the positive result of the COVID-19 test, the questions written below were waiting for answers:

1. One can continue surveillance of a CS patient with COVID-19 in the hospital or not?
2. One can prescribe antiviral for COVID-19 or not?
3. One can prescribe medication for CS or not?

The first challenge: "Can the surveillance of a CS patient with COVID-19 be continued in the hospital or not?

According to the national COVID-19 guideline published by the Ministry of Health in Turkey, cases with respiratory distress, shortness of breath, and feeding difficulties are evaluated as severe pneumonia and treated in the hospital. Home monitoring is recommended for those with mild to moderate pneumonia, uncomplicated, and asymptomatic patients. Hydroxychloroquine and/or favipiravir treatment can be planned in this group and monitored at home.[7] Being elderly (≥65 years), cancer, chronic obstructive pulmonary disease, cardiovascular disease, hypertension, diabetes mellitus (DM), obesity, and smoking are the risk factors for COVID-19 infection to be more severe. These patients should be followed more closely at home.[7]

In our case, no pneumonia was detected in thorax high-resolution computerized tomography

(HRCT). The patient did not show the symptoms such as fever, cough, loss of smell or taste, etc. and did not develop tachypnea and hypoxia during the three-day hospital follow-up. For this reason, there was no indication for hospitalization of the patient.

The patient's pituitary mass did not compress the optic chiasm, and the visual field examination was normal. Therefore, there was no urgent surgery indication for a pituitary mass. Her blood pressure was regulated by metoprolol. She had no diabetes. Her hypokalemia was held with oral potassium tablets and a potassium-rich diet. Despite hypercortisolemia, the patient was clinically stable in terms of CS. Hypercortisolemia-associated co-morbidities like DM and hypertension should be actively managed, as they are significant risk factors for adverse outcomes from COVID-19.[2,5] It was inappropriate to follow up in the endocrine clinic as isolation could not be provided. The 18F-Fluorodeoxyglucose Positron Emission Tomography (18F-FDG PET) scan and inferior petrosal sinus sampling (IPSS) examinations were planned for the differential diagnosis of hypercortisolemia. Still, further tests could not be performed during the COVID-19 infection. As a result, the inpatient investigations were delayed to protect the healthcare staff and other patients and prevent viral spread. We evaluated all factors and discharged the patient to have the active COVID-19 phase isolated at home.

The second challenge: "Can antiviral treatment for COVID-19 be prescribed or not?"

In the national COVID-19 guidelines, it is stated that asymptomatic PCR-positive patients can be given hydroxychloroquine and/or favipiravir. However, there is no clear opinion on the necessity of providing treatment to asymptomatic immunosuppressive patients.[7]

Antiviral treatment and broad-spectrum prophylactic antibiotic treatment are recommended due to the risks of prolonged viral infection and secondary infection, especially in patients with COVID-19 positive CS who are followed up in hospitals.[6] In our case, with the recommendation of the Department of Infections Diseases of our University Hospital, antiviral treatment was not initiated because the patient was asymptomatic, and there was no COVID-19 pneumonia in HRCT. A close follow-up on the phone was planned for the patient regarding symptom monitoring.

Third challenge: "Can medication for CS be prescribed or not?"

Endogenous hypercortisolemia leads to the development of DM, hypertension and obesity and increases the risk of cardiometabolic complications and cardiac failure. DM, hypertension and obesity are the best-known risk factors for the poor prognosis of COVID-19. For this reason, it is thought that COVID-19 may have a worse prognosis in patients with CS.[2,6]

The reason for acute respiratory distress syndrome in critically ill patients infected with COVID-19 is thought to be a severe cytokine storm in the body. These patients respond well to anti-inflammatory and anti-cytokine treatments.[8] It has been reported that cases who received disease-modifying antirheumatic drugs (DMARDs) therapy due to arthritis during the pandemic. There was no change in the risk of COVID-19 in patients using DMARDs compared to the normal population. These patients did not have serious respiratory tract infections and did not need intensive care.[9] In hypercortisolemia, the natural and adaptive immune responses are reduced. The patient's ability to cope with infections is reduced. From a different point of view, it can be speculated that the clinical picture may be milder in CS since the immune response is suppressed, and COVID-19-positive patients with CS might not have severe cytokine storm.[6] From our point of view, it is impossible to comment on this issue since our patient had no severe COVID-19 infection with lung involvement.

A minimum number of laboratory and imaging tests should be planned to prevent COVID-19 transmission in patients presenting with hypercortisolemia during the pandemic. Diagnostic tests of patients with mild hypercortisolemia should be delayed for 3-6 months, and patients should be evaluated by telephone intermittently.[10] After excluding adrenocortical carcinoma and ectopic CS, urgent surgical therapy is no longer needed unless there are severe compressive symptoms, and the operation can be postponed. Supraorbital craniotomy should be performed instead of transsphenoidal surgery to reduce viral spread.[11]

Cortisol-lowering treatments are primarily recommended for controlling hypercortisolemia in patients with CS who were followed up during the COVID-19 period without surgery.[11] It is thought that the treatment will eliminate the immunosuppression developing secondary to hypercortisolemia and reduce the risk of infection with COVID-19. At this stage, ketoconazole, metyrapone, osilodrostat, and mifepristone can be used in COVID-negative CS.[11] There is no clear recommendation for COVID-19-positive CS patients. Ketoconazole treatment can interact with COVID-19 treatment and increase the effect of QT prolongation. Therefore, it is not recommended for use with COVID-19 therapy.[12] COVID-19 infection is more common in male patients and is more severe. This is thought to be due to the increased androgenic effect on TPRSS2 expression in the bronchial epithelium.[13] By a similar mechanism, metyrapone therapy can increase androgenic precursors in the pathway while blocking cortisol synthesis. It is thought that this situation, in which androgenic activity in the body leads to an increase in TMPRSS2 expression in the lung, may cause a poor prognosis in the covid-associated ARDS clinic.[12] Considering this situation, a good clinical evaluation should be made when metyrapone therapy is given to COVID-19-positive CS patients because of its possible effects.

Adrenal insufficiency (AI) may occur in patients taking hypocortisolemic medications for CS. The patient should be informed about the symptoms of AI and have glucocorticoids for possible insufficiency.[10] If AI develops, the risk of being infected with COVID-19 increases, and the prognosis worsen. Therefore, while the pandemic continues, mild hypercortisolism may be preferred to adrenal crisis, especially in the short term.[10] It can be predicted that AI caused by any treatment may have severe effects on the course of COVID-19 infection. As shown in Table 1, there is very little data on cases followed up due to CS in the literature. The first patient was a 55-year-

Table 1. Summary of the previous published cases of CS infected with COVID-19.

Case report	Age/Sex	CS disease activity	Comorbidities	Presenting features	Treatment	Outcome
Serban et al. (2020) [14]	55 F	Remission with hypoadrenalism	End-stage chronic kidney disease, and malnutrition		Continuous positive airway pressure and hydroxychloroquine	Dead after six day of hospitalization
	77 M	Active hypercortisolism (under metyrapone treatment)	Obesity, hypertension, dyslipidemia		No treatment was given	Discharged
Beretta et al. (2020)[15]	67 M	Active disease (under metyrapone, cabergoline, pasireotide treatment)	Diabetes, dyslipidemia, secondary hypothyroidism	Dry cough, low grade fever, and symptoms of adrenal insufficiency	Azithromycin, ceftriaxone, hydroxychloroquine	Discharged
Our current cases	76 F	New diagnoses CS, active disease	Hypertension, primary hypothyroidism, impaired glucose metabolism	Asymptomatic	Low molecular weight heparin treatment	Discharged
	32 F	Newly operated with ectopic CS for lung origin	Hypertension, obesity, impaired glucose metabolism	Fever, cough, COVID-19 pneumonia	Favpiravir, low molecular weight heparin, convalescent plasma treatment	Discharged

CS: Cushing's syndrome, F: female, M: male.

old woman who had already AI secondary to the treatment for CS. Later, she was hospitalized for COVID-19 pneumonia and died six days after hospitalization despite hydrocortisone infusion therapy.[14] Similarly, a 67-year-old male patient had active hypercortisolemia and was under treatment. This patient was hospitalized for AI, possibly due to a COVID-19 infection.[15] These cases indicate that COVID-19 also may cause a worsening or development of AI in patients with CS.

Cushing patients may not show typical COVID-19 symptoms such as cough and fever because they are immunosuppressive. Therefore patients should be monitored for a more specific discomfort, taste/odor.[6] Quick control of current hyperglycemia and hypertension is recommended, as diabetes, hypertension, and obesity are the best-known risk factors for the poor prognosis of COVID-19.[6] Anti-thrombotic therapy with low molecular weight heparin should be given. The possible thromboembolic risks of Cushing's disease are known. The pathway of thromboembolic events and the importance of anticoagulant therapy in the pathogenesis of COVID-19 have been demonstrated.[2,5] It is known that hypercortisolemia causes prolonged viral infections and the development of opportunistic bacterial and fungal infections.[16] Co-trimoxazole is recommended for Pneumocystis pneumonia (PCP) prophylaxis in cases evaluated as severe CS (spot cortisol >37 mcg/dL or plasma ACTH >100 pg/mL).[17]

The SARS-CoV-2 virus enters the cell membrane through the ACE 2 receptor.[18] This results in hypokalemia with the help of increased activity of the renin-angiotensin-aldosterone system (RAAS) system. The activity of SARS-CoV-2 on RAAS in patients with hypokalemia due to Cushing's disease may lead to a deepening of hypokalemia.[2] This point should also be considered in COVID-19-positive patients with CS.

So, how did we manage the case?

Primarily, we thought that there is a possibility that AI caused by the CS treatment may worsen the severity of the COVID-19 infection. Secondly, it is unknown whether giving cortisol-lowering therapy to a stable patient with CS during the pandemic increases the risk of cytokine storms in the case of COVID-19. Therefore, we did not initiate cortisol-lowering treatment because of our patient's mild form of CS (no severe hypertension or hypokalemia). We prescribed enoxaparin sodium to prevent thromboembolic complications and co-trimoxazole for PCP prophylaxis. The patient had no symptoms other than malaise and fatigue at home. On the 14th day, the SARS-CoV-2 PCR test was negative in the nasal swab. The patient did not accept additional examinations and surgical treatment for CS during the pandemic. Low-dose metyrapone treatment was given for the patient's hypercortisolemia in the long term. Low-dose treatment was preferred due to the possibility of AI in the patient and the difficulty of following the patient during the pandemic. In the literature, similar to our patient, a 71-year-old male was reported with CS who discontinued metyrapone one month ago due to gastrointestinal complaints. Although he had active disease, he recovered after one week of isolation without COVID-19 treatment.[14]

Case Report 2

A 32-year-old female patient was admitted to the endocrinology clinic with the complaint of weight gain, flushing, early bruising, and purple-coloured stretch marks for six months. The patient didn't have any previously diagnosed disease. She was a non-smoker and non-drinker. High blood pressure (190/100 mmHg) and severe hypopotasemia (2.59 mmol/L) were determined. The patient had a baseline cortisol value of 27.5 mcg/dL, an ACTH level of 101 pg/mL, and UFC 1,848 mcg/24 h.

Serum cortisol level was not suppressed with 2 mg and 8 mg dexamethasone tests. IPSS was performed for the differential diagnosis of ectopic CS, which was found to be precisely peripheral ACTH elevation. Lesion scanning was performed considering ectopic CS in the patient with a resistant hypertension clinic and severe hypokalemia. Thoracic CT was performed, and it was observed that the patient had a 22 mm lesion in the left lung. In our centre, an 18F-FDG PET scan is first performed to screen patients with ectopic CS. If the lesion is not detected, the gallium-68 DOTATATE PET scan method is

used. In this patient, an 18F-FDG PET scan was performed, and the same lesion was observed with a high SUV max (11.78) in the left lung. There was no pathological involvement in other organs and systems. The diagnosis of ectopic CS was confirmed in the patient, and left lung lower lobectomy was planned. Due to the COVID-19 pandemic, the SARS-CoV-2 PCR test was performed two times before surgery, and the results were negative. Left lung lower lobectomy was performed for the patient whose pathology was presented as neuroendocrine, and the Ki-67 proliferation index was 2-3%. AI did not develop in postoperative follow-up. No cortisol was suppressed with 1 mg dexamethasone in the first week after surgery, but the UFC level decreased to 156 mcg/24 h. On the other hand, hypertension regulation of the patient was easily achieved with a single agent in the postoperative period, and her hypopotasemia requiring daily high-dose parenteral potassium replacement was resolved entirely. She lost six kilograms within ten days.

The first problem we faced in the post-surgical management of the patient was a non-COVID-19 infection. Approximately three weeks after surgery, she presented with fever, temporary loss of consciousness and chest pain. SARS-CoV-2 PCR test was performed, considering the high probable cause of the COVID-19 pandemic in the patient. COVID-19 was excluded in the patient whose thoracic CT imaging and PCR test were negative. At the same time, other opportunistic causes of infections such as fungal infections were excluded. Especially for PCP, it was ruled out due to the characteristic interstitial pneumonia appearance and lack of increased oxygen demand. Aspergillus infection was removed because there was no cavity known as a fungus ball in thoracic imaging, and serum galactomannan antigen was found to be negative.

Newly developed areas of large emboli were observed in the cranial imaging, which was done due to changes in the consciousness of the patient. Transthoracic echocardiography was performed to find the source of the emboli and revealed vegetations in the mitral valve. The patient was diagnosed with infective endocarditis because of fever, accompanying mitral valve vegetation and areas of septic embolism in both frontal lobes. In the patient's thorax and abdomen CT imaging, septic embolism was also detected in the lungs and spleen. Empirical antibiotic therapy was initiated with the diagnosis of infective endocarditis in the patient with no neurological deficits except temporary confusion. Methicillin-susceptible *Staphylococcus aureus* was grown in blood culture. Surgery planned for approximately 2 cm of vegetation on the mitral and aortic valves was postponed due to the risk of hemorrhagic cerebrovascular events. We planned to give the patient parenteral antibiotic therapy for at least four weeks.

Another problem we faced was giving cortisol-lowering therapy to this COVID-19-positive patient in the event of possible ongoing hypercortisolemia. The reasons might be the lack of AI in the postoperative period and the lack of cortisol suppression with 1 mg dexamethasone in the second week after lung surgery. Whereas serum ACTH, cortisol and two times 24-hour UFC levels were in the normal range. These confounding results were considered due to the patient's active severe infection status and the ongoing very high stress.

The main problem at this stage, in our case, was COVID-19 pneumonia which was added to the complex clinical situation of our patient because of infective endocarditis. SARS-CoV-2 PCR was found to be positive in the patient who was screened for infection in the 3rd week of infective endocarditis treatment due to deterioration in the clinical display of fever and cough. Laboratory and thorax CT were supportive of COVID-19 pneumonia. With the findings, the surgery planned for the valve vegetation could not be performed on the patient who was started treatment for COVID-19 pneumonia. During the pandemic, the immunosuppressive patient who developed COVID-19 pneumonia was started on favipiravir treatment according to the treatment scheme in Turkey (discussed in detail above).[7] Strict control was provided for hypertension and hyperglycemia. She was followed closely in terms of possible hypopotasemia with close electrolyte monitoring. At the same time, due to the increased thromboembolism risk for both CS and COVID-19, the patient was given anticoagulant therapy, which is strongly recommended in the

literature.[11,19] When the patient received treatment for COVID-19 pneumonia, there was no need for oxygen and no organ failure developed in septic condition. Convalescent plasma therapy was also given as there was minimal improvement in the patient's newly developed tachypnea and progression of lung infiltration at the end of antiviral treatment. The valve surgery plan of the patient, whose PCR test became negative on the 10th day after the treatment and whose aggravation was not observed due to COVID-19 pneumonia, came up again. Mitral valve replacement surgery was performed after the SARS CoV-2 PCR test was negative two times in the patient who did not have additional trouble in the follow-up. The PCR sent from the deep tracheal swab during the intubation was positive (approximately four weeks after the first PCR positivity). There was no deterioration in the postoperative clinical condition of the patient due to COVID-19 infection, it was accepted as asymptomatic PCR positivity, and the patient was not given another COVID-19 treatment. The patient was followed up in the isolation unit during this period.

Similar questions to those we discussed in the first case should be asked here as well;

1. Is there an indication for hospitalization and investigation of the aetiology of hypercortisolemia during the pandemic?
2. Surgical or medical treatment in a patient with CS?
3. Should cortisol-reducing therapy be given if mild hypercortisolemia persists in a CS patient with COVID-19 positive and active infective endocarditis?

First challenge: "Is there an indication for hospitalization and investigation of the aetiology of hypercortisolemia during the pandemic?"

In our case, it was decided that the diagnosis stage should not be delayed due to severe hypercortisolemia, resistant hypertension and hypokalemia. The recommendations in the publications regarding the management of CS patients during the COVID-19 pandemic were in this direction.[6,11]

Second challenge: "Surgery or medical treatment in a patient with a diagnosis of CS?"

It was thought that definitive treatment should be performed because the patient had severe hypercortisolemia, resistant hypertension, and profound hypokalemia. On the other hand, the patient's hospital exposure, the increased risk of opportunistic infections and the pandemic brought other problems. Surgery seemed more reasonable because the lesion detected in the lung of our patient could be malignant, lung cancer could not be excluded without a tissue diagnosis, and the location of the lesion was not suitable for diagnostic biopsy. We did not delay the treatment in this case, considering that definitive therapy would be more beneficial for the patient.

Third challenge: "Should cortisol-reducing treatment be given in a CS patient with COVID-19 pneumonia and active period of infective endocarditis in case of ongoing mild hypercortisolemia?"

She might be in remission in terms of CS due to the improvement in blood pressure regulation, hypopotasemia, and weight loss after surgery. However, a re-examination was planned for possible hypercortisolism but could not be performed due to the prolonged active infection status of the patient. AI did not develop during the postoperative period. However, possible hypercortisolism could not be detected due to ongoing complications. Cortisol-lowering therapy could not be started in our patient because its side effects may worsen the course of the infection in the patient with COVID-19.[12] Since it is a new disease and it is not known precisely how it will affect the course of COVID-19, cortisol-lowering treatment was not given to the patient for possible hypercortisolism existing after the lung surgery.

Conclusion

Endocrinologists frequently consider managing patients with CS has been often regarded as highly challenging. At the same time, the increased risk of COVID-19 infection during the pandemic days creates further serious difficulties in disease management. Nevertheless, there is inadequate data to help us in the direction of

these two diseases when they coincide. To the best of our knowledge, very few patients with CS were infected with COVID-19. Table 2 shows the clinical and laboratory features of our cases. Based on our experience, we suggest that differential diagnosis and treatment can be delayed until COVID-19 infection recovers in mild forms of CS. In cases with severe hypercortisolemia, an appropriate method should be followed for a definitive diagnosis and treatment by considering the patient and calculating profit and loss. There is a need for more case-based data on the disease management and selection of therapy in patients with CS during the COVID-19 pandemic.

Table 2. Clinical and laboratory features of our cases.

	Case 1	Case 2
Age / Sex	76-year-old female	32-year-old female
Laboratory values	Baseline serum cortisol: 27.7 mcg/dL ACTH: 184 pg/mL 24-h UFC: 1,657.5 mcg/24h Serum potassium: 2.9 mmol/L (3.5-5.1 mmol/L) Night cortisol: 24.4 mcg/dL 2 mg dexamethasone suppressed cortisol to 16.42 mcg/dL	Baseline serum cortisol; 27.5 mcg dL ACTH: 101 pg/mL 24-h UFC: 1,848 µg/24h Serum potassium: 2.59 mmol/L (3.5-5.1 mmol/L) 2 mg dexamethasone suppressed cortisol to 24 mcg/dL 8 mg dexamethasone suppressed cortisol to 22 mcg/dL
Clinical situation	Hypertension, muscle weakness, impaired glucose metabolism	Resistant hypertension, obesity, impaired glucose metabolism
Imaging examinations	Pituitary MRI: 15x20 mm mass in the pituitary gland	Pituitary MRI: 3 mm mass in the pituitary gland Thorax CT: 2 cm lesion was detected in the left lung 18F-FDG PET scan: 2 cm lesion was detected in the left lung with high SUVmax (11.78).
IPSS	Could not be performed.	Peripheral ACTH secretion was detected.
Diagnosis	Pituitary mass was present, differential diagnosis tests could not be performed.	Ectopic Cushing's syndrome (lung mass) Pathology: neuroendocrine tumor ki-67 index 2-3%
When was COVID-19 diagnosed?	At the time of the first diagnosis	3 weeks after lung mass surgery
How was COVID-19 diagnosed?	PCR positive No pneumonia in thorax CT No symptoms	PCR positive COVID-19 pneumonia in Thorax CT Fever and cough
How was the clinical course of COVID-19?	Asymptomatic PCR positive patient	Infective endocarditis, mitral valve vegetation, septic embolism in the both frontal lobes, lung and spleen (MSSA in the blood culture) and COVID-19 pneumonia
Was treatment given for COVID-19?	No, antiviral treatment was started Low molecular weight heparin treatment	Favipiravir treatment Low molecular weight heparin treatment Convalescent plasma treatment
Was the control SARS CoV-2 PCR test negative?	The 14th day control PCR test was found to be negative.	Oropharyngeal nasopharyngeal swab samples were found to be negative (10th day and 21st day control PCR), Tracheal swab sample (4 weeks after the first PCR positivity).
Has the patient been treated for hypercortisolemia?	Low-dose metyrapone was started in the patient who did not accept re-hospitalization for further examination during the pandemic period.	Lung surgery was performed for ectopic CS. Post-operative hypercortisolemia was evaluated as stress response, no treatment was given.
Last clinical condition	The patient is followed in a stable condition with low dose metyrapone treatment.	She was operated on for mitral valve vegetation. Clinical condition remained stable in the postoperative period.

CS: Cushing's syndrome, MRI: magnetic resonance imaging, CT: computed tomography, IPSS: inferior petrosal sinus sampling.

Conflict of Interests

The authors declare that they have no conflict of interest. Statement of human and animal rights.

Data Availability

Data sharing does not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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