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RESEARCH

Clinical, histopathological features and malignancy frequency of patients with idiopathic inflammatory myopathy

İdiyopatik inflamatuar miyopatili hastaların klinik, histopatolojik özellikleri ve malignite sıklığı

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Abstract

Purpose: Idiopathic inflammatory myopathy (IIM) group diseases are strongly linked to cancer. This study aims to describe the clinical and histopathological features of IIM patients diagnosed in our clinic, evaluate the frequency and subtypes of accompanying malignancies, and examine the relationship between pathological staining patterns and IIM subgroups.

Materials and Methods: This retrospective study included 74 patients with IIM diagnosed between 2010 and 2023 who had a muscle biopsy at the time of diagnosis. Age, gender, imaging, electromyography, and muscle biopsy results were obtained using the hospital's electronic system.

Results: Of the 74 patients with IIM, 45 are polymyositis (PM), 27 are dermatomyositis (DM) and two are inclusion body myositis (IBM). Malignancy developed in 12 (16%) of 74 IIMs, two (16.6%) of whom had malignancy before the diagnosis of IIM (one breast cancer, one thyroid papillary cancer). Malignancy was diagnosed in five patients (41.6%) in the PM group (the most common breast cancer), five patients (41.6%) in the DM group (the most common endometrial cancer, and two patients (16.8%) in the IBM group. It was found that positive staining with membrane attack complex was higher in the DM group compared to the PM group.

Conclusion: Cancer screening should be performed at regular intervals in IIM patients. Breast and endometrial cancer screening should be prioritized in female patients, as well as lung cancer screening in male patients. Large cohort studies are needed to explain the relationship between pathological staining patterns and IIM subtypes.

Keywords:. Polymyositis, dermatomyositis, inclusion body myositis, membrane attack complex, malignancy

Öz

Amaç: İdiyopatik inflamatuar miyopati (İİM) grubu hastalıklar kanser ile güçlü bir şekilde ilişkilidir. Bu çalışmada kliniğimizde tanı konulan İİM hastalarının klinik ve histopatolojik özelliklerinin tanımlanması, eşlik eden malignitelerin sıklığı ve alt tiplerinin değerlendirilmesi ve patolojik boyanma paternleri ile İİM alt grupları arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya 2010-2023 yılları arasında İİM tanısı konan ve tanı anında kas biyopsisi yapılan 74 hasta dahil edilmiştir. Yaş, cinsiyet, görüntüleme, elektromiyografi ve kas biyopsisi sonuçları hastanenin elektronik sistemi kullanılarak elde edildi.

Bulgular: İİM'li 74 hastanın 45'i polimiyozit (PM), 27'si dermatomiyozit (DM) ve ikisi inklüzyon cisimciği miyozitidir (İCM). İİM'li 74 hastanın 12'sinde (%16) malignite gelişti, bunların ikisinde (%16,6) İİM tanısından önce malignite vardı (bir meme kanseri, bir tiroid papiller kanseri). PM grubunda beş hastada (%41,6) (en sık meme kanseri), DM grubunda beş hastada (%41,6) (en sık endometriyal kanser) ve İCM grubunda iki hastada (%16,8) malignite tanısı konmuştur. Membran atak kompleksi ile pozitif boyanmanın DM grubunda PM grubuna kıyasla daha yüksek olduğu bulunmuştur.

Sonuç: Bu sonuçlar, İİM hastalarında kanser taramasının düzenli aralıklarla yapılması gerektiğini göstermektedir. Kadın hastalarda meme ve endometriyal kanser taramasına ve erkek hastalarda akciğer kanseri taramasına özel önem verilmelidir. Patolojik boyama modelleri ile İİM alt tipleri arasındaki ilişkiyi açıklamak için geniş kohort çalışmalarına ihtiyaç vardır.

Anahtar kelimeler: Polimiyozit, dermatomiyozit, inklüzyon cisimcikli miyozit, membran atak kompleksi, malignite

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INTRODUCTION

Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) are subgroups of idiopathic inflammatory myopathies (IIM)[1]. The most common clinical phenotype is polymyositis[2]. IIM is diagnosed through a patient history, physical examination, autoantibodies, electroneuromyography (EMG), and muscle biopsy.

Muscle biopsy is the diagnostic gold standard for IIM. Perifascicular atrophy characterized by perivascular and perimysial inflammatory infiltrates composed of dendritic cells, B cells, CD4+ T cells, and macrophages is a pathognomonic histological feature of DM[3]. For PM, distant necrotic and regenerated fibers, variability in fiber size, and inflammation of the endomysium are prominent microscopic features[4]. Apart from these features which are known and accepted in current studies, upregulation of C5b-9 membrane attack complex (MAC) and HLA-1 have been investigated in IIM group diseases. There are studies claiming that HLA-1 and MAC staining show high specificity for the diagnosis of IIM and that the diagnosis of IIM can be excluded if they are negative. However, there is no staining specific to subtypes such as PM or DM[5]. And also; there is also an opinion that an early histological anomaly that can be detected under a light microscope in DM, the accumulation of complement or C5b-9 membrane attack complex (MAC) in perifascicular endomysial capillaries, is specific to DM[6-9]. Similarly, studies are showing that HLA-1 upregulation is common in PM biopsies[10]. In conclusion; although the specificity of HLA-1 and MAC deposition to IIM subtypes is controversial, there is consensus that it is an indicator of IIM

Even though IIMs are thought to be related to cancer, there are different results in the literature A comprehensive review found a strong association between DM and the development of malignancy, and a minimally increased association in the PM group compared to the healthy population[11,12]. The strong association between DM and malignancy is supported by a case report reporting complete recovery of DM after tumor resection in a patient with breast cancer[13]. A recent study reported that solid tumor and hematological malignancies were higher in IIM patients than in patients with knee osteoarthritis[14]. Malignancy can be diagnosed before, during, or after IIM[11,12]. While breast and ovarian cancers are the most common cancer types in women, lung and prostate cancers are the most common in men. Lymphoma, colon, pancreas, and bladder cancer are among other malignancies[11].

In our study, we aimed to describe the demographic characteristics of IIM patients diagnosed in our clinic, and to determine the frequency and subtypes of concomitant malignancies. Additionally, we aimed to investigate the relationship of HLA-1 and MAC staining patterns with IIM subgroups and to contribute these results to the literature. We hypothesize that HLA-1 staining is specific for PM and MAC staining is specific for DM.

MATERIALS AND METHODS

Sample

This study was conducted at Çukurova University Rheumatology Clinic. The study was approved by the ethics committee of Çukurova University (Number: 138/ Date: 3 November 2023). The informed consent form was obtained from all participants. With a 5% margin of error and 80% power, the standard effect size was determined as 1.03 and the minimum n = 15 cases were determined to be taken[5].

This retrospective study included 74 IIM patients who were admitted to the Çukurova University Rheumatology outpatient clinic between 2010 and 2023 and diagnosed using Bohen and Peter diagnostic criteria[15,16]. Inclusion criteria were defined as being over 18 years of age, having muscle biopsy at the time of diagnosis, and having regular follow-up at Çukurova University Rheumatology Clinic. Exclusion criteria were being under 18 years of age, being diagnosed without muscle biopsy, and not being followed up for malignancy development.

Procedure

Data analyzed included laboratory (creatinine kinase (CK), sedimentation (ESR), C-reactive protein (CRP)) electromyography (EMG), histopathological evaluation of muscle biopsy, and imaging results. The hospital's electronic record system was used to access the demographic data of the patients.

EMG and muscle biopsy

EMG, following the myopathy protocol, was performed to detect myogenic changes in the muscles. Muscle biopsy was taken from any of the

proximal muscle groups (deltoid or quadriceps femoris muscles) and examined. The histopathologic evaluation included MAC and HLA-1 staining patterns.

Statistical analysis

Statistical analyses were performed using SPSS for Windows 25.0 software. The conformity of the variables to normal distribution was analyzed using visual analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). A p-value above 0.05 in the Kolmogorov-Simirnov test was accepted as a normal distribution. The Chi-square test was used for the relationships between the qualitative data of the groups such as gender distribution, EMG, overlap syndrome, development of malignancy, HLA-1, and MAC staining characteristics. Fisher's Exact test was used when the Chi-square test condition was not met. ESR, CRP, and CK results of the groups were compared using the Mann-Whitney U test because the distribution was not normal. $P<0.05$ was considered statistically significant.

RESULTS

In this study, 74 patients diagnosed with IIM including 45 PM, 27 DM, and 2 IBM patients were included. Among 45 PM patients, 64.4% (n=29) were female, 35.6% (n=16) were male, mean age was 49.44±12.74 years, among 27 DM patients 88.8% (n=27) were female, 11.2% (n=3) were male, mean age was 50.67±14.66 years, among two IBM patients both were female, mean age was 65±24.04 years. There was no difference between PM and DM groups in terms of gender distribution (p=0.061). The results are given in Table 1.

Mean CRP, CK, and ESR values at diagnosis were recorded in PM, DM, and IBM patients. There was no significant difference between the groups (p=0.880, p=0.253, p=0.547, respectively) (Table 1).

Table 1. Evaluation of age and laboratory characteristics of patients with idiopathic inflammatory myositis

Variable	PM Mean±SD n=45	DM Mean ±SD n=27	IBM Mean ±SD n=2	P-value
Age (Years)	49.44±12.74	50.67±14.66	65±24.04	0.707*
Gender (Male/Female)	16/29	4/24	0/2	0.061*
CRP(mg/dl)	4.458±9	4.3±8.8	26.5±33.2	0.880
CK(IU/L)	1526±1522.9	1438±1974	458±263	0.253
ESR(mm/hr)	20.58±21.8	23.74±23.77	31.5±14.8	0.547

CRP: C-reactive protein, DM: Dermatomyositis, ESR: Erythrocyte sedimentation rate, IBM: Inclusion body myositis, PM: Polymyositis,*: It is the evaluation between PM and DM groups.

When patients in the PM, DM, and IIM groups were evaluated in terms of lung involvement, accompanying overlap syndromes, and myogenic involvement evaluated by EMG, there was no statistical difference (p=0.640, p=0.264, p=0.232, respectively) (Table 2). EMG evaluation was not performed in six patients (4 patients PM, 2 patients DM).

When patients with overlap syndrome were evaluated; anti-Ro, anti-ribonucleoprotein antibodies (anti-RNP), and anti-smith antibodies were found positive in two patients each. Anti-cyclic citrullinated protein (snti-CCP), anti-centromere, and anti-topoisomerase-1 (Anti-scl)-70) antibodies were found positive in one patient each. Of the 9 patients evaluated for overlap syndromes, 4 patients met the criteria for overlap syndrome.

When the patients were evaluated for malignancy development, 12 of 74 (16%) developed malignancy; two (16.6%) were diagnosed with malignancy before IIM diagnosis, and 10 (84.4%) were diagnosed with malignancy after IIM diagnosis. One of the two patients who had been diagnosed with cancer before IIM had breast cancer, and the other had thyroid papillary carcinoma. These two patients were later diagnosed with PM. Three patients had breast cancer, while three had endometrial cancer. Lung cancer, thyroid papillary cancer, chronic lymphocytic leukemia, colon cancer, basal cell skin carcinoma, and cervical cancer each develop in different patients. A patient was diagnosed with multiple myeloma following breast cancer. Five patients (41.6%) were diagnosed with cancer in the PM group, five patients (41.6%) in the DM group, and two patients (16.8%) in the IBM group. The overall malignancy rate was

16% in the IIM group, 18.5% in the DM group, and 11% in the PM group, with malignancy detected in two patients in the IBM group. There was no statistically significant difference in malignancy development between the PM and DM groups (p = 0.415) (Table 2). The most common cancer in the DM group was endometrial cancer, and the most common cancer in the PM group was breast cancer.

Table 2. Evaluation of clinical characteristics of patients with idiopathic inflammatory myositis

Variable (n %)	PM	DM	IBM	P-value
EMG	64.4(29)	74(20)	11.1(2)	0.640
Lung involvement	24.4(11)	18.5(5)	-	0.264
Overlapping syndrome	8.8(4)	18.5(5)	-	0.232
Malignancy	11(5)	18.5(5)	-	0.415

DM: Dermatomyositis, EMG: electromyography, IBM: Inclusion body myositis, PM: Polymyositis (Comparison was made between PM and DM groups.)

When pathological findings are evaluated; HLA-1 staining was positive in 91.8% (n=68) of 74 IIM patients. Positive HLA-1 staining was seen in 95.5% (n=43) in the PM group and 85% (n=23) in the DM group. There was no statistically significant difference between the groups (p = 0.137). When the MAC staining pattern was examined, staining was observed in 48.6% (n = 36) of 74 patients. Staining was observed in 19 (42.2%) patients in the PM group and 17 (70.3%) patients in the DM group. When the relationship between these groups was evaluated, a statistically significantly higher rate of positive staining with MAC was observed in the DM group compared to the PM group (p = 0.015). Endomysial infiltration was detected in 30% (n=28) of all IIM patients. This rate was 35.5% (n=19) in the PM group and 29.6% (n=8) in the DM population. The distribution was not statistically significant (p=0.765). Infiltration in the perimysium was 20% (n = 15) in all IIM patients, with no difference between the PM and DM groups (17.7%, and 25.9%, respectively, p = 0.278). When patients with and without malignancy were compared based on endomysial and perimysial inflammation, MAC, and HLA-1 staining patterns, no statistically significant differences were found (p=0.060, p=0.735, p=0.705, p=1) (Table 3).

Table 3. Evaluation of malignancy rates and histopathological features of idiopathic inflammatory myositis patients

Variable (n %)	PM	DM	IBM	Total	P-Value
Malignancy	5 (11)	5 (18.5)	2 (100)	12 (16)	0.415
HLA-1	43 (95.5)	23 (85)	2 (100)	68 (91.8)	0.137
MAC	19 (42.2)	17 (70.3)	0 (0)	36 (48.6)	0.015*
Endomysial inflammation	19 (35.5)	8 (29.6)	1 (50)	28 (30)	0.765
Perimysial inflammation	8 (17.7)	7 (25.9)	0 (0)	15 (20.2)	0.278

DM: Dermatomyositis, HLA-1: Human leukocyte antigen, IBM: Inclusion body myositis, MAC: Membrane attack complex, PM: Polymyositis, *: p<0.05

DISCUSSION

In our study, patients in the PM and DM groups; were evaluated in terms of malignancy development, malignancy subgroups, and histopathological staining characteristics. Of the 74 patients diagnosed with IIM, 12 (16%) developed malignancy, of which two patients had developed malignancy before the diagnosis of IIM; The most common malignancy in the PM group was breast cancer, and in the DM group, endometrial cancer. When histopathological findings were evaluated, MAC and HLA-1 staining were highly positive in all IIMs, while MAC staining in the DM group was significantly higher than in the PM group.

Numerous studies have found that IIMs are linked to an increased risk of cancer[11, 17, 18]. Although both PM and DM increase the risk of cancer, DM has a stronger association with increased malignancy. A large study involving 618 patients with DM and 914 patients with PM, as well as data from three countries, found that DM increased the risk of ovarian, lung, gastric, colorectal, pancreatic, and non-Hodgkin's

lymphoma[11]. The United States DM Cohort Study included cancers of the breast (24.5%), hematological (17%), colorectal (9.4%), and prostate (9.4%)[19]. In a separate study involving 35 PM/DM patients, hematological, gastrointestinal, breast, ovarian, and lung tumors, as well as malignant melanoma and metastatic carcinoma of unknown primary origin, were reported[18].

The prevalence of endometrial cancer was highest in the DM group, while breast cancer was highest in the PM group. Breast and endometrium were seen most frequently and evenly across all IIMs. Eleven of the twelve cancer patients in our study were female. Breast, thyroid, colorectal, and endometrium cancers are the most common among women aged 25 to 70, according to data from Turkey's General Directorate of Public Health. Because of the small number of patients with malignancies, we believe the ratio is skewed in favor of these cancers, and the evaluation results differ.

IIMs exhibit distinctive histopathological characteristics. Immunostaining of inflammatory markers, including MHC and MAC, has diagnostic value for IIMs, according to studies[20]. Positive MAC staining and perimysial infiltrates are frequently observed in DM, whereas HLA-1 staining and endomysial infiltrates are frequently observed in PM[8]. A recent study indicates, however, that HLA-1 staining may also be present in patients with PM, IBM, and other unclassifiable myositis, and that HLA-1 staining is not specific to PM[21]. There is disagreement about the specificity of HLA-1 for PM. When examining the studies associated with MAC accumulation in DM, it was reported that MAC accumulation was specific for DM with 35% sensitivity and 93% specificity in one study and 88.9% sensitivity and 90.3% specificity in another study[8,20-22]. According to studies, immunostaining of inflammatory markers such as MHC and MAC can be used to diagnose IIMs[20]. Positive MAC staining and perimysial infiltrates are common in DM, while HLA-1 staining and endomysial infiltrates are common in PM[8]. A recent study, however, suggests that HLA-1 staining may be present in patients with PM, IBM, and other unclassifiable myositis and that it is not specific to PM[21]. There is disagreement about the specificity of HLA-1 for PM. When examining studies associated with MAC accumulation in DM, it was reported that MAC accumulation was specific for DM with 35% sensitivity and 93% specificity in one study and 88.9% sensitivity and 90.3% specificity in another study[8,20-22].

The limitations of our study are the small number of patients, retrospective and single-center nature. Myositis-specific antibodies of the patients could not be evaluated. Due to the lack of a healthy control group in our study, the sensitivity and specificity of histopathological findings could not be calculated. With studies conducted with a larger number of IIM patients who developed malignancy before or after diagnosis, parameters with predictive value in terms of the development of malignancy in IIM patients can be obtained. In this respect, prospective studies in which pathological findings can be examined from the time of diagnosis will be valuable. The study's strengths lie in its unique evaluation of the relationship between IIMs and the development of malignancies, as well as its examination of specific subgroups of malignancies. Furthermore, it contributes significant insights to the existing literature regarding the relationship between histopathological staining patterns (such as HLA-1, MAC) and the diagnoses of DM and PM. Although previous studies have explored this connection, a definitive conclusion has not yet been reached.

In conclusion, malignancy was detected in 16% of the IIM patient group, with the DM group having a higher rate than the PM group. These findings may point to the need for cancer screening at regular intervals in the IIM group. Breast and endometrial cancer screening should be prioritized in female patients, as well as lung cancer screening in male patients. In our study, no link was discovered between pathological features and malignancy development. Based on the results of our study; we believe that the fact that HLA-1 upregulation and MAC accumulation in muscle biopsies are high in all IIM groups and that MAC accumulation is specific to the DM group will help our pathological evaluation.

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