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Original Investigation

Inflammatory myopathies: One-center experience

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Abstract

Objective: Our aim was to report our experience with inflammatory myositis.

Material and Methods: In total, 60 patients were evaluated retrospectively, and 43 of them (71.7%) were female. The median age was 45 (17-81). Of all patients, 33 (55%) were diagnosed as polymyositis, 22 (36.6%) as dermatomyositis (classical, amyopathic, and malignancy-associated), and 5 (8.33%) as undifferentiated myositis. The 3 patients with malignancy-associated dermatomyositis had lung cancer, nasopharyngeal carcinoma, and endometrial cancer. Two patients with polymyositis had a history of low-grade gastric mixed tumor and thymoma but were diagnosed 7 and 12 years ago, and no recurrences have been reported during the routine controls.

Results: All patients, other than two with malignancy-associated dermatomyositis, were treated via immunosuppressive agent, and the third patient with lung cancer was diagnosed later and gave up immunosuppressive therapy. Thirty-nine (65%) of the patients were treated via oral low-dose steroid, and 19 (31.7%) were treated via intravenous high-dose pulse steroid therapy. All patients were treated with steroid, which was tapered by time, and 23 (38.3%) were treated with azathioprine, 6 (10%) were treated with cyclophosphamide, 3 (5%) were treated with methotrexate, and 6 (10%) were treated with isolated steroid therapy at the time of diagnosis. The median follow-up period was 37 (2-135) months. Six patients (10%) have died-3 due to myocardial infarction, 1 due to septic shock, 1 due to malignancy, and 1 with an unknown reason. The 5-year survival rate was 76.9%, and the 10-year survival rate was 40%.

Conclusion: Other than the high ratio of PM in our series, all other results were compatible with the literature. We faced few resistant diseases; therefore, biologic agents were used rarely.

Key words: Inflammatory myositis, polymyositis, malignancy-associated myositis

Introduction

Idiopathic inflammatory myopathies (IIMs), in other words, myositis, usually present with muscle weakness and decreased endurance of skeletal muscle, and histopathologically inflammatory cells are usually present in the muscle tissue. According to the clinical and histopathological findings, IIMs have been classified into mainly three groups: polymyositis (PM), dermatomyositis (DM), and sporadic inclusion body myositis (sIBM) (1, 2). Major organ involvement is a frequent feature of both PM and DM but not of sIBM. DM mostly affects the lung and the skin together, but PM only affects the lung (2). These features suggest that 'myopathies' are actually systemic connective tissue diseases.

A formal international consensus for the diagnosis and classification of inflammatory myositis is necessary, but generally, sIBM is considered separately from the others, because this subtype does not respond to immunomodulatory treatments and is not a pure inflammatory myopathy (2). The pathologic aspects in DM are humorally mediated involvement of microcirculation, early capillary deposition of the complement C5b-9 membranolytic attack complex (MAC), and secondary ischemic changes. On the other hand, CD8 T-cell mediated and MHC-1 restricted autoimmune attack of myofibers occur in PM (2).

The auto-antibodies in IIMs come out against Mi-2 protein, aminoacyl tRNA synthetase, and signal-recognition particle. Positivity of anti-PL7 and PL12 in combination with anti-Jo-1 usually reflects pulmonary involvement; also, anti-CADM 140 antibody accompanies rapidly progressive interstitial lung disease and amyopathic DM (2).

The clinical trials searching for the best therapeutic approach for IIMs are inadequate, and since IIMs are rare diseases, trials with large populations are not possible. Corticosteroids (CS) have not been studied in randomized controlled trials, but the general expert consensus confirms CS as the first-line choice. Because CS toxicity may lead to significant disability, additional immunosuppressive agents are necessary. Intravenous immunoglobulin (IVIG) is an appropriate option with proven benefit in a controlled trial, but the long-term effectiveness remains unknown. Other frequently used immunosuppressive therapies are methotrexate and/or azathioprine, followed by cyclosporine (especially for patients with interstitial lung disease), tacrolimus, and mycophenolate mofetil (3). Newer trials with rituximab report encouraging results, but larger trials are necessary.

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Nearly 20% of patients with DM and 5% of patients with PM emerge with malignancies, and for these patients the first-line therapy is chemotherapeutics (4).

Herein, we present our experience with IIMs other than sIBM in 60 patients.

Material and Methods

Data of IIM patients who applied to our rheumatology clinic from January 2000 to December 2011 were all analyzed retrospectively, and there were 60 patients in total. Their treatment protocols, presenting manifestations, survival analysis, laboratory data, electromyelographic evaluations, pathologies, and radiologic evaluations were all recorded. All patients were also classified as PM and DM (amyopathic DM and also malignancy-associated dermatomyositis).

Follow-up visits

After the diagnosis, all patients were re-evaluated for the laboratory data and disease progression in 2 months. After the first control visit, all patients were checked with laboratory data, physical examination, and radiologic evaluation every 6 months. Any patient with an acute complaint was evaluated between the follow-up visits.

Treatment schedule

Two patients with malignancy-associated DM were treated with chemotherapy and radiotherapy, and the third one, with lung cancer, gave up immunosuppressive therapy and took chemotherapy later. Others were treated via oral or IV steroids and also with immunosuppressive agents. The most frequently preferred agents were CS, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, IVIG, and hydroxychloroquine. Patients with lung involvement or with severe disease were treated via IV cyclophosphamide.

Assessment of response

All patients were checked at 6-month intervals if they had no complaints with whole blood count and blood biochemistry, erythrocyte sedimentation rate, C-reactive protein, creatinine kinase, lactate dehydrogenase, and also with physical examination. The doses were tapered according to the clinical situation and patient tolerability, as well as the laboratory results.

Statistical analysis

The follow-up period was defined as the time that passed between the diagnosis and the analysis. Fischer's exact test and x^2 test were used for nominal variables, and Mann-Whitney U-test was used for numeric variables. All p-values were 2-sided, and a value ≤ 0.05 was considered significant. The Statistical Package for Social Sciences, version 15.0 (SPSS, Inc, Chicago, IL, USA) software was used for analysis.

Table 1. Patient characteristics

Parameters		n	%
Number of patients		60	100
Sex	male	17	18.3
	female	43	71.7
Median age at diagnosis (years)		45	17-81
Creatinine kinase (median)		1471	14-12704
Lactate dehydrogenase (median)		732	165-7276
ANA	-negative	28	46.7
	-1/100	12	20.0
	-1/160	5	8.3
	-1/320	7	11.7
	-1/1000	6	10.0
ENA	-Negative	44	73.3
	-Positive	13	21.7
	-Missing	3	5
ENA subtypes	-Jo-1	6	46.1
	-SsA	5	38.4
	-Others	2	15.3
Aspartate amino transferase (median)		74	8-1256
Interstitial lung disease (CT)	Present	15	25
	Not present	37	61.6
	Suspicious	2	3.3
	Missing	6	10
Electromyography	Involvement present	39	65
	Normal	5	8.3
	Not done	16	26.6
Malignancies	+	5	8.3
	-	55	91.6
Muscle biopsy	Compatible with myositis	29	48.3
	Not compatible with myositis	19	31.6
	Not done	12	20

ANA: anti-nuclear anticore; ENA: extractable nuclear anticore

Results

Patient characteristics

In total, 60 patients applied to our clinic with a diagnosis of IIM, and 43 of them (71.7%) were female (Table 1). The median age at diagnosis was 45 (17-81). The patients were classified into subtypes of myositis (Table 2). Of all patients, 33 (55%) had polymyositis, 22 (36.6%) had DM, and 5 (8.33%) had undifferentiated myositis. There were 3 patients with malignancy-associated DM, and their malignant diseases were one lung cancer, one nasopharyngeal carcinoma, and one endometrial cancer. Also, 2 patients with polymyositis had a history of thymoma and one low-grade gastric mixed tumor 7 and 10 years ago, but there were no recurrences or metastasis at the time of diagnosis. In total, 30 (50%) patients revealed positive results for antinuclear antibody (ANA), and 13 (21.7%) revealed positive results for extractable nuclear antigen (ENA). The most frequently detected subtype of ENA was Jo-1 (6 patients; 46.1%). The presence of interstitial lung disease (ILD) was evaluated with computed tomography, and 15 patients (25%) had radiologically proven ILD. Thirty-nine patients (65%) had muscular involvement on electromyography.

Treatments

Thirty-nine (65%) of the patients were treated via oral steroid, and 19 (31.7%) were treated via intravenous high-dose pulse steroid therapy and IV cyclophosphamide. Two patients were treated with only chemotherapy, and the third one was treated with immunosuppressive agent before the diagnosis of lung cancer and then was treated with chemotherapy. All patients were treated with a tapering dose steroid protocol, decreasing from 60 mg prednisolone or equivalent, and 23 (38.3%) were treated with azathioprine, 6 (10%) were treated with cyclophosphamide, 3 (5%) were treated with methotrexate, and 6 (10%) were treated with isolated steroid therapy at the time of diagnosis. Fourteen patients were resistant to first step therapy and needed a second step protocol. At the second step, 3 patients were treated with methotrexate, 1 was treated with cyclophosphamide, 2 were treated with azathioprine, 4 were treated with mycophenolate mofetil (MMF), 2 were treated with rituximab,

Table 2. Subtypes of myositis

Subtypes	n	%
Polymyositis	33	55
Dermatomyositis	22	36.6
-Malignancy ass. DM	3/22	13.6
-Amyopathic DM	10/22	45.4
-Classic DM	9/22	40.9
Undifferentiated myositis	5	8.3

DM: dermatomyositis

Table 3. Myositis-specific autoantibodies

SubtyName	Antigen	Manifestations
Jo-1	Histidyl tRNA synthetase	PM/DM and ILD
PL-7	Threonyl tRNA synthetase	PM/DM and ILD
PL-12	Alanyl tRNA synthetase	ILD > PM/DM
EJ	Glycyl tRNA synthetase	DM > PM and ILD
OJ	Isoleucyl tRNA synthetase	ILD and PM/DM
KS	Asparaginyl tRNA synthetase	ILD > PM/DM
Zo	Phenylalanyl tRNA synthetase	ILD and NM with inflammatory cells
SRP	Signal recognition particle	Severe, acute, resistant NM
Mi-2	DNA helicase	Treatment-responsive DM
P155/140	Transcriptional intermediary factor 1-gamma (TIF-γ)	Cancer in adult DM; severe cutaneous JDM
Anti-CADM 140	Melanoma differentiation-associated gene 5 (MDA5)	Amyopathic DM; rapidly progressive ILD
MJ	Nuclear matrix protein NXP-2	Most common in JDM; rare in adult DM with cancer
Anti-SAE	Small ubiquitin-like modifier-activating enzyme	DM and ILD

DM: dermatomyositis; ILD: interstitial lung disease; JDM: juvenile dermatomyositis; PM: polymyositis; NM: necrotizing myopathy

and 2 were treated with intravenous immunoglobulin (IVIG).

On the other hand, the patients on IV steroid therapy (500-1000 mg/cycle methylprednisolone) also were treated with cyclophosphamide 250-500 mg/cycle plus mesna 400 mg/cycle (and prednisolone 500-1000 mg/cycle). The IV agents were given with a range of increasing time periods-first with 7-day intervals, then with 10-day intervals, 15-day intervals, 20-day intervals, and then every month for 2 years. As the maintenance therapy, 6 patients were treated with MMF, 1 was treated with IVIG, and 1 was treated with azathioprine.

Survival and follow-up

The median follow-up period was 37 (2-135) months. There were 10 patients with a follow-up period shorter than 12 months. At the time of analysis, 6 patients (10%) have died: 3 due to myocardial infarction, 1 due to septic shock, 1 due to malignancy, and 1 with an unknown reason. The 5-year survival rate was 76.9%, and the 10-year survival rate was 40%.

Discussion

Herein, we have reported our experience with inflammatory myositis.

Inflammatory myositis is mainly grouped as polymyositis, dermatomyositis, inclusion body myositis, and autoimmune necrotizing myopathies. We had no patients with ınclusion body myositis or necrotizing myopathies. These are very rare disorders, and the annual incidence is reported to be 1/100,000. Other than juvenile DM, all are diseases of adult age and mostly affect women. The peak incidence is seen in the sixth decade. The age and gender distribution in our series was compatible with the literature (5).

Dermatomyositis usually presents with an acute, progressive, and painless muscle weakness with typical rash. Patients with subcutaneous calcifications may also report pain. Near-classical DM amyopathic, adermopathic DM, and also antisynthetase syndromes are the less frequent subtypes in DM. Antisynthetase syndrome presents with arthritis, interstitial lung disease, and Reynaud phenomenon. Shawl sign, Gottron's sign, papules, and V sign are the most frequent type of rashes in DM (6-9). The frequency of amyopathic DM was reported to be 20% among patients with DM, but in our trial, the rate was 41.6% (10/24; 9 classical DM, 3 malignancy-associated DM, and 10 amyopathic DM) (9). This may be because some patients were referred from the dermatology department, but none was referred from neurology and muscle disease departments.

Polymyositis is usually an exclusionary diagnosis where rash and other neurologic and other muscle diseases are absent. Like DM, PM also presents with neck and proximal muscle weakness and develops slowly among weeks and years. Myalgia, tenderness, dysphagia, facial weakness, quadriparesis, and weakness of jaw opening are the other clinical features (10-14). In our series, 55% of the patients were diagnosed as polymyositis, but in the literature, the frequencies of DM and PM are nearly equal (5). This may be due to the small number of the series or due to race differences.

Interstitial lung disease, autoimmune disorders, cancer, and cardiac disorders are associated with inflammatory myopathies. Ten percent to 25% of patients with IIMs have ILD at the time of diagnosis, and the symptoms are generally cough and dyspnea. Anti-Jo-1 positivity is known to be a risk factor for both ILD and anti-synthetase syndrome. Interstitial lung disease has mostly a chronic course but rarely may present with an acute feature. Nearly one-third of IIM patients have radiologic ILD during the course of the disease. ILD is a prognostic complication in patients with IIM, and in our series, the patients were evaluated with high-resolution computed tomography for the presence of ILD, and 15 (25%) had ILD proven with radiology (15-20).

Although malignancy in DM was reported to be as high as 45% in some reports, the general ratio is between 15%-25% and may present before, with, or after DM. Ovarian cancer and lung cancer are the most frequent cancers. On the other hand, PM has a slightly increased cancer risk. The frequency of malignancy-associated dermatomyositis was low in our trial, 5% (21-26). Other complications of IIMs are arrhythmias, congestive heart failure, and pericarditis. Some reports state that myocarditis is present in one-third of PM patients. Also, cardiovascular diseases are higher among these patients (27-29).

Screening for malignancy is offered in DM but also in PM at the time of the diagnosis. The data on the cost-effectiveness of screening in IIM are limited to some retrospective reports. A careful skin examination; computed tomography (CT) scan of the chest, abdomen, and pelvis; a mammogram and pelvic examination; and testicular and prostate examinations are indicated (30).

Serum creatine kinase levels are mostly increased in DM, but 10% of the patients may present with normal levels at the beginning. On the other hand, serum creatine levels are always increased in PM. The rapid decrease in the serum level shows a good response, but an increase may be a sign for relapse (27-30). Ac-

cording to the literature, 60%-70% of patients with inflammatory myositis have positive tests for ANA, but in our trial, the rate was 50% (15). The frequency of Jo-1 positivity was reported to be 10% in the literature, as in our series (15). The importance of Jo-1 is that 50% of the patients with a positive test result have or will develop ILD. There are also fewer available myositis-specific antigens (Table 3) (19, 20).

Electromyography (EMG) shows increased insertional and spontaneous activity, with small-amplitude low-frequency fibrillation potentials and positive sharp waves at the time of diagnosis and occasionally pseudomyotonic and complex repetitive discharges in the chronic stage. Muscle fibrosis may result in reduced insertional activity, especially in advanced cases. EMG is helpful in assessing relapsing weakness during treatment with corticosteroids, differentiating relapse from steroid-induced myopathy. Electromyography (EMG) positivity is a criterion for the diagnosis of DM and PM other than amyopathic DM (16). In our series, 43 (71.6%) of the patients were evaluated with EMG, and 39 (65%) had compatible results with myositis (17). Another diagnostic criterion is the histologic evaluation of the muscle and biopsy, performed in 48 (80%) patients, and 29 (48, 3%) had pathologies compatible with myositis (1).

Corticosteroids, methotrexate (Mtx), azathioprine, cyclophosphamide (Cyc), MMF, IVIG, and hydroxychloroquine are the most often preferred agents in the treatment of IIMs. In our trial, we treated 39 (65%) patients via oral agents and 19 (31.7%) via intravenous drugs. All patients were treated with an alternate-dose steroid protocol to lower the steroid-related side effects. Of all patients, 90% was treated with combination therapies, and azathioprine was the most frequently preferred agent for the combination. MTX and Cyc were used rarely, and the treatment options were compatible with the literature (14-17). Rituximab and IVIG were used only for 4 patients (2, 2) with resistant disease.

Although there are no controlled trials of corticosteroids, the authors agree that they are effective in DM and PM. Prednisone 1 mg/kg/d (60-100 mg) is often preferred at the beginning, mostly tapered to an every-other-day schedule. One or a few courses of intravenous methylprednisolone may be administered first in patients with severe weakness. A daily corticosteroid schedule needs close control for hypertension and serum glucose levels. Patients mostly feel better after starting corticosteroids, but strength improves over 2 to 3 months. Steroids may be used alone or may be combined with a second-line immunosuppressive agent, such as azathioprine, methotrexate, or IVIg, mostly for patients with refractive diseases. On the other hand, these immunosuppressive agents may be started with steroids concomitantly (31-36).

Methotrexate (MTX) is an effective and rapidly acting second-line steroid-sparing immunosuppressant for patients with IIM. The maximum weekly dose is 25 mg, and folic acid replacement should not be forgotten. The most prominent side effects are stomatitis, bone marrow suppression, liver toxicity, alopecia, pneumonitis, teratogenicity, induction of malignancy, susceptibility to infections, and renal insufficiency. Methotrexate-induced pneumonitis can be difficult to distinguish from myositis-associated interstitial lung disease; therefore, many clinicians do not prefer Mtx for patients with ILD or those with Jo-1 antibody positivity (31-36).

Azathioprine (AZA) is another very effective second-line steroid-sparing immunosuppressant. Azathioprine is administered in divided doses of 2 to 3 mg/kg/d, ranging from 100 to 250 mg per day. The clinical response begins in 4 to 8 months and peaks at 1 to 2 years. The most common adverse effects are a flulike reversible acute hypersensitivity reaction, myelosuppression, hepatotoxicity, susceptibility to infection, malignancy, teratogenicity, rash, alopecia, fever, and arthralgias (31-36).

Another option for myositis is ıntravenous immunoglobulin (IVIg). The complex immunomodulatory mechanism of IVIg probably involves reduced autoantibody production and binding, suppression of proinflammatory cytokines, Fc receptor blockade, increased macrophage colony-stimulating factor and monocyte chemotactant protein-1, altered T cell function, decreased circulating CD54 lymphocytes, and inhibition of cell transmigration into the muscle. IVIg 2 g/kg administered monthly for 3 months seems to be very effective in 75% of treatment-resistant DM patients (33). American Academy of Neurology guidelines recommend IVIg as an option for refractory DM (37). An initial dose of 2 g/kg is divided over 2 to 5 days. Maintenance dosing is 0.4 to 2 g/kg per month, administered every 1 to 4 weeks (37).

Mycophenolate mofetil, rituximab, and cyclophosphamide are the other treatment options for refractory patients with myositis. There are also rarely used options, such as etanercept, cyclosporine, tacrolimus, and chlorambucil. A large, multicenter clinical trial randomized 200 DM, JDM, and PM patients with refractory disease to receive rituximab and reported 83% benefit (38, 39). In a controlled trial of etanercept, 5 of 11 treated patients were successfully weaned off prednisone compared with none of the five placebo-treated patients (40).

For patients with ILD, corticosteroids are the first-line drugs, but immunomodulating drugs are usually necessary. Second-line mycophenolate mofetil, cyclosporine, and tacrolimus have been shown to be effective, but third-line Rtx and cyclophosphamide are also effective. One-third of patients with ILD experience resolution of pulmonary involvement, whereas 16% deteriorated, and nearly half have stable lung functions (41). Older age, symptomatic ILD, lower values of vital capacity, diffusing capacity for carbon monoxide, a pattern of interstitial pneumonia on high-resolution CT scan and lung biopsy, and steroid-refractory ILD seem to be poor prognostic factors for ILD.

The prognosis of idiopathic inflammatory myopathies is generally favorable, but associated malignancy leads to a poor prognosis for recovery and increases mortality. Concomitant ILD Jo-1 or SRP antibodies also predict a poorer prognosis. Recent series show that only 20% to 40% of patients will achieve remission, whereas 60^ to 80% will have a polycyclic or chronic continuous disease (42, 43). The most common causes of death are cancer, lung and cardiac complications, and infections. The poor prognostic factors are older age, male gender, non-Caucasian ethnicity, longer symptom duration, ILD, cardiac involvement, dysphagia, cancer, and serum myositis-specific antibodies (44-48). The survival rate in our series was also compatible with the literature. The 5-year survival rate was 76.9%, and the 10-year survival rate was 40%.

In conclusion, other than the higher ratio of PM in the series and higher ANA positivity, all other results were compatible with the literature. We have faced few resistant diseases, and therefore, preferred biologic agents were used rarely.

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