

Idiopathic Inflammatory Myopathy Associated with Malignancy: A Retrospective Cohort of 151 Korean Patients with Dermatomyositis and Polymyositis

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ABSTRACT. *Objective.* To define the standardized incidence ratio (SIR) of malignancy and factors associated with malignancies in Korean patients with dermatomyositis (DM) and polymyositis (PM).

Methods. The demographic, clinical, and laboratory features of 151 patients diagnosed with DM/PM were compared in patients with and without malignancies.

Results. Malignancies were found in 23 of 98 patients with DM (23.5%) and in 2 of 53 with PM (3.8%). Lung cancer (8 patients) was the most common malignancy. Compared with the period-specific, sex-matched, and age-matched Korean population, the SIR for malignancy in patients with DM was 14.2 (95% CI 9.0–21.3). Univariate analysis showed that factors associated with malignancy included older age ($p < 0.001$), DM ($p = 0.002$), dysphagia ($p < 0.001$), the absence of interstitial lung disease (ILD; $p = 0.001$), and lower elevations in aspartate aminotransferase ($p = 0.005$) and lactate dehydrogenase concentrations ($p < 0.001$). Multivariate analysis showed that factors independently associated with malignancy included older age (per 10 years, OR 2.3, 95% CI 1.6–3.5, $p < 0.001$), DM (OR 5.9, 95% CI 1.3–26.2, $p = 0.020$), dysphagia (OR 2.6, 95% CI 1.2–6.6, $p = 0.042$), and the absence of ILD (OR 0.1, 95% CI 0.01–0.9, $p = 0.040$).

Conclusion. DM was associated with a greater risk of concomitant malignancies, especially lung cancer, than PM. Independent factors associated with malignancies in patients with DM/PM were older age, the presence of dysphagia, and the absence of ILD. (First Release Aug 15 2011; J Rheumatol 2011;38:2432–5; doi:10.3899/jrheum.110320)

Key Indexing Terms:

DERMATOMYOSITIS

POLYMYOSITIS

NEOPLASMS

RISK

Dermatomyositis (DM) and polymyositis (PM) are idiopathic inflammatory myopathies (IIM), a group of systemic autoimmune diseases characterized by progressive, symmetrical weakness of the proximal muscles and, in patients with DM, by cutaneous lesions. Since the first report of a malignancy related to IIM in 1916¹, studies have reported that patients with IIM, especially DM, had a higher incidence of malignancy than the general population^{2,3,4,5,6,7,8,9}. Although several studies have focused on demographic, clinical, and laboratory markers associated with underlying malignancy in patients with IIM^{10,11,12}, the standardized incidence ratio (SIR) of malignancy and the factors associated with malignancy have not been thoroughly assessed in Korean patients. We therefore sought to determine the SIR of malignancy and factors associated with concomitant malignancies in Korean patients with DM/PM.

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MATERIALS AND METHODS

Patients. We retrospectively reviewed the medical records of 179 patients diagnosed with DM or PM at a single tertiary care hospital between 1989 and 2010. We included a total of 151 patients with DM/PM after excluding 6 patients with juvenile myositis, 3 with amyopathic DM, 14 with other connective tissue disease, 3 with malignancies diagnosed 2 years after the diagnosis of myositis, and 2 patients with malignancies diagnosed 5 and 3 years before the diagnosis of myositis. IIM was diagnosed as described⁴. Patients were subdivided into those with and those without malignancies, and at the time of DM/PM diagnosis, comparisons were made in the 2 groups with their demographic factors (age, sex), clinical findings [Raynaud's phenomenon, dysphagia, arthralgia, cutaneous involvement, interstitial lung disease (ILD)], and laboratory results [erythrocyte sedimentation rate (ESR) and concentration of aspartate aminotransferase (AST), albumin, lactate dehydrogenase (LDH), creatine kinase (CK), anti-nuclear antibodies, and anti-Jo-1 antibody]. ILD was diagnosed by both chest radiograph and high-resolution computed tomography of the lung.

Our study protocol was approved by the Institutional Review Board of the University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea, which waived informed patient consent.

Statistical analysis. Baseline characteristics between groups were compared using Student's *t* test or the Mann-Whitney *U* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Multivariate analysis was performed employing a Cox's proportional hazard regression model. Multivariate models used a stepwise backward elimination procedure based on a likelihood ratio test with $p > 0.10$ for removal and $p < 0.05$ for entry of variables. To avoid using too many variables, those that were significant in the univariate analysis were included in the multivariate models. The numbers and rates of malignancies according to the period-specific sex and age groups, as compiled by the National

Cancer Information Center of the Ministry of Health and Welfare of Korea (<http://www.cancer.go.kr>), were used to measure the SIR of malignancy. Results are reported as means \pm SD, and *p* values < 0.05 were considered significant. All statistical calculations were performed using SPSS version 12 (SPSS Inc., Chicago, IL, USA).

RESULTS

Each patient was monitored from the time of initial diagnosis of DM/PM to either the date of death or the date of latest followup at our hospital. Patients were followed up for a mean 48.9 \pm 49.3 months (range 12 days to 211 months). The 151 patients consisted of 98 with DM (81 definite and 17 probable) and 53 with PM (28 definite and 25 probable). Demographic and clinical data on these patients are presented in Table 1. Patients with IIM were predominantly women (60.9%). The patients with DM had significantly younger age and higher incidence of dysphagia than those with PM. However, there were no significant differences between the groups in sex, followup period, and rate of ILD.

Of the 151 patients, 25 (16.6%) had malignancies, with 2 patients having 2 malignancies each, during and after the diagnosis of DM/PM. These included 23 of the 98 patients with DM (23.5%) and 2 of the 53 with PM (3.8%). The incidence of malignancy in patients with DM was significantly higher than that in patients with PM (Table 1). The median time from diagnosis of myositis to malignancy was 6 days (range 0 days to 23 months). In 22 (88.0%) of the 25 patients, comorbid malignancies were detected within 1 year of diagnosis of IIM. Lung cancer was the most frequent form of malignancy observed (8 patients), followed by gastric cancer (5 patients), breast cancer (4 patients), biliary, nasopharyngeal, and thyroid cancer (2 patients each), and colon, pancreatic and ovarian cancer and non-Hodgkin’s lymphoma (1 patient each). Lung cancer and breast cancer were the most prevalent forms in men and women, respectively. When we compared our patient cohort with the period-specific, age-matched and sex-matched Korean population, we found that the SIR for malignancies was 8.1 (95% CI 5.3–12.0). The SIR for overall cancer risk among patients with DM was 14.2 (95% CI 9.0–21.3), and 15.6 (95% CI

Table 1. Baseline demographic and clinical data of patients with idiopathic inflammatory myopathies.

Category	Total	Dermatomyositis	Polymyositis	p
N (%)	151 (100)	98 (54.9)	53 (35.1)	—
Sex, women, n (%)	92 (60.9)	58 (59.2)	34 (64.2)	NS
Age, yrs, mean \pm SD	49.5 \pm 15.7	47.1 \pm 15.4	53.8 \pm 15.4	0.013
Dysphagia, n (%)	40 (26.5)	32 (32.7)	8 (15.1)	0.021
ILD, n (%)	50 (33.1)	32 (32.7)	18 (34.0)	NS
Followup, mo, mean \pm SD	48.9 \pm 49.3	44.5 \pm 50.0	57.0 \pm 47.2	NS
Malignancy, n (%)	25 (16.6)	23 (23.5)	2 (3.8)	0.001

NS: not significant; ILD: interstitial lung disease.

8.5–26.2) in men and 12.5 (95% CI 5.7–23.7) in women. In contrast, cancer incidence was not significantly higher in patients with PM than in the general population.

A comparison of the demographic, clinical, and laboratory findings in the 25 patients with and the 126 without malignancy are presented in Table 2. Patients with malignancy were significantly older (*p* < 0.001) and more frequently had dermatomyositis (*p* = 0.002) than those without malignancy. Clinically, the incidence of dysphagia was significantly higher (*p* < 0.001) and of ILD (*p* = 0.001) significantly lower in patients with malignancy than in those without. Patients with malignancy showed reduced elevation of AST (*p* = 0.005) and LDH (*p* < 0.001) compared to those without malignancy. Cox’s proportional hazard regression analysis was performed to determine the independent factors associated with malignancy. We found that having DM, older age, the presence of dysphagia, and the absence of ILD were independent factors associated with malignancy in Korean patients with IIM (Table 3).

DISCUSSION

The aim of our study was to determine the SIR of malignancy and the factors associated with concomitant malignancies in Korean patients with DM/PM. The frequency of malignancy in large studies of patients with DM and PM has been reported to range from 13% to 42% and from 3% to 18%, respectively^{2,3,5,6,7,8,9,11}. We found that the frequen

Table 2. Factors associated with malignancies in patients with idiopathic inflammatory myopathies.

Variables	With Malignancy	Without Malignancy	p
N (%)	25 (16.6)	126 (83.4)	
Age, yrs, mean \pm SD	62.4 \pm 11.5	46.9 \pm 15.2	< 0.001
Sex, men, n (%)	14 (56.0)	45 (35.7)	NS
Dermatomyositis, n (%)	23 (92.0)	75 (59.5)	0.002
Clinical findings (%)			
Arthralgia, n = 143	3 (13.0)	39 (32.5)	NS
Dysphagia, n = 151	17 (68.0)	23 (18.3)	< 0.001
RP, n = 140	1 (4.3)	6 (5.1)	NS
Heliotrope, n = 148	9 (39.1)	34 (27.2)	NS
Gotttron, n = 146	11 (47.8)	33 (26.8)	NS
ILD, n = 151	1 (4.0)	49 (38.9)	0.001
Laboratory data (mean \pm SD)			
ESR, mm/h, n = 125	48.2 \pm 30.6	46.3 \pm 28.6	NS
AST, IU/l, n = 147	143.8 \pm 184.4	220.3 \pm 198.5	0.005
Albumin, g/dl, n = 138	3.2 \pm 0.7	3.2 \pm 0.7	NS
LDH, IU/l, n = 148	656.2 \pm 464.0	1248.1 \pm 970.9	< 0.001
CK, IU/l, n = 146	3380.4 \pm 7182.3	4399.7 \pm 5528.1	NS
Antinuclear antibody, n = 136, %	15 (62.5)	48 (42.9)	NS
Anti-Jo-1 antibody, n = 110, (%)	0 (0)	8 (8.7)	NS

RP: Raynaud’s phenomenon; ILD: interstitial lung disease; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; NS: not significant.

Table 3. Independent factors associated with malignancy in patients with idiopathic inflammatory myopathies. The analysis was performed using a Cox's proportional hazard regression model. Δ AST (or LDH) was defined as the difference between the true AST (or LDH) concentration and the upper normal limit of AST (or LDH) concentration.

Variables	Hazard Ratio (95% CI)	p
DM	5.9 (1.3–26.2)	0.020
Age, per 10 yrs	2.3 (1.6–3.5)	< 0.001
Dysphagia	2.6 (1.2–6.6)	0.042
ILD	0.1 (0.01–0.9)	0.040
Δ AST, per 100 IU/l	0.9 (0.9–1.1)	0.755
Δ LDH, per 100 IU/l	0.9 (0.9–1.1)	0.062

AST: aspartate aminotransferase; LDH: lactate dehydrogenase; DM: dermatomyositis; ILD: interstitial lung disease.

cies of malignancy in patients with DM and PM in our study were 23.5% and 3.8%, respectively, within the ranges reported in previous studies. The overall cancer risk was significantly elevated among patients with DM (SIR 14.2, 95% CI 9.0–21.3), but not among those with PM (SIR 1.4, 95% CI 0.2–5.0). While several large studies reported a significant relationship between PM and malignancy^{2,3,5,6}, other studies are in agreement with ours^{13,14}. These differences were likely due to differences in the ethnicity of the patient population, whether the study was of patients in a single institution or population-based, the diagnostic criteria for DM/PM, and the methods used to screen for malignancies.

We found that lung cancer and breast cancer were the most prevalent forms of malignancies in men and women, respectively, in good agreement with previous findings^{2,3,5}. Western literature reviews have demonstrated that certain cancers, such as ovarian and breast carcinoma in women and lung and prostate carcinoma in men, are highly associated with IIM relative to the general population^{5,13,15}. In contrast, nasopharyngeal carcinoma has long been reported as one of the frequent cancers associated with IIM in Southeast Asia, including Hong Kong, Singapore, and Taiwan^{9,16,17}. These results suggest that the type and site of malignancy in patients with IIM parallels the expected probability of that cancer in each of those ethnic or regional populations. Gastric and lung cancers are the most frequently observed types of malignancies among Korean men, while thyroid and breast cancers are the most frequent types of malignancy among Korean women.

Factors associated with malignancies in patients with IIM have included cutaneous necrosis, low serum CK concentration, increased ESR, decreased serum albumin concentration, poikiloderma, dysphagia, older age, male sex, absence of arthralgia, and absence of ILD^{10,11,12,18,19,20}. Most of the factors we found associated with malignancy in patients with IIM had been identified previously. In most studies^{11,14,16,18,19,20}, older age at onset has been associated with the risk of underlying malignancy and our multivariate

analysis also found that older age was independently associated with the development of malignancy. Our results also suggested that dysphagia was independently associated with malignancy. One possibility is that dysphagia may be caused by a mechanical component of the malignancy, particularly in gastric and nasopharyngeal cancer. However, after excluding patients with gastric (5 patients) and nasopharyngeal (2 patients) cancer, we found that patients with malignancy had a significantly higher incidence of dysphagia than patients without malignancy (56.9% vs 18.3%; $p = 0.001$). Consequently, the mechanisms of malignancy-associated dysphagia may be other than mechanical compression.

We found that the occurrence of ILD at the time of diagnosis of IIM was associated with a significantly lower frequency of malignancy in our patients. One possibility is that patients with ILD have a poor prognosis²¹, suggesting that they may die earlier and before the development of malignancies. However, in our study the followup periods for patients with and without ILD were similar (48.7 ± 53.6 months vs 54.8 ± 51.3 months; $p = 0.271$) and most comorbid malignancies were detected within 1 year of diagnosis of IIM (88.0%). Consequently, it remains unclear why the absence of ILD is associated with malignancy.

Laboratory results showed that an initial lower serum AST and LDH elevation was associated with malignancy in patients with IIM on the univariate analysis, but failed to show a significant difference on the multivariate analysis.

Our study had a few limitations. First, because of its retrospective design, our searching strategy for malignancy was not homogeneous and there were many missing results, e.g., testing with anti-Jo-1 antibody was performed in only 72.8% of the patients with IIM. Second, the risk of individual cancer types in patients with DM/PM could not be estimated in our study because of the small number of each type of malignancy. Lastly, our study was performed on patients treated in a single-center tertiary care referral clinic, which may attract sicker patients with an increased number of malignancies or ILD.

Korean patients with DM but not those with PM were at a higher risk of concomitant malignancies, especially lung cancer. The independent factors associated with malignancies in patients with IIM were having DM, older age, the presence of dysphagia, and the absence of ILD.

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