Dermatomyositis and Polymyositis Associated with Malignancy: A 21-year Retrospective Study

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ABSTRACT. Objective. To analyze clinical and laboratory data of patients diagnosed with dermato- or polymyositis between 1985 and 2006, retrospectively, with particular emphasis on association with malignant diseases.

Methods. A thorough clinical assessment was performed on the immunological features and therapeutic responses, as well as survival data. In the case of 155 myositis patients, HLA haplotypes were also investigated.

Results. Out of 309 patients with myositis in our database, malignant disease was found in 37 cases. Thirty patients had dermatomyositis (28.8%), and 7 had polymyositis. In 64.8% of the cases, the malignancy and myositis appeared within 1 year. The highest probability for tumor recognition was before 2 years and after 3 years of the diagnosis of myositis (28 cancer-associated myositis): most frequent was breast tumor, and adenocarcinoma was the predominant histological type. The skin lesions and diaphragmatic involvement were more severe; distal muscle weakness was conventional, along with proximal muscle weakness and frequent immobility. Creatine kinase and lactate dehydrogenase elevations were lower than in primary myositis, and when controlled 1 month after surgical treatment of the malignant disease, these values showed significant reduction. Tumor markers did not predict the occult tumors. We found no correlation between the presence of tumor and DRB1-0301 and -01 alleles.

Conclusion. In patients with tumor-associated myositis, it was more frequently necessary to administer other immunosuppressive drugs along with glucocorticoids. The successful treatment of the underlying malignant disease improved the clinical course of myositis. The overall survival rate was considerably worse when compared to other forms of myositis. (First Release Jan 15 2008; J Rheumatol 2008;35:438–44)

Key Indexing Terms: DERMATOMYOSITIS POLYMYOSITIS MALIGNANCY

Dermatomyositis (DM) and polymyositis (PM) belong to the group of idiopathic inflammatory myopathies (IIM). These are systemic autoimmune diseases characterized by progressive, symmetrical weakness of the proximal muscles and in the case of DM, by cutaneous lesions. Researchers and clinicians have been interested for decades in the association of malignant diseases with IIM, mainly with DM. In 1916, Stertz was the first to describe a patient with biopsy-proven DM and stomach adenocarcinoma1. Later, several studies examined the relationship between DM/PM and malignant diseases, and an increased incidence of malignancy in myositis patients, particularly in DM, was reported in most studies2,3. In addition to DM/PM, other types of IIM may be associated with malignancy: juvenile DM, amyopathic DM, and inclusion body myositis4-6.

The following reasons have been considered probable for the association of myositis and malignant diseases7; (1) paraneoplastic syndromes — bioactive mediators produced by the tumor induce immune reactions against muscle fibers and skin; (2) causal role of the compromised immune system in the outbreak of tumor and myositis8; (3) malignant transformation induced by the second-line cytotoxic agents used in the treatment of myositis; (4) common carcinogenic environmental factors that can trigger immune reaction at the same time; and (5) immune reactions against the tumor, which transforms into an autoimmune syndrome as a consequence of the cross-reactivity with skin and muscle antigens9. Some observations suggest a model of paraneoplasia focusing on common autoantigen expression and immune targeting between cancer tissues and muscle tissue in myositis10.

We assessed the clinical and laboratory data of patients with DM/PM with particular emphasis on association with malignant diseases.
MATERIALS AND METHODS
At the Division of Clinical Immunology, 3rd Department of Medicine, University of Debrecen, patients with DM/PM have been treated and regularly followed up since 1985. In a median 102-month (range 8–190) followup period, out of 309 myositis patients we evaluated the clinical, immunological, and therapeutic characteristics of myositis cases associated with cancer. We performed a retrospective analysis of the clinical and laboratory data of PM/DM patients between 1985 and 2006 and analyzed the symptoms affecting skeletal muscles, the skin lesions characteristic of DM, and the existence of extramuscular manifestations in PM/DM [arthralgia, Raynaud’s phenomenon, cardiac involvement, and interstitial lung disease (ILD)]. The diagnosis of PM/DM was made according to the Bohan and Peter criteria. Skin and muscle biopsies were performed at the 2nd Department of Surgery and histologically evaluated at the Institute of Pathology. Pulmonary involvement was assessed by high-resolution computed tomography in cases of respiratory muscle insufficiency, blood gas analysis, and spirometry, while in dysphagia, an esophageal radiograph was performed. An electrocardiogram was done for each patient.

The following laboratory examinations were performed: assessment of the enzymes that are released during the necrosis of striated muscle and are suitable for monitoring of the clinical severity of myositis, lactate dehydrogenase (LDH) and creatine kinase (CK). Other values examined: tumor markers (carcinoembryonal antigen, cancer antigen 19-9, CA 72-4, CA 15-3, CA 125, and alphafetoprotein, and prostate-specific antigen in men), immune serology markers [antinuclear factor (ANF), extractable nuclear antigen (ENA), anti-Jo1]; genetic markers: different alleles of the HLA-DRB1, DQA1, and DQB1 markers and alphafetoprotein, and prostate-specific antigen in men), immune serology markers [antinuclear factor (ANF), extractable nuclear antigen (ENA), anti-Jo1]; genetic markers: different alleles of the HLA-DRB1, DQA1, and DQB1 antigens. In each case the diagnosis of the malignant disease was based upon histological assessment.

Statistical analysis was performed using SPSS for Windows 13.0 statistics software (SPSS Inc., Chicago, IL, USA). The survival curves were drawn using the Kaplan-Meier method. We used log-rank tests to determine the statistical significance of the observed differences in survival rates between patient groups. We considered p values < 0.05 significant. Routine statistical methods were used to describe the demographics of the patient groups and to examine the subgroups. Patient groups were compared using Student’s t-test and Fisher’s exact test.

RESULTS
Three hundred nine patients with PM/DM were admitted to our department, of whom 206 had PM and 103 had DM. Of the 206 PM patients there were 7 cases associated with cancer (3.8%). Tumors were found in 30 out of 103 patients with DM (28.8%). Myositis was associated with neoplasms in 37 patients with DM/PM (11.9%).

Association between myositis and neoplasms. In 2 patients the 2 diseases appeared simultaneously, in 6 patients the tumor appeared ≥ 3 months after the presence of myositis (16.2%), in 11 patients 4–12 months later (29.7%), in 2 patients between 13 and 24 months (5.4%), in 1 patient 3 years after the appearance of myositis (2.7%), and in 6 cases more than 5 years (5, 6, 7, 10, 20, and 30 yrs) elapsed between the appearance of myositis and the tumor (16.2%). In 4 cases the diagnosis of the malignant tumor had preceded the appearance of myositis by ≥ 1 year (10.8%), in 2 patients by 18 months (5.4%), and in 2 other patients 72 months passed between the recognition of the malignant disease and the expression of myositis symptoms (5.4%). Altogether, 64.8% of the tumors developed within the first year (24 patients; Figure 1).

In a single case, several primary tumors appeared during the life of a patient with DM (endometrial carcinoma 16 years prior to myositis, kidney carcinoma 2 years prior, and colon and stomach cancers 9 and 11 years, respectively, after the expression of DM). However, malignancies always occurred independently from the myositis activity, therefore the association between the tumors and DM is questionable. Based on previous population studies and our findings, we considered the following cases as cancer-associated myositis (CAM) or paraneoplastic myositis: the tumor preceded the myositis by < 2 years; the diagnosis of cancer was achieved during the first 3 years after myositis appeared; or the symptoms of myositis and tumor presented simultaneously (± 1 yr). Of the 37 DM/PM patients with tumors described above, 28 corresponded to these more severe criteria; in these situations a paraneoplastic origin was probable. In the remaining 9 cases, the tumor and myositis association was random. All 37 patients who in their patient history had myositis and tumor are termed T+M.

The mean age of patients with DM at the time of the diagnosis was lower than that of the patients with CAM: 43.25 ± 12.6 yrs vs 57.11 ± 10.06 yrs (we considered baseline to be the patient’s age at the time of diagnosis). The mean age of all treated patients with IIM (40.9 ± 11.6 yrs) was lower compared to the mean age of patients with primary DM (43.25 ± 12.6 yrs). The patients with PM were the youngest, mean age 39.8 ± 12.01 yrs. The age of the T+M population was lower compared to the CAM population, 54.28 ± 12.91 vs 57.11 ± 10.06 yrs, respectively. Figure 2 shows the age and sex distribution.

Tumor localization, pathological subtypes. Breast and gastrointestinal tumors were the most frequent, followed by the occurrence of lung tumors. If we disregarded the 9 patients who did not fulfill CAM criteria, the following cancer phenotypes were found: in our 24 patients with DM we found 6 cases of breast cancer, 4 of lung tumor, 3 of stomach neoplasm, 1 intestinal tumor, 2 epitharynx carcinomas, 2 cases of Kaposi’s sarcoma, and 1 case each of cervix, bladder, prostate, brain, ovarian tumor and non-Hodgkin’s lymphoma (NHL); adenocarcinoma was the most frequent histological subtype. In 4 patients with PM, 1 breast, 1 lung, 1 cervix, and 1 T-cell lymphoma developed.

Clinical features. We examined the course, progression, and changes of the clinical symptoms in our patients with cancer-associated DM and in patients where DM was the only disease. Such comparison was not performed in PM because of the relatively low number of cancer cases. In both groups the skin lesions were characteristic and specific to DM — heliotrope rash (cancer-associated vs non-associated: 83 vs 89%), Gottron’s papule (88% vs 63%), Gottron’s sign (68% vs 51%), V-sign (72% vs 66%), and facial erythema (83 vs 91%). It is to be noted that in more severe cancer-associated cases, generally therapy-resistant skin changes could be observed, e.g., ulcerations and itching (cancer-associated vs non-associated: 44% vs 12%; p < 0.05). Limb muscle weakness was present in both groups, but in the tumor-associated group,
besides proximal muscle involvement (95% vs 99%), distal muscle weakness (57% vs 6%; p < 0.05) was also present. The limb muscle weakness of the cancer patients was strikingly severe and frequently was associated with immobility (39% vs 12%; p < 0.05). Dysphagia (50% vs 36%), oropharyngeal dysfunction (32% vs 13%), and respiratory muscle involvement (32% vs 16%; p < 0.05) were more frequent in the tumor group; the respiratory insufficiency due to respiratory muscle involvement was frequently lethal in this group. The presence of ILD (19% vs 25%; p < 0.05) and cardiac involvement (0% vs 7%) was more rare in the cancer-associated than in the primary myositis group. Other symptoms, such as arthritis/arthralgia (16% vs 51%; p < 0.05), Raynaud’s syndrome (11% vs 26%; p < 0.05), and fever (0% vs 29%; p < 0.05), differed significantly between the 2 subgroups.

The CK and LDH activity was high in both groups, but more elevated levels were observed in the primary myositis group (CK, p = 0.039 and LDH, p = 0.047); the mean ± SD CK in CAM was 1776 ± 551 U/l, and in primary DM 3912 ± 1850 U/l. The mean LDH in CAM was 743 ± 234 U/l, and in primary DM 1637 ± 764 U/l (Figure 3). We measured the CK and LDH levels before and one month after surgery for the primary tumor in 16 CAM cases. The decreases were significant: the mean CK before surgery was 2310 ± 646 U/l, and after surgery 110 ± 76 U/l. LDH level before intervention was 1312 ± 820 U/l, and after intervention 470 ± 98 U/l (p < 0.05; Figure 4). Positive ANF and ENA titers were significantly more frequent in the primary myositis group (16% vs 39%, 0% vs 41%, respectively; p < 0.05). Presence of anti-Jo1 antibodies was detectable in only 16% of primary DM cases. In
patients with CAM this antibody was not present. For cancer screening and followup purposes we measured the serum tumor marker levels. Only CA 15-3 showed the simultaneous presence of breast cancer in one case. Concerning gastrointestinal and prostate cancers, we did not observe the expected elevated CEA, CA 19-9, and PSA serum levels. Due to the low number of patients, statistical evaluation was not performed.

Genetic findings. To study the genetic background of myositis, we conducted genetic studies in 145 patients with DM/PM and 10 patients with tumor (CAM). Subclass member HLA-DRB1*0301, -01, -03, and HLA-DQA1*0501, -01, -05 alleles and the occurrence of HLA-DQB1*02, -03 alleles were investigated. No associations were found regarding the DRB1*0301 and -01 alleles and patients with CAM (Table 1).

Therapeutic observations. Compared to the 79 patients with primary DM, during the treatment of the 24 patients with tumor-associated DM, the administration of secondary immunosuppressive therapy simultaneously with or after high-dose glucocorticosteroid therapy was necessary significantly more often (64% vs 42%; p < 0.05). Along with myositis treatment, the treatment of the tumor (surgery, chemotherapy, radiotherapy) resulted in complete recovery from the myositis symptoms in 16 patients.

Survival rates, causes of death. The type and stage of the underlying malignant tumor and their association with severe myositis symptoms such as respiratory insufficiency determined the survival prognosis of the cancer-associated cases. According to our results, the 1 and 5-year survival was significantly higher in the primary myositis group compared to the CAM patient group (Figures 5 and 6). Assessing the survival data of all 37 patients (T+M) confirms that in the 9 patients the simultaneous presence of the 2 disease entities happens randomly; therefore, by adding the data of these patients to the CAM patients, the survival rates improved (Figure 7).

In patients where the tumor appeared simultaneously with DM, the course of the disease was more severe than in those cases where the tumor preceded the appearance of myositis by years. We lost 9 of the 28 patients with CAM (32%), one patient due to dissemination of the tumor and involvement of the respiratory muscles, 3 due to pneumonia, and 2 due to severe respiratory muscle involvement. In these 6 cases, respiratory insufficiency was detected. One patient died of pulmonary embolism. One patient had to undergo surgery due to ileus and that patient died after surgery. One patient died due to heart insufficiency. In the 6 cases with respiratory failure, the tumor and myositis occurred within 1 year and despite the intensive myositis therapy, the simultaneous existence of both tumor and acute myositis symptoms led to death of the patient. The most common cause of death was respiratory insufficiency, while in primary IIM the most common cause of death was of cardiac origin.

In 16 of the 28 patients (57%) the tumor was removed sur-
gically, 13 patients (46%) received chemotherapy, and 11 patients (39%) received radiotherapy. Twenty-two patients received some type of active oncological treatment (78%), while many patients received complex oncological management. In 4 patients oncological treatments were not possible due to severe respiratory failure; these patients died, and 2 patients could not undergo antitumor therapy due to overall weakness caused by the spread of the tumor. In 7 cases the symptoms persisted despite therapy, while 16 achieved remission. Relapse of the myositis occurred in 5 cases months or years after complete regression of symptoms, but no underlying tumor could be detected; the reason for this is not known. All cases responded well to steroid therapy; mild myositis symptoms were observed. The disease course could not be considered monophasic in these cases; it was regarded as relapsing-remitting.

DISCUSSION
In our study the association of DM and PM with malignancies was examined retrospectively in 309 patients during the study period of 21 years. Prevalence of the joint occurrence of the 2 conditions was determined, as well as the frequency of the different histological types of tumors observed. We attempted to identify genetic markers and clinical prognostic factors that could reliably predict the development of malignant tumors in patients with DM/PM. The clinical course of both conditions was followed. Based on our observations we tried to formulate some recommendations for the therapeutic management of patients with CAM.

According to previous observations, the incidence of the association between malignant diseases and myositis varies between 7% and 66%14-17. One study, however, could not find any relation between PM/DM and malignancy18.

Several studies have determined the relative risk (RR) of neoplasm in patients with PM/DM. In a metaanalysis, Zantos and colleagues analyzed the data of 1078 patients with PM/DM and found that the RR of tumors was 4.4 and 2.1 in DM and PM, respectively2. Stockton and colleagues examined 705 patients and they found the RR was 7.7 in DM and 2.1 in PM19. By summarizing and revising the results of recent cohort surveys carried out in Sweden, Finland, and Denmark, Hill and colleagues determined the RR of neoplasm as 3-fold in DM and 1.3-fold in PM3. Buchbinder, et al investigated the risk of malignancy in patients with biopsy-proven IIM; RR was 6.2-fold in DM, 2.0-fold in PM20.

Previous data and our own findings support the theory that patients with malignancy-associated myositis are older than those who do not have cancer. Although this association is more frequent in older people (> 45 yrs), the risk is also higher in patients under 45 as compared to the normal population3,19. The mean age of our patient population was 57 years. The association between myositis and malignancy is more frequent in women than in men19. Our results showed that in 64% of the patients the symptoms of DM/PM developed in the
same year as the tumor, and the interval with highest probability for tumor recognition was between 2 years preceding and 3 years following the diagnosis of myositis.

Although a wide spectrum of cancer types can be associated with myositis, certain types can be observed more frequently, i.e., ovarian carcinoma\textsuperscript{21}, lung cancer\textsuperscript{22}, lymphoma, and gastric cancer in adults; and hematological cancers develop more frequently in children. But other forms of malignancy are also associated with myositis, like testicular cancers and thymoma\textsuperscript{15}. In the Asian population the most frequent type is nasopharyngeal carcinoma\textsuperscript{16,23}, in which both the genetic background and the different nutritional habits may play a role. The epidemiological study performed by Hill, et al\textsuperscript{24} examined a population large enough (1532 patients with myositis) to determine the RR for the individual types of tumors\textsuperscript{3}. In DM, ovarian carcinoma, lung cancer, pancreatic tumor, gastric and colorectal cancer, and NHL had the highest RR, whereas in PM the highest RR was observed in NHL, lung cancer, and bladder carcinoma. The highest frequencies in DM were represented by adenocarcinoma and in PM by hematological cancers. Our findings did not fully correspond to the previous observations of the National Cancer Registry (NCR). In our patient cohort, among patients with DM the most frequent tumor types were breast, lung, gastric, and epipharyngeal cancers, whereas the most frequent tumor types as described by the NCR are lung, skin, colorectal, and breast cancer\textsuperscript{24}. The difference in the frequency of myositis-associated and non-associated tumors raises the possibility that there are cancer types that are more often associated with myositis (paraneoplastic myositis). Among patients with DM the most frequent histological type was adenocarcinoma.

As in most autoimmune diseases the strongest risk factor for disease development is the presence of certain MHC alleles, the genetic background of the association between myositis and neoplasms was also examined in our study. Among the first published IIM-associated alleles were HLA-B8 and HLA-DR\textsuperscript{25}. Later, HLA-DRB1*0301 and HLA-DQA1*0501 alleles were described in connection with IIM\textsuperscript{25-28}. We conducted genetic analysis on 145 patients with DM/PM and 10 patients with CAM. We found no association between HLA DRB1*0301 and -01 alleles and CAM cases.

We also tried to identify clinical prognostic factors that can predict the simultaneous presence of the malignant disease and myositis. Case reports suggest the predictive role of the following factors: elderly age, therapy-resistant erythroderma, extended or atypical cutaneous lesions, rapidly progressing severe muscle weakness, lack of serological abnormalities, and other risk factors for malignant diseases\textsuperscript{29}. Gallais and colleagues identified necrotizing cutaneous lesions and severe pruritus as predictive factors\textsuperscript{30,31}. Hunger, et al\textsuperscript{29} described the presence of cutaneous leukocytoclastic vasculitis in patients with DM associated with malignancy\textsuperscript{32}. In our patients the Gottron’s papules were ulcerated and healed very slowly. Respiratory muscle involvement was more frequent; severe proximal and also distal limb muscle involvement was present in cancer-associated DM. Despite the severe symptoms, the serum CK levels often remained within the normal range\textsuperscript{3,7}. The significant decrease of the CK and LDH levels observed 1 month after tumor surgery further supports the theory of paraneoplastic origin. The anti-Jo1 autoantibody was not present in the sera of our and other investigators’\textsuperscript{2} patients with CAM\textsuperscript{33-35}. Some authors suggested that tumor markers have significant prognostic value\textsuperscript{36}, but our observations did not support this hypothesis.

Our observations showed that the clinical course of myositis correlated with the concomitant malignant disease. Because of the severity of the clinical symptoms in most cases of paraneoplastic DM it is necessary to use second-line immunosuppressive drugs besides corticosteroids. After the administration of effective cancer treatment the skin and muscle symptoms of DM rapidly improve. The essential aim of disease management is the recognition and treatment of the neoplasm, which also ameliorates both the muscle and skin symptoms. Based on these findings we suggest that in patients with CAM the tumor should be discovered as early as possible and the surgical removal performed as soon as possible. The survival data of patients with CAM are unfortunately still unfavorable\textsuperscript{37}. We believe that the cause could probably be the poor disease course of the underlying malignant process. In our cohort of patients, the 1-year survival rate of 56% is considered favorable, especially compared to a recently published Japanese survey, where the rate was 10%\textsuperscript{13}. The considerable difference could be due to the fact that in our Clinical Immunology Department the patients with IIM have been regularly and thoroughly followed up since 1985, and we also enrolled a significantly larger patient population in this study. It is important to emphasize that once the diagnosis of DM is reached in a patient, a systemic tumor investigation is absolutely necessary within 3 years, as the risk of neoplastic transformation is still high. The multidisciplinary management of patients with CAM is also important.

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