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Clinical, Serologic, and Immunogenetic Studies in Patients with Dermatomyositis

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Dermatomyositis is a disease of unknown etiology characterized by progressive, symmetrical, proximal muscle weakness with accompanying compatible cutaneous findings. Thirty-nine patients with dermatomyositis from the Louisville, Kentucky area were enrolled in this study. Patients were grouped into those with or without a malignancy. Ten patients (26%) either had or have had a malignancy. Twenty-five Caucasian patients were HLA typed for the A, B, DR and DQ locus antigens, of whom 5 had an associated malignancy and 20 did not have a malignancy. We found that no single antigen had a significantly increased or decreased frequency as compared with our control population for the entire group, or for any clinical subset we examined. Serologic testing revealed 4 patients with anti-Mi-2 antibodies and 1 patient with anti-PM-SCL antibodies. No patient had a positive anti-Jo-1 antibody in this group. The results of serologic tests in this group did not correlate with any clinical subset or HLA antigen. Our findings were in agreement with the previous reports in which approximately 25% of patients with DM have an associated malignancy. Our findings also support the notion that untargeted malignancy searches are not warranted. Contrary to previous reports we did not observe an inverse relationship between cancer and pulmonary disease in the dermatomyositis patient. This study does not indicate that there are any HLA associations or clinical associations, other than age, that distinguish patients with dermatomyositis as running a greater risk of developing malignancy.

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The relationship of dermatomyositis with malignancy remains an area of controversy (1–4). We have had an opportunity to review the experience of our region, which has included both patients referred to one of us (J.P.C.) as well as those seen in the general population of the Louisville area. Immunogenetic data from previous studies have suggested that some subsets of inflammatory myopathy may have HLA correlates (5–7). We have studied 39 patients seen in the Louisville area since 1977 in an attempt to evaluate the frequency of malignancy, and possible clinical and/or immunogenetic associations.

PATIENTS AND METHODS

Thirty-nine cases of adult dermatomyositis (DM) or cutaneous dermatomyositis ('dermatomyositis sine-myositis') were included in this study. These patients were recruited from the Louisville, Kentucky area by contacting local physicians and by having the medical records departments of eight local hospitals perform searches for patients with the diagnoses of dermatomyositis and/or polymyositis.

Only patients with definite or probable DM, as defined by Bohan & Peter (3), were included in this study. We chose to also include 2 patients with cutaneous findings of DM in the absence of muscle disease, since these patients often develop myositis (8). The records of all patients were reviewed for clinical history, the presence of muscle weakness on physical examination, and the presence or absence of cutaneous signs of DM. Laboratory analysis results, including muscle enzymes and urinary creatine determinations, muscle biopsy, electromyography, rheumatoid factor, antinuclear factor determination, and erythrocyte sedimentation rate were recorded. In addition, we reviewed each record to determine the extent of evaluation for a potential underlying malignancy that was undertaken at the time of the diagnosis of DM.

An attempt was made to obtain blood for HLA typing on patients in the study group. The blood samples were typed for HLA-A, -B, -DR and -DQ antigens by the Tissue Typing Laboratory at the University of Louisville School of Medicine (J.B.K.). The procedure and antigens used have been detailed in a previous report (9). Only 25 of 39 patients could be typed, due to patient's death or inaccessibility. Serum was also obtained for serologic studies at the Oklahoma Medical Research Foundation (I.N.T.). The procedures used which included Ouchterlony immunodiffussion, indirect immunofluorescence, nucleic acid pre-

cipitation and protein immunoprecipitation, have been detailed elsewhere (10, 11).

The information from the data sheets and the results of the HLA typing were collected and examined statistically by analysis of variance (ANOVA) and χ^2-tests where appropriate. The *p*-values obtained for the HLA data were corrected for number of antigens tested statistically.

RESULTS

There were 32 (86%) patients with definite DM, 5 (14%) patients with probable DM and 2 with cutaneous DM. These patients were then divided into two groups: patients without a documented malignancy (29 patients) and those with a documented malignancy at any time in their course (10 patients).

Epidemiologic features

The mean age of the patients with malignancy (mean = 60.0) was statistically higher than in the group without a malignancy (mean = 46.2) ($p < 0.02$). The sex ratio (female/male) of the group with malignancy (9 : 1) was greater than that of the group without a malignancy (20 : 9). The number who had died was also greater for the group with malignancy (4 : 10 vs 4 : 29).

Moreover, the time interval from the patient's first report of a characteristic symptom of DM to the definitive diagnosis of DM was shorter in the patients with malignancy (mean = 8.36 months) than in those without malignancy (mean −24.6) ($p < 0.03$). This fact may indicate that the disease is more aggressive in the former.

Clinical features

All of the patients in the study had symmetrical proximal muscle weakness, except for the 2 with cutaneous DM in whom an inflammatory myopathy could not be detected. With respect to dermatological manifestations, 21 (54%) patients had a characteristic heliotrope rash, 25 (69%) patients had Gottron's papules, and 10 (31%) were observed to have a poikilodermatous rash, generally in a distribution that would suggest photosensitivity. The cutaneous rash present and its presumed character did not differ with the presence or absence of an internal malignancy.

Dysphagia was reported by 16 (41%) of the 39 patients. Of those with an associated malignancy, 5 of the 10 patients had dysphagia, whereas 11 of the 29 patients without malignancy had dysphagia. This difference was not statistically different. Dyspnea occurred in 11 patients, 5/10 with malignancy and 6/29 without malignancy (*p*: N.S.). Dysphonia was present in 4 patients, 3 of whom had an associated malignancy and 1 who did not.

Laboratory findings

Tests confirmatory of the myositis such as abnormal muscle enzyme levels, increased excretion of urinary creatine, abnormal electromyography, and abnormal muscle biopsies, were routinely present by definition. Only the 2 patients with cutaneous dermatomyositis had normal tests. An elevated erythrocyte sedimentation rate was more frequently observed in the patients in whom an associated cancer occurred (8/10 versus 14/23), but this difference was not statistically significant. Antinuclear antibodies preformed by a local laboratory (titer > 1 : 40) were commonly observed (27/35), but were no more frequent in those with malignancy or with pulmonary disease. We were able to obtain serum from 27 patients, most of whom were also HLA tested. Twenty patients proved positive by indirect immunofluorescence testing (19, nuclear; 2, nucleolar; 4, cytoplasmic; and 1 speckled). Anti-Mi-2 was present in 4 patients who producted the four sera with the strongest antinuclear staining by indirect immunofluorescence. Three of these 4 patients had abnormal pulmonary function study results, but only one had pulmonary fibrosis by chest roentgenography. One patient had an anti-synthetase antibody (PL-12) but had normal pulmonary function. One other patient had both anti-Ku and anti-PM-Scl antibodies, but clinically did not demonstrate evidence of a myositis-scleroderma overlap. None of these patients exhibited features of other collagen-vascular diseases despite the presence of a positive ANA.

Pulmonary evaluations were undertaken in 17 of the patients, which included all of the patients who had symptoms of dyspnea or those who had an abnormal chest X-ray (CXR). Pulmonary fibrosis as demonstrated by an abnormal CXR was present in 5 patients, which included one of the patients with malignancy. Pulmonary function tests were abnormal in 9 of the 17 patients in whom they were performed. Restrictive disease was observed in 6 patients, and obstructive disease was present in 3 patients.

Immunogenetic testing (HLA) was performed in 25 of our patients, all of whom were Caucasian. We tested for HLA antigens at the A, B, DR, DRw52

and DQ loci. Five of the patients in the group we tested had an associated malignancy, while 20 did not. We were unable to demonstrate an increased frequency of any antigen at any of the loci exceeding what would be expected. Specifically in examining the DR locus there was no increase in DR2 or DR3. Furthermore, there were no differences noted in those with associated cancer.

Dermatomyositis and malignancy

Ten of our 39 patients (26%) had a malignancy at some time in their course. These 10 patients had a total of 12 malignancies. In a majority of the patients the malignancy preceded the diagnosis of dermatomyositis, often by several years. However, in 4 of the patients, metastatic disease was present at the time of the diagnosis of the dermatomyositis. There was no predominant cell type or site of malignancy in this group of patients. A majority of these patients were females and thus malignancies of the breast (4) and the genitalia (cervix, 2; uterus, 2) were the most frequently observed tumors. In only 2 of our patients was the malignancy discovered within a short time of the diagnosis of dermatomyositis, which we considered as possible 'concurrent' cancer. One patient was evaluated for abnormal uterine bleeding, and found to have a uterine mass by physical examination, but following her hysterectomy and radiation therapy she developed dermatomyositis. In another patient's evaluation at the time of diagnosis of dermatomyositis, an abnormal breast examination led to the discovery by mammography of her breast tumor.

A total of 83 diagnostic procedures were performed at the time of diagnosis of the inflammatory myopathy in our 39 patients with dermatomyositis. Of these procedures, only in one patient did the procedure lead to the discovery of the malignancy at the time of the diagnosis of the patient's myositis. However, in the 8 patients in whom a malignancy was present by history, 2 were discovered to have metastatic disease at the time of the diagnosis of their dermatomyositis. In none of these patients was the treatment of malignancy associated with any observable or measurable alleviation of the dermatomyositis.

DISCUSSION

Dermatomyositis is an immunogenetically heterogeneous disorder which may be associated with internal malignancy. In our study we found that 26% of the patients had an associated malignancy, but that it was rarely directly discovered or related to the muscle disease or the cutaneous manifestations. We failed to identify an immunogenetic or serologic correlate in the DM patients, regardless of their status regarding the presence or absence of an associated cancer. As in previous studies, the malignancies in our patients were discovered by historical abnormalities, abnormalities found on physical examinations, or abnormalities found during age-related 'routine' testing, rather than by non-targetted malignancy evaluations.

Histocompatibility antigens (HLA) have been reported to correlate strongly with several autoimmune disorders (5). It might be possible to identify individuals predisposed to a disease state, identify and prevent or treat the triggering agent(s) and thus prevent disease expression. Arnett et al. (5) have reported that HLA-DR3 incidence was increased in Caucasian patients with myositis, and that HLA-DRw52 correlated strongly with the presence of the Jo-1 antibody in both races. In studies on children with dermatomyositis, HLA B8/HLA DR3 has been associated with disease (6, 7). We only tested adult Caucasians, but failed to demonstrate increases in any HLA antigen tested. Further, we were unable to note any tendency which would correlate with the presence of malignancy, pulmonary abnormalities, laboratory findings or serological testing. It is possible that patients with DM are a heterogeneous group, and that current HLA markers are not predictive of a predisposition to develop this disorder.

Serologic testing in our group of patients with DM, all of whom had typical cutaneous features, identified a positive ANA in the majority of patients tested. However, we were able to identify only 4 patients with anti-Mi-2, an antibody which has been associated with DM but not PM. This frequency is similar to that observed in a previously studied population (11). Of the 4 patients with anti-Mi-2 antibody, 3 had abnormal pulmonary function tests, but only one had evidence of pulmonary fibrosis by CXR. Only one of our patients had an anti-synthetase antibody despite the presence of pulmonary disease in 9 of the 17 patients evaluated. Furthermore the patient with anti-PL-12 had normal pulmonary function. One of our patients had anti-PM-Scl and anti-Ku antibodies, a combination not previously reported. Furthermore, this patient had typical DM with pulmonary fibrosis, but without any fea-

tures of a scleroderma overlap. The PM-Scl antibody has previously been associated with the scleroderma-myositis overlap. These data did not demonstrate an antibody test which was specific for any clinical subset within our group (e.g. those with cancer, those with pulmonary fibrosis, etc.).

Ten patients in our group had an associated malignancy at some time in the course of their disease. These patients tended to be older, had the DM diagnosed at a shorter interval from the onset of symptoms and were more often female than those without cancer. However, they did not have any other clinical feature that might distinguish the groups. Those with malignancy were found to have pulmonary disease just as frequently as those without cancer. This is different from previous studies in which there appears to be an inverse correlation between cancer and pulmonary fibrosis (12, 13). The tumors were those which were common to the sex and age of our patients. Thus, tumors of the breast and female genitalia were most common in our study. We only examined DM patients, and did not have an adequate control group for comparison of the frequency of malignancy, however our data is consistent with that of Manchul et al. (14) in which they found preceding and concurrent malignancy to be more common than subsequent malignancy.

Even if the frequency of malignancy is higher in DM than the normal population, the exact nature of this relationship is important. A majority of our patients had a history of malignancy prior to the diagnosis of DM, but 4 of these 8 patients had active malignant disease at the time of diagnosis of DM. In only one of these patients was the recurrent malignancy discovered in relation to the evaluation of a new symptom shortly after the diagnosis of DM. None of our patients seemed to respond to treatment of their malignancy. In fact, several of the patients had active DM in the absence of demonstrable cancer, and their DM was quiescent at the discovery of active malignant disease. Although there are reports in which individual cases are suggestive of a direct relationship of DM and cancer, (13, 14) a majority of the reports (15–21) including the data presented here, fail to suggest that DM and cancer are directly related (paraneoplastic phenomenon).

Beginning in 1975, with the landmark article of Bohan & Peter (3), the value of malignancy evaluation was questioned (14–16, 20, 22, 23). In the first report dealing with this controversy, Moss & Hanelin (23) clearly demonstrated that radiological testing was of limited value. Similarly, Callen et al. (16) failed to note the value of extensive radiological or endoscopic testing. Our current data demonstrate the lack of value of these tests, including the use of CT scanning in 10 patients. Callen (1) suggested that malignancy evaluation be carefully conducted to include a complete and thorough anamnesis and physical examination, and testing including a CBC, chest X-ray, urinalysis, serum multiphasic analysis, stool guaiac, and appropriate age-related cancer screening tests such as sigmoidoscopy, mammography, and other radiological or endoscopic studies as recommended by the American Cancer Society. Further evaluation of any abnormal symptom and/or physical finding should be undertaken. Our current data suggest that this approach is appropriate.

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