Routine vs Extensive Malignancy Search for Adult Dermatomyositis and Polymyositis

A Study of 40 Patients

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Objective: To identify potential risk factors and the yield of routine screens for early detection of malignancy associated with dermatomyositis (DM) and polymyositis (PM).

Design: Retrospective study of malignancies in all patients with DM or PM followed up between the years 1981 and 2000 and a review of the relationship of DM and PM to malignancy, the usefulness of various tests or examinations for malignancy search, and the patients' course.

Setting: Departments of internal medicine and dermatology in a teaching hospital.

Patients: Forty consecutive adult patients with DM (33 cases) or PM (7 cases).

Main Outcome Measures: (1) Rate of false-negative results of routine workup and yield (percentage of positive results) of blind malignancy search and (2) comparison of 16 characteristics in patients with malignancy vs those without.

Results: Malignancy occurred in 16 patients: 13 with DM and 3 with PM. In all cases, the diagnosis of malignancy was made concurrently with or shortly after the diagnosis of DM or PM. Factors associated with malignancy were recruitment in the internal medicine department ($P = .02$), constitutional symptoms ($P < .01$), a rapid onset of DM or PM ($P = .02$), the lack of Raynaud phenomenon ($P < .01$), and a higher mean erythrocyte sedimentation rate ($P < .01$) and creatine kinase level ($P < .01$). Initial routine search failed to discover 4 malignancies, 3 of which were discovered at an advanced stage by more extensive investigations. The positive result yield of blind malignancy search was only 13% (11 of 87), but reached 28% (5 of 18) for blind abdominal-pelvic and thoracic computed tomographic scans.

Conclusion: Extensive search for malignancy, particularly computed tomographic scans, may be warranted in at least a subset of patients with DM or PM and risk factors of malignancy.

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DERMATOMYOSITIS (DM), a rare inflammatory myopathic disorder characterized by proximal, symmetric muscle weakness and specific skin lesions, has been associated with an increased incidence of malignancies, although the exact risk and incidence in these patients is controversial. In almost two thirds of all patients, there is a close temporal relationship between the diagnosis of myositis and the diagnosis of malignancy, suggesting that the 2 processes are linked.

For editorial comment see page 969

For Callen et al, Callen, and Richardson and Callen, most formerly published data do not support the usefulness of an extensive malignancy evaluation in otherwise nonsymptomatic patients with DM or polymyositis (PM). In our opinion, further studies are warranted to clarify the optimal screening strategies for malignant neoplasm in patients with DM or PM because (1) there is, to our knowledge, no published study that has prospectively compared the value of routine and extensive workup; (2) routine malignancy screening did not enable all authors to detect malignancies at an early, potentially treatable stage; (3) in 2 recent case-control studies, colon and rectal carcinoma were found to be overrepresented in elderly patients, justifying routine lower digestive tract investigations in this group of subjects; (4) pelvic computed tomographic (CT) scans

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PATIENTS AND METHODS

Forty adult patients with DM or PM (age ≥18 years) seen between 1981 and 2000 in the Departments of Dermatology (19 cases) and Internal Medicine (21 cases) of Dupuytren Hospital, Limoges, France, were enrolled in a retrospective study. Diagnosis was based on the criteria of Bohan and Peter24 and of Strongwater.25 Patients with inclusion body myositis and macrophagic myofascitises were excluded. Dermatomyositis was considered definite with the presence of 3 or more criteria, probable with 2, and possible with 1. Cutaneous signs were always present. In cases of amyopathic DM, cutaneous signs were clinically characteristic and were confirmed by a skin biopsy findings. Polymyositis was considered definite with 4 criteria and probable with 3. Constitutional symptoms were defined as more than 5% of body weight loss and/or body temperature above 38°C for at least 1 week or recurring. The onset of DM and PM was considered rapid if the diagnosis was made within 2 months after the appearance of initial signs and/or symptoms. Dysphonia, proximal dysphagia, abnormal swallowing, dyspnea, and rhabdomyolysis were considered signs of severity.

No specific recommendations were made regarding the extent of workup. All patients without prior cancer underwent at least a routine malignancy screening, including a careful history review, a complete physical and pelvic examination, standard biologic tests (including blood cell counts, erythrocyte sedimentation rate, general chemistry screen and liver function tests, a chest roentgenogram, a mammogram in women, and any tests or examinations directed toward abnormal symptoms or results, according to the recommendations of Callen25 and Richardson and Callen26). In addition, 38 patients had 1 to 9 (mean of 4) further blind tests or examinations (eg, nonjustified by an abnormal finding on routine screening) performed during the initial course of DM or PM. Tests and examinations that were considered helpful for the diagnosis of malignancy were those allowing subsequent directed examinations to establish the diagnosis. Most patients with a negative initial cancer workup were reinvestigated at least once during the follow-up.

Treatments were not standardized and consisted mainly of systemic glucocorticoids (26 patients). Resistance to glucocorticoids was defined as persistently elevated muscle enzyme levels or florid skin lesions after 8 weeks of treatment at a daily dose of at least 1 mg/kg.

Six patients received high-dose intravenous immunoglobulins, 2 received antimalaria drugs alone for amyopathic dermatomyositis, and 9 received immunosuppressive agents (methotrexate, azathioprine, or both). One patient with gastric carcinoma and true paraneoplastic DM underwent gastrectomy preceded by plasma exchanges. A cancer of the cervix occurred in a patient who was treated over 4 years for a refractory PM with a combination of immunosuppressive agents. This case was initially classified as PM without associated malignancy.

Clinical, biological, and radiological data were recorded and compared between cases with and without associated malignancy. Given the relatively small size of our patient sample, only univariate analysis was carried out. Statistical analyses were evaluated using the χ² method or the Fisher exact test for qualitative data and the Wilcoxon/Mann-Whitney test for quantitative data.

RESULTS

DESCRIPTION OF PATIENTS

The main characteristics of the series of patients are shown in Table 1. All 40 patients were adults (mean age, 57.1 years). Thirty-seven cases met at least 3 criteria of Bohan and Peter,23 while 3 cases corresponded to amyopathic DM. One case had overlap syndrome between definite polymyositis and systemic sclerosis. Sixteen patients (mean±SD age, 62±16 years) had DM or PM associated with malignancy, including 3 of 7 patients with PM and 13 of 33 patients with DM. As given in Table 2, 18 malignancies (16 cancers and 2 non-Hodgkin lymphomas) were discovered, always concurrently with or soon after the DM or PM onset. Two patients had 2 separate cancers diagnosed simultaneously during the initial workup. In 3 other patients, recurrence or progression of a previously diagnosed malignancy was temporally associated with the development of DM or PM. One true recurrence occurred 15 years after the diagnosis of a cancer of endometrium. One patient had simultaneously a cancer of the left breast and a squamous cell cancer of the lung occurring 14 years after a cancer of the right breast. The diagnosis of malignancy was made before the diagnosis of DM or PM in 2 patients, concurrently with DM or PM in 6, and shortly after DM or PM in 8 (mean [range] time, 5 [1-12] months).

The mean (range) follow-up time from DM or PM onset was 56 (4-216) months and was respectively 28 (4-160) and 72 (13-216) months in patients with and without associated malignancy. Sixteen patients (40%) died, including 3 patients without and 13 patients with associated malignancy (12.3% vs 75%; P<.001). Only 23% of the patients with malignancy compared with 96% of the patients without survived more than 2 years (P<.001). The cause of death was always due to progression of malignancy in patients with DM or PM with cancer, while...
RESULTS OF SCREENING INVESTIGATIONS IN THE DIAGNOSIS OF MALIGNANCY

In patients with previous malignancy, investigations were directed at least toward the demonstration of recurrence of the same tumor. Results were positive in 2 cases, including the patient with very late relapse of endometrium carcinoma. In a third case with a long history of breast cancer, more extensive investigations were performed, allowing the discovery of 2 separate new tumors. In the fourth case, pathologic evidence of recurring breast cancer was not obtained despite multiple thorough workups, but was indirectly confirmed 10 months after the diagnosis of PM, since the patient developed a disseminated intravascular coagulation, which disappeared within a few weeks with the administration of antiestrogen therapy.

In patients without a previous malignancy, the diagnosis of an associated tumor was suspected on clinical and routine screen backgrounds and confirmed by appropriate investigations in 7 of 12 cases. Initial routine evaluation failed to discover 4 silent malignancies: an anaplastic lymphoma of the psosas muscle in a 24-year-old man, a high-grade astrocytoma of the brain in a 72-year-old man, a recurrence of breast cancer in a 69-year-old woman, and an ovarian carcinoma in a 46-year-old woman. Further blind workup was only performed in the patient with breast cancer and was unsuccessful. The malignancies were diagnosed later at a mean of 7 months after onset of DM, all at an advanced stage. The 2 patients with astrocytoma and ovarian carcinoma soon died of cancer, while the other 2 patients with lymphoma and breast carcinoma survived, despite a poor initial condition. In retrospect, a late diagnosis of neuroendocrine carcinoma of the mediastinum (suspected only on a blind CT scan) was made in a fifth patient owing to the failure to recognize a mild enlargement of the upper mediastinum on the initial chest radiograph.

The description of blind screening investigations and the contribution of each to the diagnosis of malignancy associated with DM or PM are given in Table 3. Of 122 investigations, 30 (25%) were considered positive. The rate of positive results was 54% (19 of 35) for directed screens and 13% (11 of 87) for blind screens. Abdominal-pelvic and thoracic CT scans were the most useful blind examinations, with 28% (5 of 18) of the positive results.

RISK FACTORS OF MALIGNANCY

The prevalences of risk factors of malignancy are listed in Table 4. Men with cancer were older (mean of 56.2 years vs 33.2 years) but this difference did not reach significance ($P = .1$) and was not observed in women (mean of 60 years vs 57.4 years). The variables significantly associated with the occurrence of malignancy were the presence of constitutional symptoms ($P = .009$), the lack of Raynaud phenomenon ($P = .003$), and a higher mean erythrocyte sedimentation rate ($P = .008$) and creatine kinase level ($P = .01$). Both cases of DM presenting with cutaneous necrosis had associated cancer ($P = .16$). Recruitment in the internal medicine department, as opposed to the dermatology department, was also associated with a higher risk to discover a malignancy ($P = .02$). No interdepartmental differences were found between patients with respect to age, sex, and rapid onset of symptoms and signs of severity. Patients recruited by internists more often presented with constitutional symptoms ($P = .07$).

In an unselected sample of 40 adult patients with DM or PM, we found in retrospect a malignancy temporally associated with the disease onset in 16 cases (40%). The reported rate of malignancies in unselected series of patients with DM or PM has widely ranged from 11% to 43%, with a large population cohort and case-control studies reporting a rate of 13% to 25%. This high frequency of malignant diseases closely related to...
DM and PM in our series may be explained in part by a large number of patients with DM, which has been more closely associated than PM with malignancy in large population-based studies. It is worthy to note that most malignancies were diagnosed in patients observed by internists and that the risk of disclosing a neoplasm temporally linked to DM or PM was significantly higher in this population than in patients observed by dermatologists (52% vs 26%; \( P = .02 \)). Such a difference is unlikely to result from a more aggressive cancer-screening policy by internists, because patients observed by internists did not undergo much more blind investigations (mean, 4.2) than did patients followed up by dermatologists (mean, 3.6). Most probably, patients referred to internists are sicker than those referred to dermatologists and are more likely to have a malignancy.

Cancers encountered in our patients were similar in type and location to those previously described, except for a case of primary brain neoplasm, which to our knowledge has been reported only once. Lymphoma represented 13% of all malignancies. In other studies, this rate has ranged from 0% to 22%. It is worth noting that a consistent association between a rapid onset of the disease and malignancy, confirming the findings in a previous report.

**Table 3. Description and Results of Nonroutine Screening Tests and Examinations Performed in Patients With DM or PM**

<table>
<thead>
<tr>
<th>Test or Examination</th>
<th>No. Performed</th>
<th>Directed by an Abnormal Finding(\d)</th>
<th>Positive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan†</td>
<td>24</td>
<td>6 (6+)</td>
<td>11</td>
</tr>
<tr>
<td>Upper gastrointestinal endoscopy</td>
<td>28</td>
<td>8 (2+)</td>
<td>3</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>16</td>
<td>3 (1+)</td>
<td>2</td>
</tr>
<tr>
<td>Small bowel radiologic examination</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid imaging</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>2</td>
<td>2 (1+)</td>
<td>2</td>
</tr>
<tr>
<td>Positron emission tomography scan</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cancer-associated antigens</td>
<td>20</td>
<td>1 (0)</td>
<td>3</td>
</tr>
<tr>
<td>Bone marrow trephine biopsy</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other biopsies</td>
<td>12</td>
<td>12 (9+)</td>
<td>9</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>1</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>122</strong></td>
<td><strong>35 (19+)</strong></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

*DM indicates dermatomyositis; PM, polymyositis; and CT, computed tomographic.
†Abdominal-thoracic scan in men; pelvic-abdominal-thoracic scan in women.
‡Number (number +) means number of positive results of number of scans performed.

**Table 4. Factors Associated With Malignancy in 40 Patients With DM or PM**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Malignancy</th>
<th>Malignancy</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.4 ± 16.2</td>
<td>61.5 ± 16.3</td>
<td>.45</td>
</tr>
<tr>
<td>Female sex</td>
<td>19 (79)</td>
<td>10 (63)</td>
<td>.29</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>7 (29)</td>
<td>12 (75)</td>
<td>.009</td>
</tr>
<tr>
<td>Rapid onset of myositis</td>
<td>5 (21)</td>
<td>10 (63)</td>
<td>.02</td>
</tr>
<tr>
<td>Signs of severity</td>
<td>13 (54)</td>
<td>8 (50)</td>
<td>.99</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>10 (42)</td>
<td>0</td>
<td>.003</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>11 (46)</td>
<td>3 (19)</td>
<td>.1</td>
</tr>
<tr>
<td>Cutaneous necrosis</td>
<td>0</td>
<td>2 (13)</td>
<td>.16</td>
</tr>
<tr>
<td>Poor control of myositis</td>
<td>15 (68)</td>
<td>6 (40)</td>
<td>.11</td>
</tr>
<tr>
<td>Anti-Ro antibodies present</td>
<td>9 (38)</td>
<td>5 (39)</td>
<td>.99</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>25.4 ± 15.7</td>
<td>47.8 ± 29.1</td>
<td>.008</td>
</tr>
<tr>
<td>C-reactive protein level, mg/L</td>
<td>17.6 (5-142)</td>
<td>28.6 (3-144)</td>
<td>.08</td>
</tr>
<tr>
<td>Blood hemoglobin level, g/dL</td>
<td>12.8 ± 1.6</td>
<td>11.9 ± 1.7</td>
<td>.08</td>
</tr>
<tr>
<td>Serum albumin level, g/L</td>
<td>40.1 ± 3.6</td>
<td>40.1 ± 4.5</td>
<td>.44</td>
</tr>
<tr>
<td>Serum creatinine level, µmol/L</td>
<td>79.2 ± 25.2</td>
<td>84.1 ± 24.9</td>
<td>.53</td>
</tr>
<tr>
<td>Serum creatine kinase level, U/L</td>
<td>1346 (35-10 000)</td>
<td>2840 (96-12 100)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*DM indicates dermatomyositis; PM, polymyositis. Data are given as number (percentage) of cases or mean value ± SD or (range).

*References 1, 6, 13, 17, 30, 32-34, 40, 41.

**References 2, 13, 14, 17, 28, 30, 32, 37, 39, 43.
therefore, of limited value in clinical practice.\textsuperscript{4} We agree with Callen’s recent propositions\textsuperscript{41,47} that patients with a history of cancer should be more carefully evaluated because we found in all 4 such patients either recurrence of a prior malignancy or a new cancer synchronously with the DM or PM onset.

Finally, our experience is at variance with the classic recommendations of Callen and others. Strikingly, we found that in all cases the tumor onset coincided closely with the onset of DM or PM. Other studies have shown that malignancies occur concurrently with or within 1 year after the diagnosis of myositis in 26\% to 70\% of the cases.\textsuperscript{2,3,6,17,43} These data support the performance of a meticulous malignancy screen in patients with DM or PM. It is widely accepted that the presence of an associated malignancy represent a major indicator of poor prognosis in DM and PM.\textsuperscript{5,24,27,28,34,48,49} Likewise, in our series the rate of deaths was impressively higher in cases of DM and PM associated with malignancy than in idiopathic DM and PM (75\% vs 12.5\%; \textit{P}<.001). This distressing figure, together with the observation that death always occurred as the result of progression of malignant disease, even in cases where DM or PM was only partially or poorly controlled, underscores the potential harmful effects of delayed diagnosis of malignancy in patients with DM or PM, as exemplified in at least 3 personal patients’ stories. Delaying the diagnosis of malignancy might therefore be dangerously misleading in some patients.

The main limitations of our study are the retrospective nature of the work, the relatively small sample size (which did not allow us to determine unquestionable risk factors of cancer using logistic regression analysis), and the extremely protean locations and presentations of the tumors encountered, which prevented us from providing precise guidelines for blind investigations. Nevertheless, as nondirected abdominal-thoracic (in men) and pelvic-abdominal-thoracic (in women) CT scans yielded a fairly good rate of positive results in our patients, we always include it in the workup. Our attitude is in agreement with that of Hill et al,\textsuperscript{19} who recommend that patients with DM undergo body CT scans, in view of the notably increased risk of non-Hodgkin lymphoma and ovarian, lung, and pancreatic cancer. As suggested by our results and other studies,\textsuperscript{13,14} endoscopic studies of the upper and lower gastrointestinal tract should be done according to the patient’s age. Whether new imaging techniques (such as positron emission tomography) would help uncover some tumors and expedite the malignancy workup in patients with DM or PM deserves prospective studies.

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