Case Report

Cancer-Associated Myositis in the Presence of Anti-Jo1 Autoantibodies and the Antisynthetase Syndrome

DOMINIC LEGAULT, JOHN McDERMOTT, ANA MARIA CROUS-TSANACLIS, and GILLES BOIRE

ABSTRACT. We describe 3 patients with inflammatory myositis in association with a neoplasm whose serum also contained anti-Jo1 antibodies, one of which presented characteristic features of the antisynthetase syndrome. No patient had a rash, and muscle biopsy was suggestive of polymyositis in all 3. Immunohistochemistry confirmed the diagnosis of polymyositis in the single patient with sufficient tissue available. Our patients remind us that the presence of antisynthetase antibodies (and even antisynthetase syndrome) in a patient with inflammatory myositis does not preclude the diagnosis of cancer-associated myositis. (J Rheumatol 2008;35:169–71)

Key Indexing Terms:
MYOSITIS AUTOANTIBODIES NEOPLASMS
BIOPSY MAJOR HISTOCOMPATIBILITY COMPLEX

Dermatomyositis/polymyositis (DM/PM) is a heterogeneous group of idiopathic inflammatory myopathies (IIM) characterized by progressive symmetric proximal limb weakness, elevated serum levels of muscle enzymes, suggestive electromyographic (EMG) and characteristic pathologic findings, and, in the case of DM, a typical rash. Several myositis-specific autoantibodies have been described and are present in up to half the patients, the most prevalent being the antisynthetase group (present in 30%–35% of patients with IIM). Antisynthetase antibodies target the aminoacyl tRNA synthetase enzymes involved in the conversion of the base sequence within a mRNA molecule to an amino acid sequence of a protein. Among antisynthetase antibodies, anti-Jo1 (histidyl tRNA synthetase) antibodies are most common, being present in up to 20% of patients. The presence of antisynthetase antibodies is associated with the antisynthetase syndrome, a condition referring to characteristic extramuscular symptoms, such as idiopathic interstitial lung disease, arthritis, Raynaud’s phenomenon, and mechanic’s hand.

In clinical practice, classification of IIM is based on a combination of clinical and pathologic criteria. Limitations of the Peter and Bohan criteria have led to recent proposals to use predominantly histopathologic or clinicoserological classifications. These novel approaches to classification aim to identify more homogeneous groups of patients, genetically and in their response to treatment and prognosis. For example, the proposed clinicoserological classification suggests that antisynthetase antibodies are very rare in cancer-associated myositis (CAM). CAM is well known to be associated with DM; its association with PM is weaker and even controversial. The coexistence of anti-Jo1 antibodies and CAM has been reported in 4 patients, and only one of these patients presented an antisynthetase syndrome. The presence of antisynthetase antibodies, and even more so the antisynthetase syndrome, in a patient with IIM would thus militate against a diagnosis of CAM.

We describe 3 patients with CAM and anti-Jo1 antibodies, one of them presenting features of the antisynthetase syndrome that significantly delayed the diagnosis of the underlying neoplasia. We also review the immunogenetic associations found in these 3 Caucasian patients.

CASE REPORTS

Patient 1. A 57-year-old male smoker [HLA-DRB1*04,07 -DQB1*02,03 as defined by low resolution genomic typing using polymerase chain reaction with sequence-specific primers specific for HLA-DR and HLA-DQ class II molecules from Pel-Freez Clinical Systems (Brown Deer, WI, USA)] with diabetes and coronary artery disease initially presented with symmetrical polyarthralgia, synovitis, and prolonged morning stiffness. Rheumatoid factor was negative and synovial fluid was inflammatory, without microcrystals. He was first treated with nonsteroidal antiinflammatory drugs, with some improvement, although leg edema and shortness of breath developed rapidly. One month later, proximal muscle weakness was noted. PM was diagnosed on the basis of elevated creatine kinase (CK) levels (2395 U/l; n = 120), EMG changes consistent with inflammatory myositis, and a muscle biopsy showing atrophy of groups of muscle fibers and mild interstitial infiltrate without perivascular inflammation, suggestive of PM. Material from the biopsy could not be retrieved for retrospective immunohistochemistry analysis. Anti-Jo1...
antibodies were identified by double immunodiffusion; monospecificity of the serum for Jo1 was later confirmed by silver staining of RNA present in immunoprecipitates from HeLa cell extracts. Patchy alveolar infiltrates predominated in both lung bases were noted on the chest radiograph. Sputum culture and cytology were unremarkable. Computerized tomography scan showed nonspecific pulmonary infiltrates with small pleural effusions. Mild restriction and marked decrease in diffusion (41%) were present on pulmonary function tests. Exudative organizing pneumonitis was identified on a transthoracic lung biopsy. The features were thus consistent with the antisynthetase syndrome, and he was treated with 1 mg/kg/day (80 mg) of prednisone. Strength and CK levels rapidly returned to normal, and significant clinical improvement occurred. However, uncontrolled diabetes mellitus developed, such that prednisone dose was decreased to 50 mg/day, and azathioprine was initiated.

Six months after the diagnosis of PM, despite continuing treatment, severe weakness recurred and CK levels increased again. A second muscle biopsy was similar to the first. Despite increases in prednisone doses, muscle weakness and shortness of breath deteriorated. Progression of pulmonary infiltrates and the appearance of a large left-side pulmonary effusion were noted on chest radiograph. A lung CT scan revealed multiple nodular infiltrates (up to 3 cm in diameter) in both lungs and enlarged lymph nodes in the mediastinum. Lung biopsy revealed a poorly differentiated adenocarcinoma. The patient died 1 month later.

**Patient 2.** An 81-year-old male smoker (HLA-DRB1*11,15-DQB1*03,06) presented with loss of weight, shortness of breath, and a hoarse voice. Proximal weakness, digital clubbing, and swelling of the dorsum of both hands were noted. A 4 cm mass in the right paratracheal region with poorly defined borders was seen on chest radiograph. PM was diagnosed on the basis of elevated CK levels (2328 U/l); EMG changes were consistent with inflammatory myositis, while muscle biopsy showed rare necrotic muscle cells with no inflammatory infiltrates; there were no regenerating cells or rimmed vacuoles. Insufficient material was left from the biopsy for subsequent immunohistochemistry analysis, and the possibility of a paraneoplastic immune-mediated necrotizing myopathy could not be ruled out. Anti-Jo1 antibodies were the single autoantibody positive by double-immunodiffusion (monospecificity later confirmed by immunoprecipitation of HeLa cell extracts). Invasion of the right paratrachea and of the mediastinal pleura, as well as adrenal metastases, were seen on CT scans. Adenocarcinoma was confirmed on lung biopsy. Radiotherapy and high-dose prednisone were initiated. Despite initial strength improvement, thrombophlebitis and multiple metastases developed, and the patient rapidly died.

**Patient 3.** An 81-year-old woman (HLA-DRB1*08,11-DQB1*03,04) was admitted for general weakness, loss of weight, and progressive constipation. Iron deficiency anemia (hemoglobin 86 g/l) and hyperthyroidism (thyroid-stimulating hormone 0.12 mIU/l; free T4 30.7 pmol/l) were present. A lobular mass in the right colon was noted on colonoscopy. Multinodular goiter with hyperfunctioning nodules required treatment with propylthiouracil prior to the right hemicolectomy (adenocarcinoma Duke C). Three months after the surgery, despite correction of the anemia and normalization of the thyroid function, the patient developed severe proximal weakness (3/5). PM was diagnosed on the basis of elevated CK levels (1459 U/l), suggestive EMG changes, and a muscle biopsy with sparse necrosis and regeneration of muscle fibers with mild endomyosial inflammatory infiltrates without perivascular involvement; there were no rimmed vacuoles. Subsequent immunohistochemical analysis revealed extensive MHC-1 membrane expression on myocytes and the presence of a small number of infiltrating CD4+CD8+HLA-DR+ lymphocytes and CD68+ macrophages. Anti-Jo1 antibodies were identified by immunoprecipitation of HeLa cell extracts. Intravenous immunoglobulins, corticosteroids, and azathioprine (later replaced by methotrexate) were administered. An excellent initial clinical and biochemical response was observed. However, 6 months later, in the absence of evidence of recurrence of cancer, muscle weakness developed again, and the patient died from cardiac complications related to a highly unstable and uncontrolled thyroid function.

**DISCUSSION**

We describe 3 patients with inflammatory myositis associated with cancer (CAM) whose serum contained anti-Jo1 antibodies. These patients were identified over a 10-year period. This represents a low incidence for this association, although anti-Jo1 antibodies are not looked for in every patient with CAM in which cancer is obvious. In all 3 cases, anti-Jo1 specificity was confirmed by identification of the corresponding RNA in immunoprecipitates from HeLa cell extracts. In 2 of these patients, lung and colon neoplasms were obvious before the development of CAM, and the patient had no features suggestive of the antisynthetase syndrome. However, in our Patient 1, the presence of inflammatory nonerosive arthritis and of exudative organizing pneumonitis strongly supported the diagnosis of an antisynthetase syndrome. In this patient, corticosteroids and immunosuppressors led to marked clinical improvement, at least until the underlying lung neoplasm became widespread. In this case, the presence of antisynthetase syndrome, of anti-Jo1 antibodies, and of a good response to treatment falsely reassured the clinicians away from a diagnosis of CAM.

The pathogenesis of anti-Jo1 autoantibodies and of inflammatory myositis in our 3 patients with CAM does not appear to follow the immunogenetic predispositions reported for IIM (DRB1*0301) and antisynthetase antibodies (DRB1*0301, DQB1-02, and DRB1*1501) in Caucasians. More than 82% of the patients with anti-Jo1 antibodies in a large recent series of IIM carried the HLA-DR*0301 allele. This was not observed in our patients. Indeed, the one patient with the antisynthetase syndrome carried one HLA-DR-07 and one DR-04 allele, both said to be protective against the development of anti-Jo1 and IIM. Only Patient 2 had an allele associated with anti-Jo1, i.e., HLA-DRB1*15. For the HLA-DQB1 allele, all the patients were DQB1*03 and only Patient 1 was DQB1*02. These results suggest that the presence of cancer may alter the immunogenetic requirements to develop both myositis and antisynthetase antibodies. As a consequence, no specific HLA-DR allele appears associated with the presence of inflammatory myositis associated with cancer, even in the presence of anti-Jo1 autoantibodies or of the antisynthetase syndrome.

Finally, these 3 patients allowed us to reconsider the recent classifications proposed by Dalakas and Hohlfeld and Troyanov, et al. The very existence of PM has even been questioned. When using both light microscopy and immunohistochemistry criteria as described by Hoogendijk, et al, definite and probable DM and PM can usually be distinguished without difficulty (Table 1). Unfortunately, immunohistochemistry was not available at the time of diagnosis in our cases, as is still often the case in usual clinical practice. Subsequent immunohistochemical study of the single patient in which tissue was available confirmed the diagnosis of probable PM with widespread expression of MHC-1 molecules on myocytes and infiltrating CD8+ lymphocytes, and the absence
of infiltrating plasmocytes and of perivascular immunoglobulin deposition. On the other hand, our experience with these patients also acts as a reminder that the presence of antisynthetase antibodies (and even antisynthetase syndrome) in a patient with inflammatory myositis, although supporting the diagnosis of overlap myositis in the classification proposed by Troyanov, et al, does not preclude the diagnosis of CAM. Although the triad of myositis, cancer, and anti-Jo1 antibodies is presumably infrequent, the reassuring performance of MSA may need to be revised.

REFERENCES


Table 1. Muscle biopsy criteria for classification of polymyositis (PM) and dermatomyositis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Description</th>
<th>Technique</th>
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<tbody>
<tr>
<td>Definite PM*</td>
<td>Endomysial inflammatory cell infiltrates (T cells) surrounding and invading non-necrotic muscle fibers</td>
<td>Light microscopy</td>
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<tr>
<td>Probable PM**</td>
<td>Endomysial CD8+ T cells surrounding, but not definitely invading non-necrotic muscle fibers, or ubiquitous MHC-1 expression</td>
<td>Immunohistochemistry</td>
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<tr>
<td>Definite DM</td>
<td>Perifascicular atrophy</td>
<td>Light microscopy</td>
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<tr>
<td>Probable DM</td>
<td>Membrane attack complex (MAC) depositions on small blood vessels or MHC-1 expression of perifascicular fibers; or reduced capillary density or tubuloreticular inclusions in endothelial cells</td>
<td>Immunohistochemistry</td>
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<tr>
<td></td>
<td>OR</td>
<td>Electron microscopy</td>
</tr>
<tr>
<td>Possible DM sine dermatitis</td>
<td>Perivascular, perimysial inflammatory cell infiltrates</td>
<td>Light microscopy</td>
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<td>OR</td>
<td>Light microscopy</td>
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* Exclusion criteria: criteria for definite and probable DM (see above), and criteria for inclusion body myositis (rimmed vacuoles, ragged red fibers, cytochrome oxidase-negative fibers), and criteria for muscular dystrophies with immunopathology (including MAC depositions on the sarcolemma of non-necrotic fibers).

** Exclusion criteria: exclusion criteria for definite PM plus the following: many necrotic cell fibers as the predominant histological feature; inflammatory cells are sparse or only slight perivascular and perimysial infiltrate is not evident; MAC depositions on small blood vessels or pimplest capillaries can be seen on electron microscopy, but tubuloreticular inclusions in endothelial cells are uncommon or not evident.