Steroid-responsive inclusion body myositis associated with endometrial cancer

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ABSTRACT

Inclusion body myositis (IBM) is an uncommon chronic inflammatory myopathy. Although the association between other myopathies and cancer has been well established, the relationship between IBM and neoplasia is not completely understood. Unlike polymyositis (PM) or dermatomyositis (DM), IBM rarely responds to immunosuppressive treatment and the response is seldom long-lasting. We describe a case of IBM associated with endometrial carcinoma that also demonstrated a unique response to steroids alone which persisted despite cancer relapse. The factors that are associated with a response of IBM to steroids are discussed. An atypical, steroid-responsive form of the disease is delineated.

Introduction

Inclusion body myositis (IBM) represents a rare subset (approximately 10%) of the inflammatory myopathies (IM) (1) which also include dermatomyositis (DM) and polymyositis (PM). Its prevalence has recently been established to be 4.9 patients per million (2). Despite prior studies questioning an association of IBM with neoplasia (3), a recent large prospective study (1) associated IBM with a 2.4 standard incidence ratio for cancers, which further increased to 2.7 after the first year of follow-up. The risk for cancer persisted for 5 years. In two other studies, between 15% and 23% of the cases of IBM also had cancer (1, 4), but a causal association remains still unproven (5).

The current case, uniquely associated with endometrial cancer, presented with an unusual, high level of serum creatine phosphokinase (CK) only rarely reported in the literature (6). Atypical clinical features of IBM appear to be present in the cases responsive to steroids (6-12) (Table I), as is also illustrated by our case.

Case report

A 63-year-old woman was diagnosed with endometrial adenocarcinoma after presenting with vaginal bleeding for several months. The tumor had a mixed mesodermal histology with predominance of a serous papillary component and invasion of half the thickness of the myometrium. A total uterine resection and bilateral salpingo-oophorectomy with lymph node dissection revealed no extraperitoneal extension of the tumor (pT3a N0). However, 3 months later the patient developed malignant ascites and a right pleural effusion.

Chemotherapy with carboplatin and paclitaxel every 3 weeks was given for 8 cycles with disease stabilization, but 6 months later she developed a new abdominal recurrence. At the same time as this relapse, the patient complained of rapidly progressing profound muscular weakness in both the proximal and distal muscles resulting in inability to sit up in a chair and comb her hair. No muscle tenderness was present. Finger and wrist flexors (right more than left), as well as both quadriceps muscles were predominantly affected. The hand extension and knee flexion strength were better preserved. She also complained of dysphagia and fatigability. Deep tendon reflexes were present but moderately diminished. No sensory deficit or fasciculations were present. An electromyogram was suggestive of a myopathic pattern. The muscle biopsy (Fig. 1) showed inclusion bodies and rimmed vacuoles, as well multiple necrotic fibers with myophagocytosis and regeneration, indicating inflammatory infiltrates in the muscle. Hypertrophic and split fibers were present. A diagnosis of IBM was made based on the characteristic clinical, EMG, and histopathological findings.

Serum CK reached a peak of 17,000 u/L (n 0–170 u/L) and aldolase was 56 u/L (n 0–6 u/L) (Fig. 2 a,b,c). Chemotherapy was re-started with topotecan concurrent with prednisone at an initial dose of 90 mg daily. Ascites improved and the serum CA-125 began to decline. Muscle strength and serum enzymes improved within 2 weeks, and both recovered completely, with restoration of baseline muscle power within 2 months after starting the steroids. Prednisone was slowly tapered and was completely discontinued after 6 months. One year after the onset of IBM, a third intra-abdominal recurrence of the cancer developed, but with no clinical or biochemical evidence of myositis. The
intestinal obstruction was relieved surgically, but the neoplasm continued to progress despite additional treatment. There was no deterioration in muscle strength for the 12 months after prednisone was started until the patient died as a result of progressive neoplasia.

Discussion
Clinically IBM can be differentiated from other types of myositis by an older age at onset, male predominance, slower progression, presence of associated neuropathic findings, involvement of the wrist flexors and knee extensors, asymmetrical distribution, markedly increased erythrocyte sedimentation rate, and a lower serum CK than in other inflammatory myopathies. However, the most important distinguishing feature is considered to be the poor response to immunosuppressives (prednisone, methotrexate, IV immunoglobulin) (9, 13-19). Histologic findings of IBM include rimmed vacuoles, eosinophilic cytoplasmic inclusions, 15-18 nm tubulofilaments, and invasion of the muscle fiber by mononuclear cells (15-20).

In IBM as well as PM the muscular injury is thought to be initiated by sensitized cytotoxic CD8+ T cells that recognize MHC-I restricted muscle antigens with subsequent phagocytosis and muscle necrosis (16). A paraneoplastic nature of IBM has been proposed, as isolated cases of improvement in the myositis following regression of the malignancy have been observed (20, 21). However, this has not been a consistent finding (22). The commonly lower levels of CK in IBM (14) and cancer-associated DM (23) may suggest a paraneoplastic nature of the former, at least in selected cases. Only a few cases of IBM responding to immunosuppressive treatment have been documented, but in even fewer instances were the responses durable (6-12) (Table I).

We have described here the first case of IBM occurring in association with endometrial carcinoma, which is also the first case of IBM associated with a neoplasm to demonstrate a persistent re-

Table I. Reported cases of Inclusion Body Myositis (IBM) with favorable response to immunosuppressive treatment and their associated features.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Response</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hengstman et al.</td>
<td>Prednisone for 3 months</td>
<td>Marked and sustained (18 months)</td>
<td>*Anti-Jo1 antibody</td>
</tr>
<tr>
<td>Schlesinger et al.</td>
<td>Prednisone high-dose</td>
<td>2/4 patients responded</td>
<td>*Scapuloperoneal syndrome, post-polio-like syndrome, scleroderma, undefined autoimmune disease</td>
</tr>
<tr>
<td>Mori et al.</td>
<td>Corticosteroids, cyclosporine A, cyclophosphamide, immunoglobulin</td>
<td>Responded</td>
<td>*High creatine kinase levels, rapid progression, complicated with interstitial pneumonia</td>
</tr>
<tr>
<td>Beyenburg et al.</td>
<td>Immunosuppressive</td>
<td>1/17 patients responded</td>
<td>*Sjogren's syndrome</td>
</tr>
<tr>
<td>Jongen et al.</td>
<td>Chlorambucil long-term</td>
<td>Responded</td>
<td>-</td>
</tr>
<tr>
<td>Sayers et al.</td>
<td>Prednisone, methotrexate ± other agents</td>
<td>3/32 pts. long-term improvement 12/32 delayed progression</td>
<td>-</td>
</tr>
<tr>
<td>Lindberg et al.</td>
<td>Prednisone</td>
<td>3/18 temporary improvement</td>
<td>-</td>
</tr>
<tr>
<td>Present case</td>
<td>Prednisone</td>
<td>Marked and sustained</td>
<td>*High creatine kinase, rapid progression, associated with endometrial cancer</td>
</tr>
</tbody>
</table>

*Atypical features

Fig. 1. Muscular fibers showing rimmed vacuoles and a discrete focal mononuclear infiltrate.
response to steroids alone. Although a causal relationship between the IBM and the underlying cancer cannot be definitively demonstrated, the close temporal association between the two events makes it likely. At the time of its maximal systemic spread, the ovarian cancer appeared to act as a “trigger factor” for the development of IBM, and the two processes did not show a “paraneoplastic syndrome”-type of parallelism in their activity at the time of the third cancer relapse. Previously described in two other cases (22) associated with cancers, the independent behavior of IBM from the associated cancer may be contrasted with other situations where myositis and the cancer mirror each other’s activity (“paraneoplastic IBM”). Alternatively, it is possible that prednisone permanently disrupted the pathogenic chain that initially led to the development of myositis. The low CK and absence of symptoms during the first neoplastic relapse were probably related to the low tumoral mass. At that time the CEA was only 230 u/dL, as compared to the peak value of 660 u/dL during the second neoplastic relapse, which corresponded to the clinical myopathic episode.

The possibility that IBM was induced by the chemotherapy agents (carboplatin/paclitaxel) appears unlikely given the 14-month time lapse between them, as opposed to only 2 months between the cancer clinical relapse/peak of CEA and the myopathic episode. Furthermore, despite extensive clinical usage, none of these agents have previously been associated with the development of IBM. It also appears unlikely that the resolution of IBM was due to cancer control by the chemotherapy regimen, given its subsequent non-paraneoplastic behavior. However an immunosuppressive effect of chemotherapy might have acted synergistically with the steroids in inducing the IBM remission.

While classical IBM is poorly responsive to steroids, a small number of patients apparently do respond. This subset appears to express “atypical” clinical features. In our case, the patient presented with an uncharacteristically...
high CK. The case described by Hengstman et al. had an unusually positive anti-Jo1 antibody (10), the cases of Schlesinger et al. had atypical clinical manifestations (e.g. scapuloperoneal syndrome, postpolio-like syndrome, co-existence with scleroderma or an undefined autoimmune disorder) (7), and the patient reported by Mori et al. had high creatine kinase levels and a rapid progression that was complicated by interstitial pneumonia (6).

To summarize, IBM may present as a multifaceted syndrome with diverse clinical manifestations and a variable response to therapy. We have presented an atypical case with rapid onset of IBM during the relapse of an endometrial carcinoma, and a prolonged response to steroids despite subsequent cancer progression. Patients that respond to steroids appear to have uncommon clinical features. A better understanding of the disease process at the clinical and molecular levels is needed to further characterize this steroid-responsive subtype of IBM.

References