Hemophagocytosis associated with MPO-ANCA positive vasculitis in systemic sclerosis

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ABSTRACT

Hemophagocytosis is a histiocytic proliferative condition associated with underlying disorders such as infection, lymphoma and autoimmune disease. We describe here a patient with systemic sclerosis who developed MPO-ANCA positive necrotizing vasculitis and hemophagocytosis concomitantly. Vasculitis supervened on a prior systemic sclerosis, and no causative disorder of hemophagocytosis could be found other than active vasculitis, suggesting that an occurrence of hemophagocytosis is associated with underlying vasculitis. On the other hand, this case shows the elevated serum levels of IL-1, IL-6 and M-CSF which may be involved in the pathogenesis of hemophagocytosis. To our knowledge, this is the first demonstration indicating the possibility of vasculitis-associated hemophagocytosis.

Introduction

Hemophagocytosis is a clinicopathological process characterized by the activation of histiocytes with prominent hemophagocytosis in bone marrow and other reticuloendothelial systems. The clinical characteristics of hemophagocytosis include high fever, pancytopenia, liver dysfunction, coagulopathy and hyperferritinemia (1). Underlying disorders such as infection, lymphoma and autoimmune disease trigger this condition. Here we report a case of hemophagocytosis that was associated with myeloperoxidase (MPO) - anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis in systemic sclerosis.

Case report

A 76-year-old woman presented with Raynaud’s phenomenon, cutaneous scleroderma and bibasilar pulmonary fibrosis. She had anti-topoisomerase I antibodies and antinuclear antibodies (diffuse x5120), and was diagnosed as having diffuse cutaneous systemic sclerosis according to the established criteria. She was given D-penicillamine and limaprost, a prostaglandin E1 analogue, and maintained a relatively inactive disease state with these treatments. At the age of 82 years she developed high fever and weight loss, and was admitted to our hospital. Physical examination revealed a body temperature of 38°-39°C and a blood pressure of 130/70 mmHg. She had lost 3 kg during the last few months. The extent of her scleroderma and pulmonary fibrosis was not changed compared with her previous condition. The most notable new findings were livedo reticularis, bilateral episcleritis, bilateral proximal muscle weakness and pain and edema of the dorsalis pedis. Her blood cell count showed WBC 13.1 x 10^9/l (80% neutrophils), hemoglobin 9.4 g/dl, and platelet count 266 x 10^9/l. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated at 134 mm/h and 14.2 mg/dl, respectively. Coagulopathy was not shown and liver function was normal. There was renal dysfunction (BUN 41 mg/dl, creatinine 1.64 mg/dl, creatinine clearance rate 19 ml/min) with proteinuria and microscopic hematuria.

She was positive for antinuclear antibodies (diffuse x80), rheumatoid factor (69 IU/ml; normal ≤ 13), an indirect antitglobulin test and platelet-associated IgG (PA-IgG) (71.2 ng/10^7 cells; normal ≤ 25). Anti-topoisomerase I antibodies and a direct antitglobulin test were negative. Study for anti-neutrophil cytoplasmic antibody (ANCA) yielded positive for myeloperoxidase (MPO)-ANCA (65 ELISA unit; normal ≤ 10) and negative for proteinase 3 (PR3)-ANCA (by enzyme-linked immunosorbent assay; ELISA). Complement studies showed C3 112 mg/dl (normal 42-79) and C4 29.4 mg/dl (normal 10-29). Circulating immune complexes were detected as 2.6 gEq/ml (Clq method, normal < 1.2). Serum ferritin was increased to 2,155 g/l (normal < 120). Blood cultures for bacteria and fungus were negative. Thoracic and abdominal computed tomography scans showed no infectious lesions, despite pulmonary fibrosis. No findings suggestive of active infection were obtained. A malignancy survey did not show any significant findings. A muscle biopsy specimen of
the quadriceps revealed necrotizing vasculitis (Fig. 1). The presence of hyperferritinemia, a hallmark of hemophagocytosis, compelled us to conduct a bone marrow examination. As can be seen in Figure 2, the marrow showed the presence of hemophagocytosis. Histiocytes revealed phagocytosis of various hematopoietic cells including platelets, neutrophils, lymphocytes and erythrocytes. Hemophagocytosis is often triggered by inflammatory cytokines (1); therefore we tested the serum levels of several cytokines which have been reported to be elevated in hemophagocytosis. Using ELISA methods, we found that the levels of interleukin (IL)-1, IL-6, macrophage colony-stimulating factor (M-CSF) and soluble IL-2 receptor (sIL-2R) were increased to 13 pg/ml (normal ≤ 0.567), 14.6 pg/ml (normal 0.22 - 4.62), 3032 U/ml (normal ≤ 750) and 608 U/ml (normal 220-530), respectively. The levels of tumor necrosis factor- (TNF- ) and interferon- (IFN- ) were undetectable.

After admission the patient’s WBC count fell rapidly and serum levels of ferritin were concomitantly raised (Table I), which suggested a progression of the hemophagocytosis. We treated the patient with 500 mg/day methylprednisolone per day, intravenously for 3 days, followed by oral prednisolone 1 mg/kg/day in addition to 50 mg of cyclophosphamide every other day. She responded well to this treatment, and an excellent improvement in the vasculitis and hemophagocytosis were obtained. Fever, as well as the episcleritis, livedo reticularis, muscle weakness with pain, and edema of the dorsalis pedis, were relieved with serological improvement of CRP and MPO-ANCA levels (Table I). The recovery of the decreasing WBC count was also obtained. The ferritin level, which was the most prominent serological change with disease progression, decreased. A month after the start of the treatment, the bone marrow showed no obvious presence of hemophagocytic histiocytes. After the initial response, prednisolone was tapered and the patient was discharged. She is now in good condition with neither active systemic sclerosis nor hemophagocytosis.

Table I. Laboratory findings in the patient with hemophagocytosis associated with MPO-ANCA positive vasculitis in systemic sclerosis.

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<thead>
<tr>
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<th>On admission</th>
<th>Before</th>
<th>Treatment</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (x 10⁹/L)</td>
<td>13.1</td>
<td>5.7</td>
<td>6.9</td>
<td></td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.4</td>
<td>9.6</td>
<td>11.3</td>
<td></td>
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<tr>
<td>Platelet count (x 10⁹/L)</td>
<td>266</td>
<td>314</td>
<td>169</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>14.2</td>
<td>7.8</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Ferritin (g/L)</td>
<td>2155</td>
<td>14,000</td>
<td>1,749</td>
<td></td>
</tr>
<tr>
<td>MPO-ANCA (ELISA units)</td>
<td>65</td>
<td>57</td>
<td>&lt; 10</td>
<td></td>
</tr>
</tbody>
</table>
phagocytosis.

Discussion
We describe here a patient with systemic sclerosis who developed MPO-ANCA positive vasculitis and hemophagocytosis concomitantly. The occurrence of hemophagocytosis is usually associated with underlying active diseases, which include infection, lymphoma and autoimmune disease (1). In our case no apparent evidence of underlying infection or malignancy could be found. Systemic sclerosis can be one of the causative disorders for hemophagocytosis, as we have previously reported (2). However, we attributed hemophagocytosis in this case to vasculitis rather than systemic sclerosis. The apparent progression of scleroderma and pulmonary fibrosis could not be found, and anti-topoisomerase I antibodies were not detected at the onset of vasculitis, which suggests that the systemic sclerosis itself is inactive. Then, hemophagocytosis occurred concomitantly with vasculitis, and vasculitis supervened on a prior systemic sclerosis. Therefore, no active conditions other than vasculitis could be found as the causative disorder of hemophagocytosis. The fact that hemophagocytosis and vasculitis improved concomitantly with the immunosuppressive therapy also supports this possibility.

Few cases of hemophagocytosis related to vasculitis have been reported (3-5). Ban et al. described a case of Epstein-Barr virus (EBV) infection that revealed hemophagocytosis and systemic granulomatous arteritis (3). But in this case hemophagocytosis was caused by EBV infection (EBV-associated hemophagocytic syndrome) and seemed not to be triggered by the arteritis itself. On the other hand, cases with Kawasaki disease followed by hemophagocytosis have been reported (4, 5). They suggest the possible involvement of hypercytokinemia as the pathological mechanism. In fact, TNF-α, IFN-γ, IL-1α, IL-2, IL-6, IL-8 and M-CSF have been reported to be elevated in the serum of the patients with hemophagocytosis (1, 6-10); however, all of these cytokines have not been absolutely elevated in our case. Alternatively, levels of IL-1α, IL-6 and M-CSF were elevated in the serum. These elevated cytokines are probably an epiphennomenon of vasculitis as the phlogosis, and these cytokines can stimulate histiocytes with resultant hemophagocytosis (6, 8, 10). On the other hand, an autoantibody-mediated mechanism has been proposed in autoimmune-associated hemophagocytic syndrome (2, 11). In such a condition, hematopoietic cells are sensitized by autoantibodies and phagocytosed by histiocytes through the binding of the Fc portion of the antibodies to Fc receptors on histiocytes (antibody-dependent cellular cytotoxicity; ADCC). Furthermore, Wong and colleagues have proposed an immune complex-mediated mechanism, in which the deposition of circulating immune complex on marrow hematopoietic cells results in histiocyctic hemophagocytosis through the binding of antibody in the complex or activated complements to the receptors on histiocytes (12). The presence of autoantibodies against terminal blood elements, proved by a positive indirect Coomb’s test and PA-IgG as well as MPO-ANCA, and circulating immune complex in our case would also suggest the possible involvement of an autoantibody- and/or immune complex-mediated mechanism. However, we think that a cytokine-mediated mechanism may be largely involved in our case, because our case showed high fever and hyperferritinaemia, which are characteristic features of cytokine-mediated hemophagocytosis (1,6,10) rather than autoantibody- or immune complex-mediated hemophagocytosis (2, 11). The immunosuppressive therapy might suppress the production of cytokines immediately with the rapid improvement of hemophagocytosis.

Alternatively, several immunopathological mechanisms triggering vasculitis have been postulated (13). These include the deposition of immune complexes in the blood vessel wall, ANCA-mediated blood vessel damage, antibody-mediated damage via antibodies directed at endothelial cells, ADCC directed against blood vessel tissue, and cytotoxic T cell directed at blood vessel components. Cytokine (i.e., IL-1, TNF-α)-mediated mechanisms through the expression of adhesion molecules for leukocytes on endothelial cells, the induction of other cytokine-network by endothelial cells and the priming of neutrophils for ANCA-induced degranulation have also been proposed. These immunopathological conditions, including the dysregulated production of cytokine, might contribute, at least in part, to the occurrence of hemophagocytosis. However, the exact link between the pathogenesis of hemophagocytosis and vasculitis remains unclear and should be clarified.

MPO-ANCA develops in variable percentages of patients with microscopic polyangiitis, Churg-Strauss syndrome, crescentic glomerulonephritis or Goodpasture’s syndrome, as well as in some patients with Wegener’s granulomatosis. MPO-ANCA is rarely found in systemic sclerosis (14), although lethal cases of MPO-ANCA positive systemic sclerosis complicated by systemic necrotizing vasculitis as well as crescentic glomerulonephritis and pulmonary hemorrhage have been described (15,16). MPO-ANCA has been reported not to be a feature of systemic sclerosis and, if found, may indicate the presence of an unrelated pathology such as idiopathic or drug-induced vasculitis (14). Some drugs, including D-penicillamine, have been suggested to be related to MPO-ANCA positive vasculitis (16-18), while a negative correlation of ANCA seroconversion with these drugs has also been reported (19).

A case of systemic sclerosis demonstrating MPO-ANCA positive vasculitis without intake of D-penicillamine has been also reported (20). Thus, although the relationship between D-penicillamine and MPO-ANCA positive vasculitis seems to be obscure at present, the occurrence of vasculitis despite the inactive state of systemic sclerosis might suggest the possible association of D-penicillamine in our case. Furthermore, the pathophysiological role of MPO-ANCA in hemophagocytosis is poorly understood and needs further investigation.

Finally, the case of hemophagocytosis associated with underlying MPO-ANCA positive vasculitis has not been reported to date, and our case provides the first evidence suggesting the possi-
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The capability of vasculitis-associated hemophagocytosis. Vasculitis syndrome should be listed as one of the causative disorders of hemophagocytosis. The importance of the early diagnosis of such an unusual complication and immediate therapy should also be noted.

References