Superficial Venous Thrombophlebitis as the Initial Manifestation of Hypereosinophilic Syndrome

Study of the First 3 Cases

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Background: Superficial venous thrombophlebitis (SVT), often perceived as benign, can coexist with hypercoagulable states. Predisposing risk factors for SVT are similar to those observed for deep venous thrombosis. Association of eosinophilia with SVT is a rare situation that can reveal neoplasm, malignant blood disorders, or vasculitis, but it has never been described in hypereosinophilic syndrome (HES). We herein describe the clinical and biological features, outcome, and response to therapy of 3 patients with SVT associated with eosinophilia that revealed HES.

Observations: Superficial venous thrombophlebitis was the initial manifestation of HES in all 3 patients. The mean eosinophil count at diagnosis was 2.4 × 10^3/µL. All patients received corticosteroids and anticoagulants as the initial treatment, with marked improvement of SVT and return of the eosinophil count to reference limits. All patients experienced relapse and remained dependent on corticosteroid therapy. Two patients received interferon alfa with dramatic regression of SVT, allowing a decrease in the dose of corticosteroids.

Conclusions: We report, to our knowledge, the first 3 cases of SVT related to HES. Superficial venous thrombophlebitis was difficult to treat, with dependence on corticosteroid therapy and partial efficacy of anticoagulant and antiplatelet therapy. Interferon alfa was effective in preventing relapse of SVT related to HES. Mechanisms implied in this thrombogenesis are multiple and remain speculative.

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noting of peripheral T cells, in the absence of other diseases. Cutaneous manifestations are common. The lymphoid variant usually follows an indolent course, but some patients can develop overt T-cell lymphomas. When the myeloid and lymphocytic variants are not clearly identified, the diagnosis of idiopathic HES may be considered.

The aim of this study was to describe the clinical and biological features, outcome, and response to therapy of patients with SVT related to HES.

REPORT OF CASES

We retrospectively analyzed recurrent SVT related to HES in 3 patients. All of the patients satisfied the criteria of Chu-sid et al. Superficial venous thrombophlebitis was confirmed by Doppler ultrasonography or biopsy findings in all patients. We found no evidence of acquired or inherited thrombophilia (ie, antiphospholipid antibodies and lupus anticoagulant, hyperhomocysteinemia, factor V Leiden, the prothrombin 20210A mutation, elevated factor VIII level, or antithrombin or protein C and S deficiencies). We excluded Behcet disease, neoplasia, and Buerger disease through medical history and follow-up, and there was no detectable glycosylphosphatidylinositol-deficient hematopoietic clone (for the diagnosis of paroxysmal nocturnal hemoglobinuria). The diagnosis of HES was considered in all 3 patients after exclusion of other known causes of eosinophilia, especially parasitic disease. In all patients, results of renal function and hepatic tests were within reference limits, and results of serum electrophoresis, chest radiography, echocardiography, ophthalmic examination, bacterial cultures, tests for rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulinemia, and parasitic feces, appropriate parasitic and viral (hepatitis C virus and human immunodeficiency virus) serologic tests, and bone marrow biopsy were negative. We evaluated for the presence of hypodense eosinophils by means of blood smear examination. The patients underwent screening for the FIP1L1-PDGFRα fusion gene by fluorescence in situ hybridization, analysis of the T-cell receptor gene to detect clonal rearrangement, and peripheral T-cell phenotyping. We noted clinical and biological features, outcome, and response to therapy. The patients were monitored for endomyocardial disease by electrocardiography and echo-cardiography, and for embolic phenomena by physical examination and Doppler ultrasonography. The mean duration of follow-up was 38 months (25, 59, and 30 months).

CASE 1

In June 2003, a 36-year-old man was referred for a 9-month history of recurrent SVT of all 4 limbs, confirmed by Doppler ultrasonography. He had no previous blood tests before admission. Veins in the lower limbs were erythematous and painful palpable cords (Figure 1). At diagnosis, the blood eosinophil level was 1.8 × 10^9/L. The main results of the laboratory tests are summarized in the Table. Idiopathic HES was diagnosed. After treatment with prednisone (40 mg/d) and enoxaparin sodium, SVT completely regressed, and the eosinophil count was within reference limits. The prednisone dosage was tapered to 30 mg/d, and anticoagulant therapy was stopped in July 2003 after 1 month of treatment. Superficial venous thrombophlebitis and eosinophilia (0.6 × 10^9/L) recurred in September 2003 at the prednisone dosage of 30 mg/d. A skin biopsy specimen from the thigh showed thrombosis of a hypodermal vein with a mild lymphocytic infiltrate (but no eosinophils) of the vessel wall. An increased dosage of prednisone given with colchicine and replacement of aspirin with flunidione led to temporary improvement of SVT. About 10 relapses occurred, half of them with eosinophilia (eg, eosinophilia at a level of 1.5 × 10^9/L in June 2004 with STV relapse) while tapering the prednisone dosage to less than 20 mg/d. Flunidione and nadroparin calcium administration did not prevent SVT recurrences. In September 2004, interferon alfa (3 million units 3 times per week) resulted in dramatic regression of SVT, allowing for tapering of the prednisone dosage to less than 10 mg/d. Nadroparin was replaced by clopidogrel bisulfate. After 10 months of treatment with interferon alfa, no relapse of SVT occurred, and the blood eosinophil count remained below 1.0 × 10^9/L. In May 2005, asthma and pulmonary micronodules occurred with moderate eosinophilia (0.6 × 10^9/L). Findings for antineutrophil cytoplasmic antibodies and specific IgE anti-Aspergillus fumigatus remained negative, confirming the diagnosis of HES. Inhaled beclomethasone dipropionate therapy was added with a good efficacy for the asthma. The clinical and therapeutic time course is summarized in Figure 2.
CASE 2

A 26-year-old man was referred for recurrent SVT of the lower limbs confirmed by examination of a skin biopsy specimen, which showed thrombosis of dermal vessels with moderate reactive perivascular lymphocytic infiltration. Physical examination results showed palpable erythematous veins and a livedo of the lower limbs, and prominent purpuric macules of the toes without cutaneous necrosis. He had a 6-month history of unexplained eosinophilia of 1.5 × 10³/µL.

The main results of the laboratory tests are summarized in the Table. No Doppler ultrasonography was performed. Idiopathic HES was diagnosed. Treatment with prednisone (30 mg/d) and fluindione resulted in improvement of SVT, livedo, and purpuric lesions, and improvement of the eosinophil count to reference limits. One relapse of SVT and livedo, with an eosinophil count within reference limits (0.4 × 10³/µL), occurred after tapering of the prednisone dosage to 20 mg/d. Interferon alfa therapy (3 million U 3 times per week) was introduced and led to dramatic improvement of the cutaneous lesions. Fluindione was replaced by aspirin, and prednisone and interferon alfa dosages were tapered. No relapse of eosinophilia occurred during the 32 months of interferon alfa therapy associated with a stable dose of prednisone (5 mg/d). One month after stopping interferon therapy, livedo and SVT relapsed, associated with abdominal pain. The eosinophil count was 0.3 × 10³/µL, but a gastric biopsy specimen showed marked infiltration by eosinophils (confirming the diagnosis of HES). Interferon alfa and prednisone were readministered with rapid improvement. No relapse occurred during an additional 7 months of follow-up. The clinical and therapeutic time course is summarized in Figure 2.

CASE 3

A 59-year-old man was referred for acrocyanosis. He had an 8-month history of hypereosinophilia (maximum level, Table. Laboratory Tests of the Patients in the 3 Cases*

<table>
<thead>
<tr>
<th>Measurement†</th>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, ×10³/µL (4.0 to 10.0 × 10³/µL)</td>
<td>11.3</td>
<td>13.2</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count, ×10³/µL (1.5 to 7.0 × 10³/µL)</td>
<td>6.4</td>
<td>8.9</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Eosinophil count, ×10³/µL (&lt;0.5 × 10³/µL)</td>
<td>1.8</td>
<td>1.5</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level, g/dL (13-17 g/dL)</td>
<td>14.6</td>
<td>12.5</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>Platelet count, ×10³/µL (150 to 400 × 10³/µL)</td>
<td>236</td>
<td>435</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm in the first hour (&lt;15 mm)</td>
<td>17</td>
<td>26</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein level, mg/L (&lt;10 mg/L)</td>
<td>15</td>
<td>26</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂ level, pg/mL (298 to 881 pg/mL)</td>
<td>497</td>
<td>377</td>
<td>622</td>
<td></td>
</tr>
<tr>
<td>Total IgE level, IU/L (&lt;158 IU/L)</td>
<td>220</td>
<td>836</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>T-cell phenotyping results</td>
<td>Normal</td>
<td>Normal</td>
<td>Increased T cells</td>
<td></td>
</tr>
<tr>
<td>Analysis of TCR gene rearrangement patterns</td>
<td>Clonal rearrangement of TCR gamma</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TCR, T-cell receptor; ellipses, not measured.

SI conversion factor: To convert vitamin B₁₂ to picomoles per liter, multiply by 0.738.

*Neither cytogenetic abnormalities nor the Fip1-like 1 platelet-derived growth factor receptor α (FIP1L1-PDGFRα) gene was detected in any of the patients.
†Reference range or threshold value is given parenthetically.

Figure 2. Clinical and therapeutic time courses of the patients in the 3 cases. Arrows indicate relapses of superficial venous thrombophlebitis (SVT) or hypereosinophilic syndrome–related complications.

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Clinical examination showed hardened and painful erythematous veins, infiltrated erythematous plaques of the lower limbs, and flame-shaped subungual hemorrhage. Doppler ultrasonography showed bilateral SVT of the lower limbs without deep extension and arterial thrombosis of the upper limbs. A skin biopsy specimen of infiltrated lesions showed a dermal and subcutaneous infiltrate of eosinophils and vascular hyperplasia of a few vessels. The main results of the laboratory tests are summarized in the Table. Idiopathic HES was diagnosed. Treatment with a pulse of methylprednisolone hemisuccinate followed by oral prednisone (80 mg/d), fluindione, and aspirin resulted in improvement of arterial and venous thrombosis and improvement of the blood eosinophil count to within reference limits. Transient elevation of the eosinophil level (0.8 × 10^3/µL) occurred after tapering of the prednisone dosage to 5 mg/d, but was reversed with an increase of the dosage to 10 mg/d. No relapse occurred thereafter. The clinical and therapeutic time course is summarized in Figure 2.

**COMMENT**

Hypereosinophilic syndrome is a rare hematological disorder with abnormal production of eosinophils by bone marrow and organ damage caused by the accumulation of eosinophils in tissues. Organs and systems usually affected by HES include the heart, nervous system, skin, lungs, gastrointestinal tract, and, more rarely, blood vessels. The skin is one of the most frequently involved organs, and manifestations include angioedematous and urticarial lesions, erythema, in particular parasitic infection, allergic disease, or malignancy. Moreover, no systemic manifestation evocative of primary necrotizing vasculitis appeared during the follow-up. In 2 patients, there was no evidence of a myeloproliferative or lymphocytic variant of HES (ie, we did not detect the FIP1L1-PDGFRA fusion gene, cytogenetic abnormalities, or T-cell clonality), so the diagnosis of idiopathic HES was considered. In case 1, the detection of an isolated T-cell clonality may be consistent with the diagnosis of lymphocytic variant of HES. However, in the absence of phenotypically abnormal T,2 cells in peripheral blood, the diagnosis of idiopathic HES must be considered. Superficial venous thromboembolitis was the initial manifestation of HES in all patients. All of the patients had other organ damage, including a dermal and subcutaneous infiltrate of eosinophils, eosinophilic gastritis, and pulmonary micronodules. None of them developed cardiac or neurological manifestations.

Several mechanisms have been proposed for vascular involvement in HES, including eosinophilic vasculitis, inhibition of anticoagulant activity of thrombomodulin by eosinophil cationic proteins, a direct toxic effect of eosinophils on endothelial cells causing damage and clot formation because of exposed collagen, stimulation of platelet activation and aggregation by major basic protein and eosinophil peroxidase, and the roles of CD40L expressed on blood eosinophils and CD40 expressed on endothelial cells during eosinophil activation. Recently, Wang et al reported that hypothiocyanate, an eosinophil peroxidase product, is a potent inducer of tissue factor activity in endothelial cells and postulated that this may promote thrombogenesis in HES.

No hypodense eosinophils, corresponding to the activated degranulated cells, were found in the skin or the circulation of our patients. In addition, in cases 1 and 2, there was no consistent association of SVT relapse with peripheral blood eosinophilia. Two explanations can be proposed. First, organ damage secondary to eosinophil infiltrate is not always associated with peripheral blood eosinophilia. Fuzellier et al recently reported eosinophilic endocarditis requiring mitral valve replacement related to HES with blood eosinophil counts within reference limits, suggesting a rapid homing of eosinophils into tissues. The SVT relapses without eosinophilia in cases 1 and 2 could have been associated with superficial venous eosinophil infiltration that was not detected because the biopsies were not repeated. However, this hypothesis appears improbable because there was no infiltrate of eosinophils in the initial biopsy specimens from these patients. Second, SVT could be a consequence of the systemic release of prothrombotic substances (eg, hypothiocyanate) by tissue eosinophils (eg, gastric eosinophils in case 2).

In all of our cases, initiation of corticosteroid and anticoagulant therapy led to dramatic regression of the SVT and restoration of the eosinophil count to reference limits, but SVT relapse occurred on tapering of the corticosteroid dosage. Treatment of the relapses with interferon alfa resulted in resolution of the SVT and prolonged remission of the underlying HES in 2 patients. Interferon alfa is effective in HES by inhibiting eosinophil colony formation and interleukin 5 production by T cells and by decreasing the release of toxic eosinophilic substances. However, interferon alfa therapy can be complicated by Raynaud phenomenon and digital necrosis in HES and chronic myeloid leukemia, and direct toxic effects of interferon alfa on endothelial cells have been suggested by experimental data in mice. The rapid efficacy of interferon alfa for the treatment of SVT in our patients was likely the consequence of its direct effects on eosinophils. Recently, new treatments of HES targeted to pathogenic mechanisms have emerged, such as imatinib mesylate (especially in HES associated with the FIP1L1-PDGFRA fusion gene) and mepolizumab (monoclonal anti–interleukin 5 antibody). These treatments were not used in our patients because of the absence of gene fusion (for imatinib mesylate) and the inaccessibility of the medication (for mepolizumab).

Anticoagulant therapy is probably indicated in HES-related SVT, unlike idiopathic SVT, because of the in-
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19. We have reported, to our knowledge, the first 3 cases of SVT related to HES. Superficial venous thrombophlebitis in this setting represents a therapeutic challenge, and interferon alfa therapy can be helpful in preventing relapse and reducing dependence on corticosteroids. Further studies are needed to improve our knowledge of the mechanisms underlying thrombogenesis in HES.