Abstract

Cryofibrinogenemia is a rare disorder in which plasma, not serum, forms a cryoprecipitate. Patients with cryofibrinogenemia may be asymptomatic, or they may have painful ulcers, purpura, livedo reticularis, Raynaud phenomenon, perniosis of the extremities, thrombosis, and arthralgia. Cryofibrinogenemia may be primary or secondary to an underlying disorder such as connective tissue disease, malignancy, infection, drugs, or thromboembolic disease.

Here, we present a 41-year-old woman with a pancreatic neuroendocrine tumor who underwent a Whipple procedure in 2003 followed by 2 liver transplants for hepatic metastases. Three years posttransplant, we discovered a biopsy-proven metastatic lesion in her femur. Five years posttransplant, she developed acute, severe pain in both feet, and was found to have cryofibrinogenemia despite immunosuppression posttransplant. Testing for connective tissue diseases and hematologic malignancy were negative. She was treated with high-dose prednisone, which completely resolved her symptoms. We also conducted a review of the literature via a PubMed search to summarize the association of cryofibrinogenemia with malignancy and treating cryofibrinogenemia with corticosteroids.

Our study is the first reported case of cryofibrinogenemia that developed secondary to a neuroendocrine tumor posttransplant. Our report suggests that cryofibrinogenemia may occur despite immunosuppression adequate to prevent graft rejection, and that high-dose corticosteroids are an effective treatment for posttransplant cryofibrinogenemia.

Key words: Cryoproteins, Liver transplant, Immunosuppression, Neuroendocrine tumor, Corticosteroid

Introduction

Cryofibrinogenemia (CF) is a rare and potentially severe disease, first described by Korst and associates in 1955.1 Cryofibrinogen is a plasma protein complex composed of fibrinogen, fibrin, fibronectin and/or fibrin degradation products.2 When cooled, cryofibrinogen can precipitate at 4°C and redissolve at 37°C. Cryofibrinogen can be detected only in the plasma, not in the serum, allowing the distinction between cryofibrinogen and cryoglobulin.3

Cryofibrinogenemia has been classified into a primary (or essential or idiopathic) or a secondary form. The diagnosis of primary CF is based on the clinical presentations, the presence of cryofibrinogens in plasma, the absence of cryoglobulins, and the absence of causes of secondary CF.3 Secondary CF is associated with several diseases including connective tissue and autoimmune diseases, malignancies, infection, drugs, thromboembolic conditions, and other conditions such as chronic lung disease, acute myocardial infarction, and hypothyroidism.3-5 Secondary CF is most frequently associated with connective tissue diseases (42%), followed by vasculitis (25%), malignancy (21%), and infection (12%).6

The prevalence of CF has been estimated to be 3.4% to 13%.4,6-8 Patients with CF may be asymptomatic. The most common symptoms of CF
are caused by cutaneous ischemia including ulcerations, purpura, livedo reticularis, ecchymosis, Raynaud phenomenon, perniosis of the extremities, ischemic necrosis, and gangrene.\textsuperscript{5-7,9,10} Cutaneous lesions typically occur at distal extremities such as the hands, feet, ears, nose, and buttocks, and are often aggravated by exposure to cold.\textsuperscript{11} Other symptoms include thrombosis (which occurs in 25\% to 40\% of patients), arthralgia, and glomerulonephritis.\textsuperscript{3,5-7} The most specific finding of a skin biopsy is plugging of superficial and deep small-sized and medium-sized blood vessels with thrombi that contain cryofibrinogen. Nonspecific findings of leukocytoclastic vasculitis and necrosis of the dermis and epidermis are commonly observed.\textsuperscript{3}

The pathogenesis of CF is not fully understood. Thrombosis medicated by circulating cryofibrinogen may contribute to the pathology of CF. Fibronectin has been shown to bind to fibrin and fibrinogen, and acts as a nucleus for the cold-induced precipitation of fibrinogen-fibrin complexes in vitro.\textsuperscript{2} Immunoglobulins or immune complexes also may interact with fibronectin within the CF complex, forming an inflammatory component that may contribute to the thrombotic events in CF.\textsuperscript{12,13} Additionally, increased plasma levels of protease inhibitors, α1-antitrypsin, and α2-macroglobulin have been found in patients with CF. These proteins inhibit plasmin activity, leading to inhibition of fibrinolysis and accumulation of cryofibrinogen. Cryofibrinogen can clot with thrombin, leading to thrombotic occlusion of the small and medium arteries.\textsuperscript{3-6,14} Development of reflex vasospasm, vascular stasis, and hyperviscosity may contribute to additional vascular occlusion.\textsuperscript{3,6}

Case Report

We report a 41-year-old woman whose disease was diagnosed as a pancreatic neuroendocrine tumor. In 2003, the woman underwent a Whipple procedure. Two years later, she underwent a right hepatectomy followed by chemotherapy for hepatic metastases. Her disease relapsed with hepatic metastases, and she had a living-donor liver transplant 4 years after the Whipple procedure. The transplant failed because of a hepatic artery thrombosis. Ten days later, she was given a deceased-donor liver transplant. Since then, she has been taking tacrolimus and her liver functions have been stable. She remained disease free until 3 years after the liver transplant, when she developed a metastasis on her right femur. She had a radiofrequency ablation and showed good response during the 4 years after the liver transplant. There is a second biopsy-proven metastatic lesion in the patient’s right femur in proximity to the previously treated lesion. Two other lesions suspicious for metastatic disease also have been identified in her right seventh rib and left femur.

Five years posttransplant, she developed an acute onset of severe sharp pain on the plantar surfaces of her feet. The pain began on the first or fifth toe and radiated to the rest of toes and sometimes to her calves. The pain was exacerbated by cold and by walking, and it was alleviated by elevating her feet. The pain was so severe that she required oxycodone. Her feet also were swollen. She had no pain in her fingertips, nose, or ears. She had no symptoms to suggest connective tissue diseases such as malar rash, Raynaud phenomenon, photosensitivity, eye symptoms, sicca symptoms, nasal, oral ulcers, or hair changes. She had no constitutional symptoms, weight loss, recent infection, or skin changes. She did have scaly pruritic patches on her scalp and anus for many years.

Her medical history included a splenectomy secondary to a childhood trauma, chronic thrombocytosis, and chronic malabsorption secondary to pancreatic insufficiency after undergoing the Whipple procedure. She was taking tacrolimus 2 mg twice daily, esomeprazole 40 mg twice daily, a multivitamin, and pancreatic enzymes.

On examination, both feet were swollen around the toes. There was slight discoloration of the left third and fifth toes on plantar surface and tips. Her feet, ankles, and calves were warm to the touch. The tips of her toes were tender on palpation. There was no joint effusion or joint tenderness. Her range of motion in her toes, feet, and ankles was intact. Peripheral pulses were equal and strong bilaterally. The results of the rest of her examination were normal.

Laboratory examinations showed positive cryofibrinogens. The results of tests for cryoglobulins, hepatitis C antibody, and rheumatoid factor were negative, and her C-reactive protein level was normal. Laboratory studies disclosed the following values: hemoglobin level 95 g/L, MCV level 74 fL, white blood cell count 22.7 × 10\(^9\)/L, and platelet count 970 × 10\(^9\)/L. Laboratory studies for the patient’s electrolytes, urea, creatinine, international
normalized ratio, and partial thromboplastin time were normal. The results of tests of her liver enzymes and function were normal, except for a mildly elevated alkaline phosphatase level of 2.856 μkat/L (normal < 2.255 μkat/L). The tacrolimus level was therapeutic (4.8 μg/L). The results of a chromogranin A test were significantly chronically elevated at 400 U/L. Other tumor markers including carcinoembryonic antigen, cancer antigen 19-9, and alpha-fetoprotein were within normal limits. Her serum ferritin level was low at 20 pmol/L (normal, 33-404 pmol/L). Peripheral blood morphology revealed hyposplenic changes and changes consistent with iron deficiency anemia. Because of her thrombocytosis, she was tested for myeloproliferative diseases; both translocation t (9; 22) and JAK2 mutation was negative. Radiographic studies of her feet were negative.

Based on her laboratory and clinical findings, she was diagnosed with CF. The painful toe tips were thought to be a thromboembolic sequelae or possibly early painful perniosis. She was counseled to avoid exposure to cold, and she was started on prednisone 50 mg daily. She had an excellent response with quick resolution of her symptoms. After 1 week, the prednisone was tapered to 25 mg daily, and after 1 month it was tapered by 5 mg per week during the following month, for a total 2 months’ treatment. At the time of this writing, she has been off prednisone for 9 months and remains asymptomatic. Repeat cryofibrinogen level was < 0.2 at week 4 of prednisone treatment, and < 0.02 four weeks after discontinuing the prednisone. Her serum cryoglobulins remained negative.

Her persistent thrombocytosis was thought to be secondary to 3 factors: (1) an iron deficiency, (2) a metastatic neuroendocrine tumor, and (3) a splenectomy. She was initially treated with aspirin 81 mg daily. She also was given an iron replacement and with normalization of her hemoglobin and serum ferritin levels, her platelet count improved from a peak of 1171 × 10^9/L to 516 × 10^9/L after 1 month, which was her baseline.

**Discussion**

We report a 41-year old woman with a recurrent metastatic pancreatic neuroendocrine tumor after undergoing a liver transplant who developed bilateral pain in her feet and evidence of cryofibrinogen in the plasma. She had no features of connective tissue diseases, hematologic malignancy or infection, and she developed CF despite adequate antirejection immunosuppression after the liver transplant. In this case, the CF most likely is secondary to the recurrent neuroendocrine tumor; however, the fact that CF developed in the setting of potent calcineurin-inhibition with tacrolimus suggests that interleukin (IL)-2 and other cytokines activated by this T-cell pathway are not involved in the pathophysiology of CF-associated disease. This is the first reported case of CF occurring after a liver transplant.

To date, various malignancies have been reported to be associated with CF including lymphoma, leukemia, multiple myeloma, and adenocarcinomas of gastric, liver, lung, and colon. In addition to being the first reported case after a liver transplant, we also believe this is the first reported association between neuroendocrine tumor and CF. A previous study by Belizna and associates recommended a systematic search for lymphoma be performed in patients with an established diagnosis of essential CF, as 27% of patients diagnosed with essential CF are found to have lymphoma in a few years. Our study provides additional evidence for the association between CF and malignancy, and suggests that although it is rare, clinicians should be aware of symptomatic CF and consider screening for underlying associated diseases such as other paraneoplastic manifestations.

Treatment of CF includes avoidance of cold exposure and other environmental triggers of symptoms. Treatment for primary CF with reported success includes use of fibrinolytics (eg, streptokinase), immunomodulators (eg, glucocorticoids in combination with azathioprine or chlorambucil, and plasmapheresis), and anti-coagulants (eg, such as heparin and warfarin). Aspirin and colchicine have been shown to be ineffective.

Treatment for secondary CF is directed by screening and evaluation for possible underlying infection, malignancy or inflammatory disease, and specific treatment of the underlying disease. Studies have shown that glucocorticoids, cytotoxic therapy (such as cyclophosphamide), and plasmapheresis may be effective for treating patients with underlying connective tissue diseases and may be an effective therapy in severe cases.
therapy may be an effective strategy for patients with CF secondary to infection.28 In addition, patients with CF secondary to malignancy have been shown to respond to tumor resection.15 However, treatment approaches are based on cases reports and small case series.

In terms of immunosuppression, corticosteroid monotherapy has been shown to be effective in treating secondary CF,3 but not in primary CF unless it is combined with azathioprine or chlorambucil (Table 1).3,5,21,22 For example, Blain and associates5 reported that corticosteroids were ineffective in primary CF (0 out of 3 cases had remission) but were effective in secondary CF (4 out of 5 cases had remission). All the secondary CF effectively treated with corticosteroids in that study were associated with inflammatory or rheumatologic diseases. Similarly, Yoshida and associates29 summarized 6 patients with CF secondary to rheumatologic diseases treated with corticosteroids: 4 patients had remission or improvement of clinical symptoms, and 2 patients died from septic shock. In addition, Sakieda and associates30 presented a patient with CF secondary to hypothyroidism and arteriosclerosis obliterans who was successfully treated with prednisone and warfarin.

Table 1. Number of Previously Reported Patients and Response Rates of Corticosteroid in Primary and Secondary Cryofibrinogenemia

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of Patients Responded to Steroids (Response Rate) in Primary Cryofibrinogenemia</th>
<th>Number of Patients Responded to Steroids (Response Rate) in Secondary Cryofibrinogenemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blain, et al5</td>
<td>0/3 (0%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>Yoshida, et al29</td>
<td>N/A</td>
<td>4/6 (67%), with 2/6 death</td>
</tr>
<tr>
<td>Sakieda, et al30</td>
<td>N/A</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Our case</td>
<td>N/A</td>
<td>1/1 (100%)</td>
</tr>
</tbody>
</table>

It is interesting that despite being on tacrolimus, this patient developed secondary CF, and her symptoms resolved completely with prednisone. Tacrolimus inhibits T-cell activation, particularly TH1 cells, by inhibiting the activity of calcineurin to prevent T-cell receptor signal transduction to the cell nucleus, and by blocking cell activation and subsequent synthesis of TH1 cytokines, such as IL-2, IFN-γ, and other cytokines.31 On the other hand, glucocorticoids suppress inflammation via several molecular mechanisms.32,33 Glucocorticoids increase the transcription of many anti-inflammatory genes (eg, cytokines such as IL-10, IL-12, IL-1 receptor antagonist) and decrease the transcription of many proinflammatory genes (eg, cytokines such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-13, IL-15, TNF-α, GM-CSF; several chemokines, inflammatory enzymes, inflammatory peptides, mediator receptors, and adhesion molecules). In addition, corticosteroids have several posttranscriptional effects.32,33 It is possible that tacrolimus, primarily inhibiting TH1 pathway, is a specific immunosuppressant, and that this pathway is not involved in the clinical manifestations of CF whereas a corticosteroid, being a more broad-spectrum immunosuppressant, is needed for CF treatment.

The level of cryofibrinogen in our patient became < 0.2 at 4 weeks of prednisone therapy and almost undetectable (< 0.02) at 4 weeks after prednisone was discontinued. This is consistent with a previous study by Soyfoo and associates,9 which suggests that treating patients with CF results in progressive normalization of CF.

Our experience raises the possibility that CF may be related to a neuroendocrine tumor, and that corticosteroids may be effective in treating CF associated with malignancy. Further studies are needed to confirm whether secondary CF associated with malignancy can be treated effectively with corticosteroids and the optimal duration of therapy. Furthermore, future studies focusing on the molecular mechanisms of how CF is related to malignancy are warranted.

In conclusion, in patients presenting with unexplained cold intolerance, purpura, skin necrosis, or ulceration of an unknown cause, screening for CF should be considered. Moreover, CF can occur in the presence of T-cell–specific immunosuppression, as occurred in the current patient, and may occur in patients with neuroendocrine tumors.
References


