A 24-Year-Old Man With Extensive Lower Limb Edema and Acute Arterial Occlusion*

Francis T. Thandroyen, MD; Martin D. Phillips, MD; Denzil D’Souza, MD; L. Maximilian Buja, MD

Case History
A 24-year-old man was admitted to Lyndon B. Johnson Hospital, Houston, with the chief complaint of severe pain of the left leg associated with cyanosis and blistering of the toes. He had been well until 10 days before admission. In the intervening time period, he developed gradual swelling of both legs that extended up to the mid thigh bilaterally. He also noticed mild dyspnea. On the day before admission, he reported bluish discoloration of the toes of the left foot. He also began to experience severe pain in the left lower leg and noticed blistering of the dorsum of the foot several hours before coming to the hospital. On admission, the patient denied any past medical problems. He reported having been treated with antibiotics for pneumonia 1 month earlier. He was not taking any medications other than a diuretic that had been prescribed 1 week earlier. There were no family medical problems. He denied use of tobacco, illicit drugs, or alcohol. Clinical examination revealed a robust young black man with respiratory distress, mild pallor of mucous membranes, and a temperature of 99.3°F. There was bilateral pitting edema of the lower limbs to the mid thigh. The left leg below the knee was cool and cyanotic. The left popliteal artery and dorsalis pedis pulses were not palpable. There were two large blisters over the dorsum of the left foot.

Cardiovascular examination showed a pulse rate of 124 beats per minute; all pulses were present except for pulses below the left knee. The blood pressure was 113/60 mm Hg in both the right and left upper limbs. The jugular venous pressure could not be evaluated. The first and second heart sounds were normal; a low-pitched diastolic sound of uncertain origin was heard. A few crackles were heard at the lung bases bilaterally. The abdominal examination was unremarkable except for mild tenderness in the right upper quadrant; the liver and spleen were not palpable. The rectal examination was normal, and the guaiac test was negative. The patient was alert and oriented, and the neurological examination was normal. The admission laboratory data are shown in Table 1.

The chest radiograph demonstrated normal heart size. The lung fields were normal except for a small right pleural effusion. The ECG showed sinus tachycardia and diffuse nonspecific T-wave changes (Fig 1).

Doppler studies of the lower extremities showed no flow below the left popliteal artery. Angiography showed extreme tapering and occlusion of the left superficial femoral artery; collateral flow was present (Fig 2). The patient was taken to the operating room to relieve the obstruction. A postoperative transesophageal echocardiogram showed an opacity in the left atrium. These findings prompted further evaluation and procedures.

Clinical Discussion
Francis Thandroyen, MD (Department of Internal Medicine, Division of Cardiology)

The salient features of this case are a previously healthy young black man, significant peripheral edema, acute occlusion of a major artery, and a mass in the left atrium. These findings lead to the question, Is there a cardiac cause of right heart failure and arterial occlusion? In considering the above physical findings, the heart is central to both the acute arterial occlusion and the extensive peripheral edema. Acute occlusion of a peripheral artery is commonly the result of an embolus originating from the heart, while extensive peripheral edema may be a manifestation of severe right heart failure. In a young black man, one pertinent diagnosis would be severe mitral stenosis. Although only a low-pitched diastolic sound was heard, the presence of a tachycardia as found in this patient may make the classic diastolic rumble of mitral stenosis difficult to hear. Left atrial dilation and atrial fibrillation, which commonly occur with mitral stenosis, may each be associated with thrombus in the left atrium or appendage. In addition, dynamic smokelike echoes ("spontaneous echocontrast") are present in the left atria or appendage in patients with mitral valve disease, especially mitral stenosis.2 Recent transesophageal studies have shown that patients with spontaneous echocontrast have a higher risk of thromboembolism.1,2 If the mass detected by echocardiography is a thrombus, the arterial occlusion would represent an embolic event. Severe mitral stenosis also predisposes to pulmonary hypertension and right heart failure, which may account for the peripheral edema.

Another pertinent diagnosis is that of a dilated cardiomyopathy. Intracardiac thrombus occurs in patients

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TABLE 1. Laboratory Studies

<table>
<thead>
<tr>
<th>Blood chemistry</th>
<th>Value</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, meq/L</td>
<td>138</td>
<td>135-145</td>
</tr>
<tr>
<td>Potassium, meq/L</td>
<td>3.6</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Chloride, meq/L</td>
<td>99</td>
<td>95-105</td>
</tr>
<tr>
<td>CO₂, meq/L</td>
<td>28</td>
<td>24-32</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>96</td>
<td>65-110</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.8</td>
<td>0.5-1.4</td>
</tr>
<tr>
<td>Urea nitrogen, mg/dL</td>
<td>11</td>
<td>10-20</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>6.6</td>
<td>2.5-8.0</td>
</tr>
<tr>
<td>Total protein, g/dL</td>
<td>4.8</td>
<td>6.0-8.0</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>1.3</td>
<td>2.8-4.3</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>7.7</td>
<td>8.5-11.0</td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>3.0</td>
<td>2.5-4.5</td>
</tr>
<tr>
<td>Chol, mg/dL</td>
<td>195</td>
<td>150-200</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>69</td>
<td>45-170</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.1</td>
<td>0.2-1.0</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>10</td>
<td>7-40</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>44</td>
<td>7-40</td>
</tr>
<tr>
<td>Alk phos, U/L</td>
<td>95</td>
<td>34-108</td>
</tr>
<tr>
<td>Lactic Dh, U/L</td>
<td>227</td>
<td>83-200</td>
</tr>
<tr>
<td>WBC, x 10^3</td>
<td>13.8*</td>
<td>4.8-10.8</td>
</tr>
<tr>
<td>HGB, g/dL</td>
<td>9.9</td>
<td>12-16</td>
</tr>
<tr>
<td>HCT, %</td>
<td>31.4</td>
<td>37-47</td>
</tr>
<tr>
<td>PLT, x 10^5</td>
<td>90 000</td>
<td>133-333</td>
</tr>
<tr>
<td>PT, s</td>
<td>8.7</td>
<td>11.1-13.1</td>
</tr>
<tr>
<td>PTT, s</td>
<td>29.6</td>
<td>≤35</td>
</tr>
</tbody>
</table>

Urine

- Color: yellow
- Turbidity: clear
- Specific gravity: 6.025
- pH: 5.5
- Protein: negative
- Glucose: negative
- Ketones: negative
- Bilirubin: negative
- WBC/hpf: 1-5
- RBC/hpf: 0-1
- Bacteria: few

Arterial blood gases (room air)
- pH: 7.43; PCO₂: 39 mm Hg; PO₂: 95 mm Hg; HCO₃⁻: 25 mmol/L

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with dilated cardiomyopathy and predisposes to embolic phenomena. In addition, severe impairment of ventricular function leads to right heart failure, one manifestation of which is extensive peripheral edema. Patients with dilated cardiomyopathy are also prone to develop right ventricular thrombus, pulmonary emboli, and pulmonary hypertension, thereby facilitating the development of right heart failure. In an older man, extensive coronary artery disease associated with several episodes of myocardial infarction may manifest itself by severe impairment in ventricular function, and segmental hypokinesis may be associated with intracardiac thrombus. In view of the age of the patient and the absence of familial hypercholesterolemia or of previous myocardial infarction, a diagnosis of severe coronary artery disease seems unlikely.

In considering each of the above diagnoses, the clinical feature that requires definition is the presence or absence of right heart failure. In view of the extensive edema, the jugular venous pressure should have been markedly elevated if this patient had right ventricular dysfunction. The information provided in the case presentation indicates that the jugular venous pressure could not be evaluated. Nevertheless, if severe right heart failure is present, hepatomegaly with a tender liver should be found, and distention of the superior vena cava should be noted on the chest radiograph. Although the right upper quadrant was noted to be tender, the liver was not palpable; the chest radiograph did not reveal distention of the superior vena cava. Thus, the above findings suggest an absence of right heart failure. The presence of a normal cardiothoracic ratio, the absence of specific cardiac chamber enlargement on the chest radiograph, and the presence of a nonspecific ECG do not suggest dilated cardiomyopathy, an "ischemic" cardiomyopathy, or mitral stenosis as the correct diagnoses.

Was there a renal cause of the edema, hypoalbunemia, and arterial occlusion? The finding of profound hypoalbunemia (0.8 to 1.3 g/dL) and occlusion of a major artery is suggestive of the nephrotic syndrome. Venous thromboses occur commonly and frequently involve the renal veins, deep veins of the legs, and femoral veins. Arterial thromboses are rare; they have been reported mainly in children and frequently are associated with loss of limbs. If the mass detected in the left atrium was a thrombus, the arterial occlusion probably resulted from an embolic phenomenon. Arterial thromboses may also occur spontaneously in a peripheral artery. Increased urinary excretion of antithrombin III or thrombolytic factors and an increase in coagulation factors (fibrinogen and factors V, VII, VIII, IX), which may occur in the nephrotic syndrome, may each predispose to the hypercoagulable state. Treatment of the nephrotic syndrome with diuretics and/or steroids or trauma to the vessel wall by venipuncture have also been incriminated as factors that predispose to thromboses. Finally, antiphospholipid antibodies (lupus anticoagulant and antiphospholipin antibody) have been associated with venous and arterial thromboses. A higher incidence of antiphospholipid antibodies has been detected in patients with systemic lupus erythematosus, one cause of the nephrotic syndrome.

Another possible diagnosis in this patient is acute endocarditis. Support for the later consideration stems from the clinical findings of fever, anemia, leukocytosis,
a diastolic sound, and arterial occlusion. In a patient
with endocarditis, the finding of a mass in the left atrium
may be representative of a large vegetation of the mitral
valve. Occlusion of large peripheral arteries is com-
monly the result of vegetations caused by Staphylococcus
aureus or fungal infection. Another well-described com-
plication of endocarditis is the nephrotic syndrome,
which would explain the severe hypoalbuminemia and
marked edema. The presence of a diastolic sound and a
mass in the left atrium also raises the possibility of a left
atrial myxoma. This tumor has also been associated with
febrile episodes, anemia, leukocytosis, embolic phenom-
ena, and mitral diastolic murmurs of various intensities.

The presence of marked edema and profound hypoal-
buminemia are consistent with the nephrotic syndrome.
However, the key element required for this diagnosis,
significant proteinuria, was absent. This may represent a
spurious result or be an accurate reflection. A 24-hour
urine examination for protein is required to verify the
presence of ≥3.5 g protein before a diagnosis of ne-
phrotic syndrome can be made. If the urine protein is
negligible, a diagnosis of nephrotic syndrome is not
tenable.

Was there a hepatic or gastrointestinal cause for the
edema, hypoalbuminemia, and arterial occlusion? Were
the edema and the marked hypoalbuminemia due to
cirrhosis and portal hypertension? In this patient, there
were no stigmata of chronic liver disease, the distribu-
tion of edema was atypical for cirrhosis and portal
hypertension, the liver enzymes were normal, and pro-
thrombin time was shortened rather than prolonged.
Thus, the hypoalbuminemia and edema cannot be at-
tributed to impaired protein synthesis associated with
cirrhosis and portal hypertension.

In view of the normal protein synthesis by the liver
and if there was only negligible protein loss in the urine,
the most likely cause of the marked hypoalbuminemia
would be a protein-losing enteropathy. A myriad of
disease processes may cause protein-losing enteropathy,
including tropical and nontropical regional ileitis, ulcer-
ative colitis, Whipple’s disease, lymphoma, small-bowel
tuberculosis, systemic lupus erythematosus, congenital
lymphangiectasia, and constrictive pericarditis. Al-
though the patient did not give a history of chronic
diarrhea, steatorrhea, or weight loss, previous reports
have established that up to one half of patients with a
protein-losing enteropathy may have no gastrointestinal
symptoms. Quantification of the protein loss in the stool
requires measurement of the $\alpha_1$-antitrypsin content,11

![Fig 1. Electrocardiogram showing sinus tachycardia and diffuse nonspecific T-wave changes.](image1)

![Fig 2. Arteriogram showing occlusion of left superficial femoral artery with collateral flow in region of the knee.](image2)
and characterization of the small-bowel abnormality necessitates small-intestinal biopsy. How does one explain the finding of protein-losing enteropathy and an acute arterial occlusion? Reports of the latter association are not evident in the English-language literature. While the hypoalbuminemia is easily explained on the basis of a protein-losing enteropathy through infiltration of the bowel wall or lymphatics, for example by lymphoma, the cause of the hypercoagulable state appears complex. One postulate would be a loss of intrinsic thrombolytic factors in the stool.

In summary, the most likely diagnosis in this case appears to be the nephrotic syndrome or acute endocarditis complicated by the nephrotic syndrome. Resolving the differential diagnosis discussed requires the following investigations: first, a transesophageal echocardiogram to characterize further the mass in the left atrium; second, a 24-hour urine protein analysis to characterize the presence or absence of nephrotic syndrome; third, if the urine protein is low, \( \alpha_2 \)-antitrypsin levels in the stool are necessary to define protein-losing enteropathy, and small-bowel biopsy is required to characterize the nature of the bowel abnormality.

**Transesophageal Echocardiogram**

A highly mobile 2- to 3-cm mass on a pedicle was seen arising from the right inferior pulmonary vein and protruding into the left atrium (Figs 3 and 4). The left and right ventricles were both normal in size and function. Both the atria were normal in size. The valvular structures were normal. A small pericardial effusion was present. The differential diagnosis included

![Transesophageal echocardiogram showing mobile mass on a pedicle arising from the right inferior pulmonary vein and protruding into the left atrium. LA indicates left atrium; RIPV, right inferior pulmonary vein; and T, thrombus.](image1)

![Transesophageal echocardiogram showing mass on pedicle protruding into the left atrium. LA indicates left atrium; RIPV, right inferior pulmonary vein; and T, thrombus.](image2)
a malignant tumor, a myxoma, or a thrombus. In this clinical context, a thrombus was the most likely possibility.

**Further Hospital Course**

The patient underwent emergent surgery, and a 2-cm highly mobile and friable mass arising from the right inferior pulmonary vein was excised. Histological section showed features of an organizing thrombus. Pulmonary vein thrombosis is extremely rare, and when it occurs, it is usually associated with a bronchogenic carcinoma.12 Less frequently, pulmonary vein thrombosis may occur with a sarcoma13 or after lobectomy.14 The symptoms and signs of pulmonary vein thrombosis are nonspecific; cough, dyspnea, and hemoptysis may occur, and the chest radiograph may show acute opacification of the lobe of the lung affected by the pulmonary vein thrombus. The diagnosis of pulmonary vein thrombosis is usually made at postmortem examination. Transesophageal echocardiography, which provides high-resolution imaging of posterior cardiac structures, allows for precise antemortem diagnosis of pulmonary vein masses, as illustrated in this case. Thrombectomy and anticoagulation with warfarin have each been used in the management of pulmonary vein thrombosis.15 Dislodgement of part of the thrombus in the pulmonary vein presumably accounted for the acute occlusion of the artery in this patient.

On day 23 of hospitalization, the patient developed swelling and tenderness of the left upper extremity. A subclavian vein catheter had been in place previously at that site. A nuclear venogram demonstrated complete occlusion of the left subclavian vein with collateral flow. The patient remained well despite a low-grade temperature and positive blood cultures. Another transesophageal echocardiogram was performed to evaluate for endocarditis and also for any residual thrombus in the pulmonary vein. No evidence of valvular vegetations were detected. However, a 1.5-cm immobile opacity, in keeping with a thrombus, was detected in the right pulmonary artery; approximately 80% of the vessel lumen was occluded (Fig 5). Thus, this patient exhibited a hypercoagulable state manifesting itself with thrombosis involving the pulmonary and subclavian veins and the pulmonary artery.

![Fig 5. Repeat transesophageal echocardiogram. A 1.5-cm immobile mass is visualized in the right pulmonary artery. RPA indicates right pulmonary artery; SVC, superior vena cava; and T, thrombus.](image)

### Table 2. Factors Involved in Regulation of Hemostasis and Thrombosis

<table>
<thead>
<tr>
<th>Factors that control the generation of thrombin</th>
</tr>
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<tbody>
<tr>
<td>Protein C</td>
</tr>
<tr>
<td>Protein S (free and bound)</td>
</tr>
<tr>
<td>Factor V resistant to protein C cleavage</td>
</tr>
<tr>
<td>Antithrombin III</td>
</tr>
<tr>
<td>Heparin cofactor II</td>
</tr>
<tr>
<td>α1-Antitrypsin</td>
</tr>
<tr>
<td>α2-Macroglobulin</td>
</tr>
<tr>
<td>Plasminogen</td>
</tr>
<tr>
<td>Tissue-type plasminogen activator</td>
</tr>
<tr>
<td>Factor XII</td>
</tr>
<tr>
<td>High-molecular-weight kininogen</td>
</tr>
<tr>
<td>Prekallikrein</td>
</tr>
<tr>
<td>Lupus anticoagulants</td>
</tr>
<tr>
<td>Tissue factor</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Snake venoms</td>
</tr>
<tr>
<td>Estrogens</td>
</tr>
<tr>
<td>Excess plasminogen activator inhibitor or histidine-rich glycoprotein</td>
</tr>
</tbody>
</table>

![Fig 6. Schematic reflecting changes in the understanding of the coagulation cascade. Most coagulation is initiated by the combination of factor VIIIa and tissue factor (box). The response is amplified and maintained by a positive feedback loop of thrombin-activating enzymes earlier in the cascade (dotted arrows). Factors Va and VIIIa are cofactors, not enzymes, and are shown in italics. Factor XII, high-molecular-weight kininogen, and prekallikrein are not necessary for coagulation in vivo and are not shown.](image)
Profound Hypercoagulable State: Discussion
Martin Phillips, MD (Department of Internal Medicine, Division of Hematology)

This patient indeed appeared to have a profound hypercoagulable state, presenting with arterial embolic phenomena and subsequently manifesting pulmonary vein thrombosis, right pulmonary arterial thrombosis, and left subclavian vein thrombosis. The causes of hypercoagulability were appreciated by Virchow over 100 years ago: abnormal vessels, stasis of the blood, and abnormalities of the blood itself. All the advances of the past century are most logically placed within this framework.

Primary vascular abnormalities are most commonly associated with arterial thrombosis. Atherosclerosis and its sequelae are well known. Homocystinuria is a defect (usually congenital) of one or more enzymes involved in the conversion of cysteine to methionine. Homocysteine, an intermediate, is toxic to vascular endothelium by unknown mechanisms, and its accumulation leads to arterial insufficiency, particularly in the lower extremities in young individuals. Other endothelial abnormalities will be described in the future as the roles of endothelial cell surface molecules, such as heparans and ADPase, and intracellular metabolites, such as nitric oxide and prostacyclin, are defined.

Stasis is a well-recognized factor in the development of pathological thrombosis. The use of prophylactic measures, such as low-dose subcutaneous heparin and intermittent compression stockings, have helped to reduce but have not eliminated this risk factor.

Many abnormalities of the plasma that cause thrombosis have been defined recently. They are most logically divided into three groups: (1) decreases in level(s) of factors that control the generation of thrombin; (2) decreases in the levels of factors involved in fibrinolysis; and (3) the abnormal presence of factors that promote thrombosis. These are listed in Table 2.

Two recent advances are important in understanding of the coagulation cascade. First, the cloning of tissue factor has been critical in the appreciation that the exposure of blood to tissue factor (formerly called thromboplastin) is the initiating event for most physiological and pathological thrombi. Second, the central role of thrombin has been appreciated, not only for the generation of fibrin monomers from fibrinogen but also in that thrombin feeds back positively on factors XI, VIII, and V to maintain a procoagulant response (see Fig 6). Therefore, deficiencies of the factors that regulate thrombin activity are critical to hypercoagulability.

Proteins C and S function together to inactivate factors VIIIa and Va. Deficiencies of either are well-known causes of hereditary hypercoagulable states. However, congenital deficiencies of these two proteins combined explain <5% of clinical venous thrombosis. The loss of protein S in the nephrotic syndrome, as well as autoantibodies against protein C, are recog-
nized acquired hypercoagulable states. Very recently described is a mutation in the factor V molecule that renders it insensitive to cleavage by activated protein C, despite normal antigenic and functional assays.\(^{20,21}\) This mutation may be responsible for 25% of deep venous thrombi.

Antithrombin III (ATIII) combined with endothelial heparans is the primary control of thrombin. The role of a similar protein, heparin cofactor II, is still uncertain. Quantitative and qualitative genetic defects of ATIII are well known but rare. The loss of ATIII has been demonstrated in the urine of patients with the nephrotic syndrome and thrombosis.\(^{22}\) The precise roles of other antiproteases is not known.

Congenital or acquired defects of factors involved in fibrinolysis may also lead to pathological thrombosis. Plasminogen is activated to plasmin chiefly by tissue plasminogen activator. Deficiencies of either are recognized hypercoagulable states. Deficiencies of the "contact activation factors" (factor XII, prekallikrein, and high-molecular-weight kininogen) are associated with thrombosis because of their role, albeit quantitatively less important, in the generation of plasmin.

The last group of disorders of factors in plasma that promote thrombosis is the presence of abnormal substances. The pathophysiological mechanisms of this group are diverse. Only those relevant to this patient are discussed here.

Lupus anticoagulants, a misnomer, are a subset of phospholipid-dependent autoantibodies ("antiphospholipid antibodies").\(^{23}\) These antibodies are associated with thrombosis (more frequently venous than arterial) by unknown mechanisms. Although once considered epiphenomena, the presence of phospholipid-dependent autoantibodies in patients with autoimmune disease carries approximately a 40% lifetime risk of thrombosis. Although this patient did not meet the criteria for systemic lupus erythematosus, he had a moderately increased level of IgG antiphospholipid antibodies and a positive level of antinuclear antibodies, which cannot be completely excluded as contributing factors to his multiple thrombi. Antiphospholipid antibodies may be associated with thrombosis independent of their capacity to prolong the activated partial thromboplastin time.

This patient presented with a very low serum albumin, a short prothrombin time, and multiple thrombi. Although his protein C was normal on admission, because his albumin was very low, it was thought that he had the nephrotic syndrome and had lost other coagulation control proteins in the urine. Since thrombosis of selected arteries was progressing while he was heparinized, the patient was started on a continuous infusion of fresh-frozen plasma and maintained on heparin. With this combination, fibrinolysis was achieved, as documented by a rise in the fibrin split-product level. This regimen was chosen because the infused plasma provided all of the coagulant and anticoagulant factors and would be expected to respond normally to the heparin infusion.

When a renal source of protein loss and decreased hepatic protein synthesis were ruled out, and with the documented loss of \(\alpha_1\)-antitrypsin in the stool, it was thought most likely that the cause of his hypercoagulable state was the loss of coagulation control proteins in addition to \(\alpha_1\)-antitrypsin and albumin via the intestine. He had a biopsy of his small bowel that will be described by Dr Buja.
Pathology Discussion

L. Maximilian Buja, MD (Department of Pathology and Laboratory Medicine)

At separate operations, material was removed from the left popliteal artery and the right inferior pulmonary vein. This material was sectioned and examined microscopically. Both masses consisted entirely of unorganized thrombi composed of platelet lamellae and a fibrin mesh with trapped erythrocytes and leukocytes (Fig 7). Subsequently, the left lower leg was amputated and submitted for examination. The specimen exhibited necrotic tissue and thrombosed vessels.

Later, a small-intestinal biopsy was obtained and submitted for examination. There was no evidence of atrophy of villi or epithelium. The lamina propria of the villi contained several dilated lymphatic capillaries consistent with lymphangiectasia (Fig 8). Thus, the pathology examinations revealed evidence of (1) multiple systemic arterial and venous thrombi and (2) bowel findings consistent with intestinal lymphangiectasia.

Final Data and Comments

Denzil D’Souza, MD (Department of Internal Medicine)

Several 24-hour urine collections for protein were performed during the period of hospitalization. None of these tests showed enough protein loss in the urine to support a diagnosis of nephrotic syndrome. To evaluate for possible protein-losing enteropathy, a stool collection was obtained and analyzed for α1-antitrypsin; the result obtained demonstrated α1-antitrypsin levels greater than 10 times the upper limit of the reference range (27.8 mg/g dry wt stool; reference range, <2.6 mg/g dry wt stool). Subsequently, upper endoscopy with biopsy showed evidence of intestinal lymphangiectasia (Fig 8). Thus, the marked hypoalbuminemia and edema were due to a protein-losing enteropathy.

Further pertinent data included positive antinuclear antibody (1:320), positive anti-Ro antibody, moderately positive anticardiolipid antibody (IgG), and hypocomplementemia; the double-strand DNA was negative. The above findings do not fulfill all the criteria required for a diagnosis of systemic lupus erythematosus. Nevertheless, the above data suggest a "lupus-like" or "autoimmune-like" disease process. Lupus-associated protein-losing enteropathy has been reported and usually presents with profound hypoalbuminemia and edema in the absence of nephrosis, hepatic disease, or malnutrition.11,24,25 Diarrhea is present in only 50% of the cases; steatorrhea is usually not found. Lymphangiectasia is not usually a feature of this process; however, this association has been reported.25 The onset of the classic signs and symptoms of lupus erythematosus may be preceded by a protein-losing enteropathy by a period of months to years. Thus, one possible hypothesis is that this case may represent an early manifestation of systemic lupus erythematosus. An alternative consideration is that this patient has some other autoimmune disease process. For the above reasons, the patient was treated with corticosteroids.

How does one explain the profound hypercoagulable state? A chronic, low-grade anti-phospholipid (autoimmune) process that was associated with and exacerbated by the loss of intrinsic thrombolytic factors secondary to protein-losing enteropathy appeared to be the probable cause.

The patient has been well since discharge from the hospital. The corticosteroid dose has been tapered, and he remains on warfarin. A further antinuclear antibody titer was found to be 1:640. The serum albumin level has returned to normal, a repeat transesophageal echocardiogram shows regression of the pulmonary artery thrombus, and there have been no further arterial or venous thromboses.

Final Diagnosis

The final diagnosis is protein-losing enteropathy associated with a profoundly hypercoagulable state manifest with multiple arterial and venous thrombi. A chronic, low-grade antiphospholipid antibody process exacerbated by the loss of intrinsic thrombolytic factors in the stool presumably accounted for the hypercoagulable state. The underlying cause is undefined but appears to be an autoimmune disease process.

Acknowledgment

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References


A 24-year-old man with extensive lower limb edema and acute arterial occlusion.
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