CASE IN POINT

SPLENIC INFARCTION ASSOCIATED WITH PROTEIN S DEFICIENCY

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Protein S deficiency, which has a well documented association with venous thrombosis, also has been linked to arterial thrombosis and, in this case, was at the root of splenic infarction.

Protein S is an important vitamin K-dependent plasma protein involved in the regulation of the coagulation cascade.[1] Protein S deficiency is reported to be associated with myocardial infarction, ischemic stroke, and severe thromboembolic disease.[2–6] Here, we report a case of acute splenic infarction associated with protein S deficiency.

INITIAL EXAM

A 55-year-old, white man was admitted to the hospital with severe, generalized, abdominal pain of two days' duration. He had mild nausea but no vomiting. By the time he was seen by the physician, his pain was localized to the left upper quadrant of his abdomen. He had no constipation or diarrhea. His past medical history and family history were unremarkable.

Upon physical examination, his temperature was 99° F and he demonstrated mild tenderness in the left upper quadrant of his abdomen. An initial workup revealed an elevated leukocyte count of 15.4 x 10^3/µL (normal, 5 to 10 x 10^3/µL) with 84% neutrophils (normal, 54% to 75%), 8.1% lymphocytes (normal, 25% to 40%), and 6.5% monocytes (normal, 2% to 8%). Mean corpuscular volume was elevated at 100 fL (normal, 84 to 96 fL) and platelet count was normal. C-reactive protein and sedimentation rate were normal. Other blood chemistry studies were normal or nearly normal (Table 1).

A chest X-ray showed a small, left side pleural effusion and linear, patchy densities involving both lower lung fields, consistent with pneumonitis. A computed tomography (CT) scan of his abdomen using a contrast medium demonstrated marked, low attenuation involving approximately half of the spleen, which was consistent with a large splenic infarction (Figure). Both the splenic vein and the splenic artery appeared to be patent. The small bowel, colon, and rectum were slightly dilated—a finding consistent with adynamic ileus.

The initial diagnosis was bilateral community-acquired pneumonia and splenic infarction. It wasn't possible to obtain a sputum specimen because the patient had no cough. He began empiric treatment with broad spectrum intravenous antibiotics and subcutaneous low molecular weight heparin.

Hematologic evaluation to elucidate the etiology of splenic infarction revealed that the patient had an elevated homocysteine level and decreased levels of protein S, vitamin B_{12}, and folate (Table 2). Antithrombin III, anticardiolipin antibodies,

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Table 1. The patient's blood chemistry results upon admission

Test	Value	Normal range
Sodium	132 mEq/L	135–145 mEq/L
Potassium	4.2 mEq/L	3.5–5.0 mEq/L
Chloride	105 mEq/L	101–112 mEq/L
Carbon dioxide	27 mEq/L	22–32 mEq/L
Creatinine	0.8 mg/dL	0.6–1.2 mg/dL
Prothrombin time	13 seconds	11–15 seconds
Activated partial thromboplastin time	30 seconds	25–35 seconds
Glucose	85 mg/dL	60–110 mg/dL
Alanine aminotransferase	20 units/L	7–56 units/L
Amylase	34 units/L	20–110 units/L
Total protein	7.2 g/dL	6.0–8.0 g/dL
Albumin	4.1 g/dL	3.4–4.7 g/dL

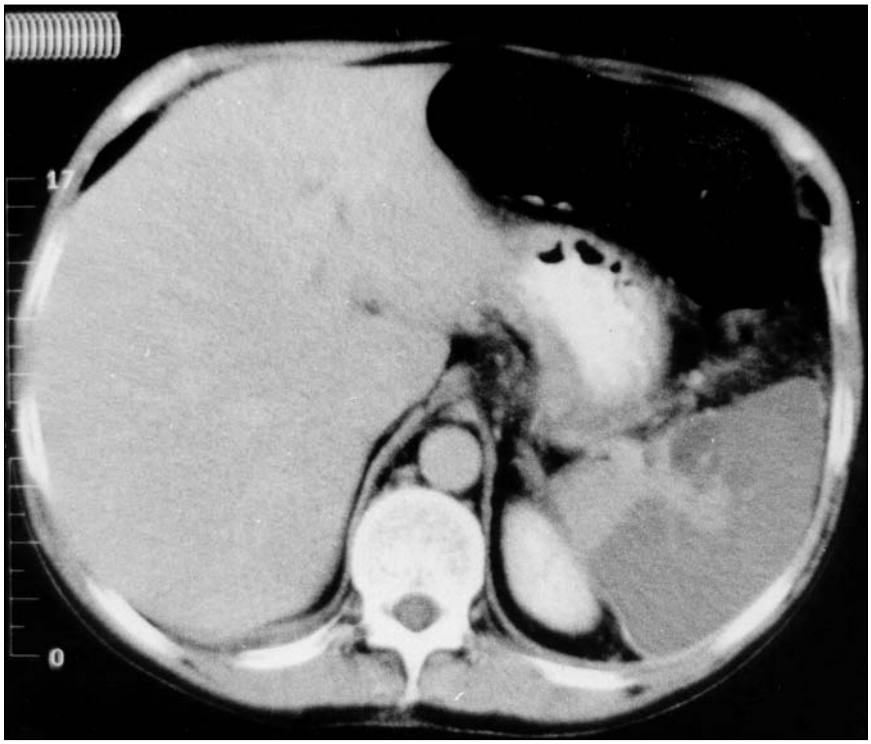

Figure. Computed tomography scan of the abdomen showing marked, low attenuation changes involving approximately half of the spleen, consistent with large splenic infarction.

and factor II procoagulant levels were normal. Assays for antinuclear antibodies, rheumatoid factor, and factor V Leiden were negative.

HOSPITAL COURSE

Shortly after admission, oral anticoagulation therapy, intramuscular vitamin B_{12}, and folic acid supplementation were added to his medication regimen. A repeat chest X-ray taken two days later showed resolving pneumonia. By that time, the patient's condition had improved significantly and he'd had no recurrence of abdominal pain. A bone marrow biopsy performed on hospital day four was normal.

The patient was discharged after a six-day hospital stay. He was asymptomatic at follow-up two and four weeks after discharge.

ABOUT THE CONDITION

Protein S is part of a system that regulates normal coagulation mechanisms in the body. It is a cofactor for the protein C system but also has independent coagulation functions.[7] In the presence of factor V, it acts as a cofactor to protein C in the proteolysis of factor VIII, thereby reducing thrombin formation. In addition, it inhibits procoagulant enzyme complexes, the significance of which is unknown.[7]

Deficiency of protein S usually is inherited as an autosomal dominant trait, but an acquired form (associated with the use of oral contraceptives, pregnancy, disseminated intravascular coagulation, nephrotic syndrome, and recovery from chicken pox) has been reported as well.[5,8–11] In human plasma, protein S may be found in two forms: circulating freely (40% to 50%) and bound with complement component C4b-binding protein (50% to 60%).[12]

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Table 2. Results of the patient's coagulation studies upon admission

Test	Result	Reference range
Antithrombin III	95%	94%–132%
Protein C (functional)	134%	80%–166%
Protein S (functional)*	43%	82%–177%
Homocysteine	15.3 µmol/L	4.0–12.0 µmol/L
Factor V Leiden	Negative	Negative
Factor II procoagulant	98%	79%–150%
Anticardiolipin antibodies Immunoglobulin G Immunoglobulin M	 Negative Negative	 Negative Negative

*Using the photo-optical clot detection method (ARUP Laboratories, Salt Lake City, UT).

Table 3. Relative risk of developing deep venous thrombosis associated with various risk factors for hypercoagulability

Risk factor for hypercoagulability	Relative risk of initial thrombotic episode
None known (normal coagulation profile)	1
Use of oral contraceptives	4
Factor V Leiden (heterozygous)	7
Factor V Leiden (homozygous)	80
Protein C deficiency (heterozygous)	7
Protein S deficiency (heterozygous)	6
Hyperhomocysteinemia	2–4

There are three types of protein S deficiency. In type I, total S antigen is decreased by about 50%, with even more severe deficiencies of free protein S antigen and protein S functional activity. This type is associated primarily with missense mutations and microinsertions or deletions of base pairs.[12,13] In type II, which is relatively rare, protein S functional activity is reduced, while total and free protein S levels are normal.[14,15] Type III protein S deficiency is characterized by a low level of free protein S, reduced protein S functional activity, and a normal level of total protein S.[16]

Patients with protein S deficiency are at elevated risk for venous thrombosis.[17] One study found that, among members of the same family, the risk of developing venous thrombosis was 50% for those with protein S deficiency and 30% for those without.[18] Relative risk for an initial episode of deep venous thrombosis varies with the patient's specific hypercoagulability risk factors (Table 3). Cases of atypical thrombosis in cerebral, mesenteric, and axillary veins also have been described in medical literature.[19]

The incidence of arterial thrombosis associated with protein S deficiency is less well documented than that of venous thrombosis. It consists primarily of case reports showing an association between this condition and cerebral infarction, myocardial infarction, and retinal artery obstruction.[2–5,20] Larger studies have not established a relationship between protein S deficiency and arterial thrombosis.[21,22]

Splenic infarction is a rarely seen clinical entity. It may be symptomatic or asymptomatic and can occur with either arterial or venous compromise. It usually presents in association with hematologic, thromboembolic disorders and rarely with vasculitis.[23,24] The most common causes of splenic infarction include myelofibrosis and chronic myelogenous leukemia. Other causes include blunt trauma, thromboembolism secondary to atrial fibrillation, and septic emboli due to endocarditis. It also is seen in sickle-cell disease, Kawasaki disease, and systemic lupus erythematosus complicated by the presence of lupus anticoagulant and anticardiolipin antibodies.[23]

In our patient, splenic infarction was associated with functional protein S deficiency coexisting with elevated homocysteine and low vitamin B_{12} and folate levels. A literature review using Medline revealed no similar reported case.

The functional protein S assay used for this patient detects both quantitative and qualitative deficiency of protein S. Symptomatic patients with protein S deficiency usually present before the age of 40.

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Protein S deficiency is managed with long-term anticoagulation therapy aimed at keeping the therapeutic international normalized ratio between 2 and 3. Generally, the decision to anticoagulate is influenced by the risks of recurrent thromboembolism and of major bleeding.

REFERENCES

1. Coller BS, Owen J, Jesty J, et al. Deficiency of plasma protein S, protein C, or antithrombin III and arterial thrombosis. *Arteriosclerosis*. 1987;7:456–462.
2. Reyes-Iglesias Y, Ortiz AA, Goitia DM, Melendez R. Coexistence of primary antiphospholipid syndrome and protein S deficiency in a Hispanic man with ischemic stroke. *South Med J*. 1998;91:296–298.
3. Beattie S, Norton M, Doll D. Coronary thrombosis associated with inherited protein S deficiency: A case report. *Heart Lung*. 1997;26:76–79.
4. Sacco RL, Owen J, Mohr JP, Tatemichi TK, Grossman BA. Free protein S deficiency: A possible association with cerebrovascular occlusion. *Stroke*. 1989;20:1657–1661.
5. D'Angelo A, Della Valle P, Crippa L, Pattarini E, Grimaldi LM, Vigano D'Angelo S. Brief report: Autoimmune protein S deficiency in a boy with severe thromboembolic disease. *N Engl J Med*. 1993;328:1753–1757.
6. Koppelman SJ, Hackeng TM, Sixma JJ, Bouma BN. Inhibition of the intrinsic factor X activating complex by protein S: Evidence for a specific binding of protein S to factor VIII. *Blood*. 1995;86:1062–1071.
7. Rezende SM, Simmonds RE, Lane DA. Coagulation, inflammation, and apoptosis: Different roles for protein S and the protein S-C46 binding protein complex [published online ahead of print]. *Blood*. August 7, 2003;DOI 10.1182/2003-05-1551.
8. Malm J, Laurell M, Dahlback B. Changes in the plasma levels of vitamin K-dependent proteins C and S and of C4b-binding protein during pregnancy and oral contraception. *Br J Haematol*. 1988;68:437–443.
9. D'Angelo A, Vigano-D'Angelo S, Esmon CT, Comp PC. Acquired deficiencies of protein S. Protein S activity during oral anticoagulation, in liver disease, and in disseminated intravascular coagulation. *J Clin Invest*. 1988;81:1445–1454.
10. Vigano-D'Angelo S, D'Angelo A, Kaufman CE Jr, Sholer C, Esmon CT, Comp PC. Protein S deficiency occurs in the nephrotic syndrome. *Ann Intern Med*. 1987;107:42–47.
11. Gouault-Heilmann M, Gadelha-Parente T, Levent M, Intrator L, Rostoker G, Lagrue G. Total and free protein S in nephrotic syndrome. *Thromb Res*. 1988;49:37–42.
12. Amiral J, Grosley B, Boyer-Neumann C, et al. New direct assay of free protein S antigen using two distinct monoclonal antibodies specific for the free form. *Blood Coagul Fibrinolysis*. 1994;5:179–186.
13. Schwarz HP, Fischer M, Hopmeier P, Batard MA, Griffin JH. Plasma protein S deficiency in familial thrombotic disease. *Blood*. 1984;64:1297–1300.
14. Borgel D, Gandrille S, Aiach M. Protein S deficiency. *Thromb Haemost*. 1997;78:351–356.
15. Comp PC, Doray D, Patton D, Esmon CT. An abnormal plasma distribution of protein S occurs in functional protein S deficiency. *Blood*. 1986;67:504–508.
16. Borgel D, Duchemin J, Alhenc-Gelas M, et al. Molecular basis for protein S hereditary deficiency: Genetic defects observed in 118 patients with type I and type IIa deficiencies. The French Network on Molecular Abnormalities Responsible for Protein C and Protein S Deficiencies. *J Lab Clin Med*. 1996;128:218–227.
17. Comp PC, Nixon RR, Cooper MR. Familial protein S deficiency is associated with recurrent thrombosis. *J Clin Invest*. 1984;74:2082–2088.
18. Simmonds RE, Ireland H, Lane DA, et al. Clarification of the risk for venous thrombosis associated with hereditary protein S deficiency by investigation of a large kindred with a characterized gene defect. *Ann Intern Med*. 1998;128:8–14.
19. Lagosky S, Witten CM. A case of cerebral infarction in association with free protein S deficiency and oral contraceptive use. *Arch Phys Med Rehabil*. 1993;74:98–100.
20. Greven CM, Weaver RG, Owen J, Slusher MM. Protein S deficiency and bilateral retinal artery occlusion. *Ophthalmology*. 1991;98:33–34.
21. Douay X, Lucas C, Caron C, Goudemand J, Leys D. Antithrombin, protein C, and protein S levels in 127 consecutive young adults with ischemic stroke. *Acta Neurol Scand*. 1998;98:124–127.
22. Mayer SA, Sacco RL, Hurlet-Jensen A, Shi T, Mohr JP. Free protein S deficiency in acute ischemic stroke. A case-control study. *Stroke*. 1993;24:224–227.
23. Toth PP, Reuter RK, MacDonald J. Spontaneous splenic infarction secondary to diabetes-induced microvascular disease. *Arch Fam Med*. 2000;9:195–197.
24. Nores M, Phillips EH, Morgenstern L, Hiatt JR. The clinical spectrum of splenic infarction. *Am Surg*. 1998;64:182–188.