Brief Report

Coagulopathy Presenting as Calf Pain in a Racquetball Player

Calvin Wong, MD, and Mark Bracker, MD
La Jolla, California

Most cases of lower leg pain in athletes result from musculoskeletal injury. Occasionally these patients do not respond to treatment in a timely fashion. This should alert the clinician to rethink the original diagnosis and consider more unusual causes of leg pain. Deep venous thrombosis must be considered in a young athletic person experiencing unexplained persistent calf pain after exercise. Further investigation may be necessary to rule out a hereditary or acquired hypercoagulable state.

Key words. Leg; athletic injuries; thrombophlebitis; thromboembolism; blood coagulation disorders; protein deficiency. (*J Fam Pract 1993; 37:390-393*)

Leg pain is a common complaint encountered in clinical practice. The differential diagnosis of lower leg pain includes fracture, gastrocnemius muscle rupture or strain, plantaris muscle rupture, partial or total Achilles tendon rupture, tibialis anterior syndrome, posterior tibial tendinitis ("shin splints"), acute or chronic compartment syndrome, tibial or fibular stress fracture, nerve entrapment, arterial disease, venous pathology, and referred pain. Although several conditions may coexist, a careful history and physical examination as well as knowledge of the natural history of the above conditions should lead to accurate diagnosis and appropriate treatment.

This case report describes a young athletic patient with leg pain caused by a hereditary illness that has been only recently described.

Case Report

C.W., a 27-year-old fourth-year medical student, reported gradual onset of calf pain in his left leg, which over the course of 24 hours became progressively more painful and awakened him during the night. The pain was poorly localized and was described as a deep, sharp pain unrelieved by stretching. Because he had been playing racquetball 2 days before the onset of the calf pain, he attributed the pain to a calf strain even though he did not recall a particular precipitating incident.

The pain resolved after the student took aspirin. He played basketball the following day, still with some tightness in the upper calf. He was then away for a month doing a clinical externship, during which time he did not experience a recurrence of his calf pain. He was fairly inactive during this time, abstaining from his usual athletic activities. On returning, he noticed that after being on his feet most of the day, he felt a dull, aching pain in his left calf.

The patient was seen at the student health clinic. There was no evidence of trauma, swelling, a palpable cord, or Achilles tendon weakness. He was told that it was probably a calf strain, and rest, ice, compression, and elevation (RICE) were prescribed, to be followed by stretching exercises. Over the course of the next few days, the student found that after stretching he developed severe calf pain.

Because he was about to depart on a trip to Europe, he sought further evaluation. His history at that time revealed a healthy young man without any past or present medical problems. He was not taking any medications. His family history was unremarkable for blood dyscrasias. The physical examination showed mild, ill-defined tenderness in the mid-calf region of the left leg

Submitted, revised, August 3, 1993.

From the Department of Family and Preventive Medicine, University of California–San Diego, School of Medicine, La Jolla, California. Requests for reprints should be addressed to Mark Bracker, MD, Department of Family and Preventive Medicine, University of California–San Diego, La Jolla, CA 92093–0807.

ISSN 0094-3509

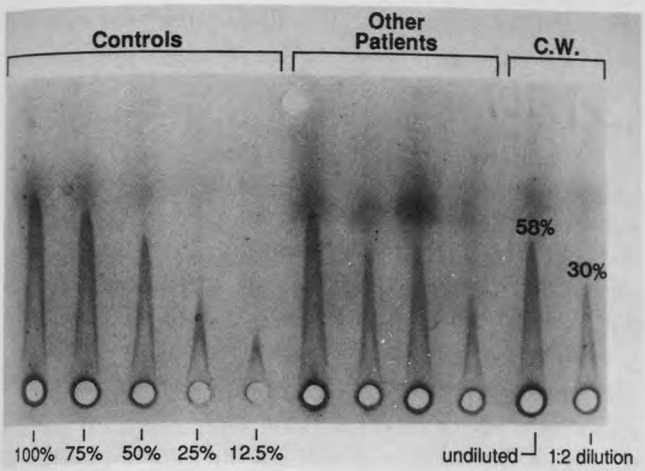

Figure 1. Rocket immunoelectrophoresis analysis reflecting total protein S antigen levels. Controls on the left represent five dilution levels of protein S antigen in control serum (range of 12.5% to 100% of normal). The patient's levels (C.W.) are at the far right and represent 58% of control value in undiluted sample and 30% of control at 1:2 dilution.

with mild lower-extremity edema. Circumferential leg measurements were made and found to be 2.5 cm greater in the left leg as compared with the right. Homans' sign was negative. A duplex ultrasound showed evidence of a deep venous thrombosis in the left leg extending to the level of the adductor canal.

The patient was hospitalized, and after 4 days of heparin treatment, he was discharged on a therapeutic dose of warfarin. He continued to receive warfarin therapy, which was titrated to a prothrombin time level of 1.3 to 1.6 times control (Internationalized Normalized Ratio [INR] of 2.0 to 3.0 for an International Sensitivity Index of 2.4). A repeat Doppler ultrasound was done after 3 months of anticoagulant therapy and revealed only a small area of noncompressibility of the left popliteal vein, which was attributed to some residual thickening of the wall from preexisting venous thrombosis. The patient was then instructed to discontinue warfarin therapy. About 2 weeks later, he was tested for hypercoagulable states (antithrombin III, protein C, and protein S deficiencies, as well as the presence of lupus anticoagulant). Test results were within normal limits except that the patient's total protein S was at the lower limit of the normal range (Figure 1) and that the free protein S was <12% by Laurell rocket electrophoresis (Figure 2). These findings were confirmed by crossed immunoelectrophoresis (CIE) (Figure 3). The patient's C4b-binding protein level was within the normal range.

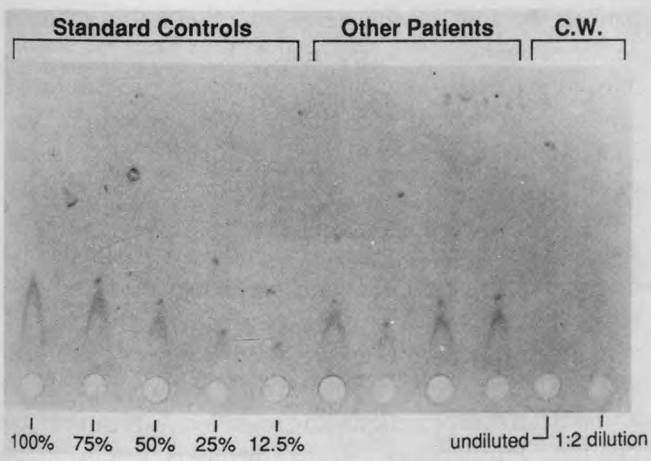

Figure 2. Rocket immunoelectrophoresis analysis reflecting free protein S antigen levels. Controls on the left represent five dilution levels of free protein S antigen in serum (range of 12.5% to 100%). The patient's levels (C.W.) are at the far right and are less than 12.5% of normal on both undiluted and diluted specimens.

Discussion

Primary hypercoagulable states involve specific abnormalities of hemostasis and include antithrombin III deficiency, protein C deficiency, protein S deficiency, lupus anticoagulant, disorders of fibrinolytic system (eg, disor-

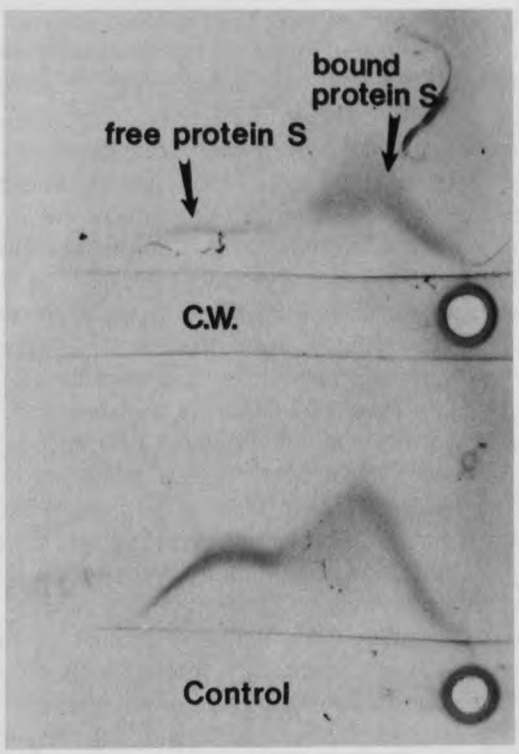

Figure 3. Crossed immunoelectrophoresis of plasma. The two peaks in the control represent free and bound protein S. Note that the patient's levels (C.W.) show no free protein S peaks as compared with normal control shown below it.

ders of tissue plasminogen activator, abnormal plasminogen and hypoplasminogenemia), dysfibrinogenemia factor XII deficiency, and anticardiolipin antibody syndrome. Secondary states involve conditions associated with an increased risk of thrombosis and include surgery trauma, pregnancy, hematologic disorders (eg, polycythemia vera, essential thrombocytosis, and paroxysmal nocturnal hemoglobinuria), malignancy, and sepsis.[1]

Protein S deficiency is the most frequent cause of idiopathic venous thrombosis, accounting for about 5% to 8% of cases.[2] It was first described by Comp and Esmon,[3] and Schwarz et al[4] in 1984. Protein S is an important vitamin-K dependent antithrombotic factor that serves as a nonenzymatic cofactor for activated protein C to have functional activity. Like protein C, it is produced in the liver. Protein S exists in two forms in plasma, an inactive form bound to C4b-binding protein (accounting for 60% of total protein S) and a functionally active free form (40%).[5] In the coagulation cascade a series of enzymatic steps occur resulting in the generation of thrombin from prothrombin. When thrombin is formed intravascularly it binds to a binding site on vascular endothelial cells called *thrombomodulin* and can then activate protein C. Activated protein C, with protein S functioning as a cofactor, catalyzes proteolytic cleavages that inactivate factors V and VIII (cofactor proteins involved in the activation of prothrombin and factor X, respectively). The end result is impairment of further generation of thrombin and consequently leads to the inhibition of fibrin formation. Activated protein C also stimulates fibrinolysis by decreasing the activity of plasminogen activator-inhibitor. Thus, patients deficient in protein S or protein C are prone to recurrent thromboembolic disease, presumably resulting from an inability to regulate the clotting cascade.

Protein S deficiency is inherited as an autosomal dominant trait with incomplete penetrance. Whereas the incidence of asymptomatic heterozygous protein C deficiency in the general population is approximately 1 in 200, the true incidence of protein S deficiency is currently unknown. In the heterozygous patient, protein S levels are usually less than 50% of normal. While the patient may present with symptoms at any age, there is a 68% probability that a thrombotic event occurs by age 35 years.[6] In one study of 71 symptomatic patients with protein S deficiency, the mean age of their first thrombotic episode was 28 years and the incidences of deep venous thrombosis, pulmonary embolism, and superficial thrombophlebitis were 74%, 38%, and 72%, respectively.[6] The recurrence rate in this study was 77%. About 56% of cases were spontaneous events; the remainder were associated with a precipitating event. Acquired states of protein S deficiency can be found in pregnancy, with oral contraceptive use, with disseminated intravascular coagulation, in liver failure, with nephrotic syndrome, with acute inflammation, and in type I diabetes mellitus.[7]

Treatment of thrombosis associated with protein S deficiency is identical to that of acute venous thrombosis resulting from any cause. Anticoagulation with parenteral heparin followed by oral warfarin is the mainstay of treatment. The necessity of long-term warfarin prophylaxis after the first episode of thrombosis is uncertain. Some have recommended initiating prophylactic therapy only after a second episode of thrombosis, whereas others believe that a single episode warrants prophylactic treatment. But before beginning lifelong anticoagulation, it would be advisable to have the test repeated. Because of the low prevalence of disease, the predictive value of a positive test may be relatively low. Therefore, repeating the test or using other test methods would be prudent to minimize a false-positive result. It is imperative that the free protein S level be determined. Some patients with protein S deficiency have normal concentrations of total protein S when it is measured immunologically. However, functional assays for protein S indicate a relative deficiency of the active free form.

There is no evidence at present that the potential protection afforded by long-term prophylactic oral anticoagulation outweighs the risks of bleeding. Thus, asymptomatic protein S–deficient patients need not be on warfarin prophylaxis. It is generally recommended, however, that, if the patient is reliable, low-dose warfarin with the goal of achieving an INR of 2 to 3 should be considered after the first thrombotic episode. Such a recommendation might not be eagerly accepted by some patients because of the necessity of curtailing certain activities owing to the potential of bleeding. No studies have as yet been done that demonstrate the efficacy of aspirin as an alternative to lifelong warfarin prophylaxis. In addition, patients should be counseled about the risk of thrombosis associated with surgery and prolonged immobilization (eg, long-distance plane trips or hospital stays). Female patients should be advised about the risk of thrombosis associated with pregnancy and oral contraceptive use. One must be particularly mindful that warfarin is teratogenic, and its use from the 6th to 12th week of gestation is associated with characteristic facial and skeletal malformations (the so-called warfarin embryopathy). Furthermore, family members ought to be tested to evaluate their risk for thrombosis. Immediate family members of C.W. were tested, and the mother and a sister were found to have deficient total and free protein S levels. However, they had not reported an occurrence of a thrombotic event. The cost of testing for protein S

and protein C deficiency in our medical center is $127 and $137, respectively.

Summary

Although guidelines on screening have not been established, one must consider the diagnosis of protein S deficiency and other inherited abnormalities of coagulation, such as protein C deficiency and antithrombin III deficiency, in a patient with a history of thrombosis, especially if thrombosis is recurrent or occurs at an early age (<40 years old), at unusual sites (ie, mesenteric venous, retinal, cerebral sinus, or renal thrombosis), or without apparent precipitating factors, or if there is a strong family history of thrombosis.[8] If such factors are present, it would be prudent to pursue an evaluation for hypercoagulability. Testing should be performed ideally at the time of diagnosis if a hypercoaguable state is suspected, or else after completion of an adequate course of anticoagulant therapy because protein S is a vitamin K–dependent factor and thus its concentration is reduced during warfarin treatment.

A diagnosis of protein S deficiency need not be devastating. While further studies are needed to elucidate the clinical course of disease and to determine the efficacy of long-term warfarin prophylaxis, patients with a history of thrombosis, as in the patient in the case discussed, can apparently be managed effectively with minimal side effects on a moderate intensity of oral anticoagulation to prevent recurrence of thrombosis. It is not known what therapy should be instituted in patients for which warfarin is contraindicated or for those who decide against lifelong low-dose warfarin, although aspirin, 81 mg daily, or placement of a Greenfield filter are suggested alternatives.

Acknowledgments

The authors wish to thank Heidi M. Buckmeier for her secretarial assistance in the preparation of this manuscript, and Kathleen Donnely in the Special Coagulation laboratory for supplying the assay gels.

References

1. Bowen KJ, Vukelja S. Hypercoagulable states: their causes and management. Postgrad Med 1992; 91:117–32.
2. Comp PC. Overview of the hypercoagulable states. Semin Thromb Hemost 1990; 16(2):158–61.
3. Comp PC, Esmon CT. Recurrent venous thromboembolism in patients with a partial deficiency of protein S. N Engl J Med 1984; 311:1525–8.
4. Schwarz HP, Fischer M, Hopmeier D, Batard MA, Griffith JH. Plasma protein S deficiency in familial thrombotic disease. Blood 1984; 64:1297–300.
5. Comp PC, Nixon RR, Cooper MR, Esmon CT. Familial protein S deficiency is associated with recurrent thrombosis. J Clin Invest 1984; 74:2082–8.
6. Engesser L, Broekmans AW, Briët E, Brommer EJ, Bertina RM. Hereditary protein S deficiency: Clinical manifestations. Ann Intern Med 1987; 106:677–82.
7. Comp PC. Laboratory evaluation of protein S status. Semin Thromb Hemost 1990; 16(2):177–81.
8. Bauer KA. Pathobiology of the hypercoagulable state: clinical features, laboratory evaluation, and management. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al, eds. Hematology: basic principles and practice. New York: Churchill Livingstone, 1991:1415–30.