Acute Subclavian and Brachial Artery Thrombosis as a Complication of the Nephrotic Syndrome

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The nephrotic syndrome is well recognized as a hypercoagulable state. However, whereas venous thrombosis occurs frequently, arterial thromboembolic complications within the context of the nephrotic syndrome are rare [1]. Arterial thrombosis is mainly observed in children. In adults, males are predominantly affected. We describe a 44 year old man who presented with an acute thrombosis of both the left subclavian and brachial arteries. Initial treatment consisted of thrombolysis and percutaneous angioplasty, and thrombectomy was eventually performed in order to achieve successful revascularization. During his admission, the patient was diagnosed as suffering from a hitherto unknown nephrotic syndrome. Renal biopsy demonstrated membranous nephropathy. The patient's course and the underlying factors inductive to arterial thrombosis in the nephrotic syndrome are discussed.

Patient Description

A 44 year old man presented to the Emergency Room complaining of severe pain in his left upper limb and, in particular, his left hand. The pain had become progressively worse during the preceding 2 weeks. The patient was a heavy smoker (40 pack-years). On examination, the left hand was cold with the first and second fingers markedly pale, distally cyanosed and tender. Subclavian and distal arterial pulses were non-palpable. On Doppler ultrasonography, only a faint signal was elicited over the proximal brachial artery. Emergency angiography via a right transfemoral approach revealed complete occlusion of the left proximal subclavian artery extending to the origin of the vertebral artery. Filling of the subclavian artery distal to the occlusion was accomplished by retrograde flow from the vertebral artery. In addition, an occlusion of the brachial artery at the level of the elbow was demonstrated. Intraarterial urokinase infusion using the pulse spray technique was begun. A repeated angiography several hours later showed a high grade stenosis of the origin and proximal segment of the

subclavian artery as well as a totally occlusive thrombosis of the brachial artery at its bifurcation. A stent was inserted into the subclavian artery, achieving good angiographic flow. However, due to distal subclavian arterial thrombi and the brachial artery thrombosis, a thrombectomy was performed. Postoperatively, the brachial artery was palpable. Further management included a 14 day course of intravenous iloprost and heparin anticoagulation followed by warfarin. At discharge, the left hand was successfully revascularized (apart from necrosis of the distal phalanx of the second finger) and fully functional.

Laboratory data during the patient's hospitalization were as follows: serum hemoglobin 12.0 g/dl, urea 23 mg/dl, creatinine 0.8 mg/dl, total protein 3.6 g/dl, albumin 1.5 g/dl and cholesterol 204 mg/dl. Urinary protein was 14 g/day. Coagulation tests showed a prothrombin time 11.6" (85%), INR 1.1, activated partial thromboplastin time 34", fibrinogen 899 mg/dl, protein C activity 66% (70–140), protein S activity 93% (65–160), protein S antigen free 62% (65–130), antithrombin 74% (80–120), activated protein C resistance ratio 2.5 (2–4) and negative anticardiolipin antibodies (immunoglobulins G and M) and lupus anticoagulant. Hepatitis B surface antigen, hepatitis C virus and human immunodeficiency virus antibodies were negative. Renal biopsy revealed histologic evidence typical of membranous nephropathy. Transthoracic echocardiography demonstrated a normally functioning left ventricle with no signs of an intramural thrombus.

Comment

This patient's course is unusual inasmuch as he presented with subclavian and brachial artery thromboses as the initial manifestations of a previously undiagnosed nephrotic syndrome. Although the severely stenosed subclavian artery was a predisposing factor, local thrombus formation as well as that of the brachial artery (either *de novo* or as a thromboembolic complication) was undoubtedly aided by the hypercoagulable state inherent to the nephrotic syndrome. Addis [2] was the first to draw attention to an increased incidence of venous thromboses in association with the syndrome. Of these, lower limb and renal vein thrombosis are the most frequent. Arterial thrombosis, however, is rare and is primarily seen in children [1]. Reported sites have included the cerebral, aorta, innominate, mesenteric, axillary, subclavian, brachial, carotid, coronary, renal, popliteal, iliac, femoral, ophthalmic and pulmonary arteries [1,3]. The most susceptible is the femoral artery possibly as a result of attempted blood sampling.

The thrombotic tendency of nephrotic patients is multifactorial in origin [1]. It involves altered blood levels of both coagulation and fibrinolytic proteins, platelet hyperaggregability, venous stasis, hemoconcentration, an increased blood viscosity, and the administration of steroids and/or diuretics. Notable among the procoagulant factors are increased levels of fibrinogen, and factors V, VII, VIII and X. These increases correlate with the reduction in serum albumin and are attributed to increased hepatic synthesis stimulated by hypoalbumonemia. In parallel, decreased levels of several fibrinolytic factors, in particular, plasma plasminogen and antithrombin, have been documented [1]. These are thought to result from urinary losses. In a study by Kauffman et al. [4], an antithrombin level of < 70% of normal was found in eight of nine patients with clinical evidence of arterial or venous thrombosis. This level correlated well with a urinary protein excretion in excess of 10 g/24 hours and is usually seen in patients with a serum albumin < 2.0 g/dl. Increased blood viscosity is due to the high hematocrit value (hemoconcentration often aggravated by diuretics) and the markedly elevated fibrinogen levels. Steroids raise the concentration of factor VIII and shorten prothrombin and activated partial thromboplastin times.

Our patient exhibited many of the hypercoagulable features listed above. He was severely nephrotic with a serum albumin of 1.5 g/dl and urine protein excretion of 14 g/day. Serum fibrinogen was 899 mg/dl and antithrombin 74%. In addition, he was a heavy smoker. Smoking is well known to increase the risk of vascular disease acting either directly or adversely influencing associated risk factors. Included among these are endothelial dysfunction, dyslipidemia (decreased high density lipoprotein cholesterol levels, hypertriglyceridemia and increased oxidation of low density lipoprotein cholesterol) and platelet activation, all of which lead to a prothrombotic state. Smoking-induced alterations in growth factors, adhesion molecules and genes can accelerate the progression of atherosclerosis [5].

In our patient, combined aggressive therapy utilizing thrombolysis, angioplasty and eventual thrombectomy led to successful revascularization with only the distal phalanx of the second finger requiring amputation. Currently, he continues with oral warfarin anticoagulation. His nephrotic syndrome is being managed with angiotensin-converting enzyme inhibitors.

References

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