CASE REPORTS

Elevated lipoprotein(a)-associated accelerated thromboangiitis: A case report

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ABSTRACT

We describe a 47-year-old African American woman affected by a rapidly progressing thromboangiitis associated with high serum levels of lipoprotein(a) (Lp(a)).

Key Words: Lipoprotein(a), Thromboangiitis, Buerger's disease

1. BACKGROUND

Lipoprotein(a) (Lp(a)) contains a low-density lipoprotein core bound to a series of glycoproteins structurally similar to plasminogen. This molecule has been purported to inhibit the conversion of plasminogen to plasmin resulting in a subsequent reduction of endogenous fibrinolysis.[1,2] The total serum levels of Lp(a) have been phenotypically correlated to allelic variation at the apo(a) site on chromosome 6.[3,4] Elevated serum levels of Lp(a) have been identified as an independent risk factor for thrombotic disease and atherosclerotic cardiovascular disease.[5–7] No screening protocol has been established to identify those with elevated serum Lp(a).[8]

This case addresses the role of Lp(a) as a thrombotic risk factor. Lp(a) has been implicated in at least one prior case of Lp(a)-associated thromboangiitis obliterans (TAO).[9] The case previously reported, highlights a disease process consistent with TAO in which Lp(a) was a contributing factor. While abundant literature is available on the identification and treatment of TAO, an extensive review of the literature did not identify any additional cases of Lp(a)-associated TAO and no cases were identified with such an atypical presentation of extensive thrombo-occlusive disease with gangrene.

2. CASE REPORT

We present a case of a previously healthy, 47-year-old African American woman employed as a cross-country truck driver who initially presented to an outside hospital with pain in her bilateral fingers and toes. Over the next three days, this progressed to firm, painful, necrotic bilateral upper and lower extremity distal phalanges with involvement of her metatarsals. The disease process was limited to the distal extremities and excluded periodontal manifestations. Other than obesity, her medical history was negative for diabetes, hypertension, cardiovascular disease, and bleeding disorders. She endorsed a 4-pack year history of smoking but had quit 4 weeks prior to this admission. She otherwise

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denied marijuana, alcohol, illicit drug use, or industrial exposures including mercury. There was no significant family history of rheumatologic or hypercoagulable diseases.

Initial workup revealed mild thrombocytopenia of 124,000/μl, as well as elevated erythrocyte sedimentation rate (119 mm/HR) and C-reactive protein (7.8 mg/L). Chest CT angiogram demonstrated right lower lobe subsegmental pulmonary embolism for which she was started on heparin. Venous Doppler studies revealed bilateral lower extremity deep venous thromboses (DVTs) of the right posterior tibial, left popliteal and left gastrocnemius veins, as well as superficial vein thrombosis of the left small saphenous, right median cubital, right basilic, left median cubital and left basilic veins. Her platelets subsequently decreased to 110,000/μl. A heparin-induced thrombocytopenia panel was negative, but she was cautiously switched to lovenox and bridged to warfarin. Upper extremity arterial studies suggested normal, patent macrovasculature with normal pressure readings and microvascular ischemia in her distal phalanges. Aorto-femoral angiogram with lower extremity runoff demonstrated normal macrovasculature, with possible corkscrewing of the distal lower extremity microvasculature. Echocardiogram did not reveal a patent foramen ovale, cardiac thrombus or infective endocarditis.

Serologic studies were negative for hepatitis B, hepatitis C, syphilis, human immunodeficiency virus (HIV), histoplasma galactoman antigen, rocky mountain spotted fever, tuberculosis and coccidiomycosis complement fixation. Vasculitis and rheumatologic workup included negative c-ANCA, p-ANCA, anti-scleroderma antibody, anti-centromere antibody, anti-cardiolipin antibody, Beta 2 glycoprotein 1 antibody, anti-nuclear antibody, and an appropriate dilute Russel viper venom time. Hypercoagulable workups were negative for prothrombin 20210 gene mutation and factor V leiden mutations; prior to anticoagulation therapy her PT and PTT were within normal range. Urine and serum heavy metal screens were both negative.

The patient had negative age-appropriate malignancy screening with mammography, PAP test, and colonoscopy. A PET scan identified increased uptake in the region of her uterus that was attributed to known fibroids. Electrocardiogram revealed a normal sinus rhythm with no evidence of atrial fibrillation. Punch biopsies were taken from the posterior calf, ankle, and right lateral second finger at the site of necrosis. All biopsies revealed evidence of necrosis and reactive fibrosis of surrounding tissue, atherosclerosis but otherwise grossly normal vasculature without inflammatory thrombi. She subsequently developed osteomyelitis of select distal necrotic phalanges and metatarsals requiring partial amputation of the left third digit of her hand and bilateral toes. Surgical pathology demonstrated evidence of gangrenous necrosis, acute and chronic inflammation, reactive fibrosis, and specifically excluded evidence of vasculitis or inflammatory thrombi. Cholesterol and triglyceride levels were elevated at 220 and 242 mg/dl, respectively; her LDL was 121 mg/dl and HDL was 51 mg/dl. Further workup revealed elevated serum Lp(a) of 391 nmol/L (lab reference range < 70). She was gradually started on niacin therapy of 800 mg twice a day, which decreased her Lp(a) level to 77 nmol/L. She was subsequently stabilized and discharged to a skilled nursing facility for rehabilitation. At follow up, she had been without disease progression for greater than 6 months.

3. DISCUSSION

The differential for dry gangrene is extensive and can be difficult to assess the etiology. In general, the differential may include poorly controlled diabetes, complications of HIV or hepatitis, infectious emboli, and other embolic sources. Rheumatologic diseases should be considered including, antiphospholipid antibody, systemic lupus erythematous, and vasculitis including TAO. In some cases, patients may require work up for malignancy that can contribute to hypercoagulable states. Patients should be questioned regarding family history of hypercoagulable disease and screened for hematological abnormalities. Common etiologies for occlusive disease were negative and further investigation of atypical TAO was warranted.

The most common initial manifestations in a patient with TAO are the development of intermittent claudication, superficial thrombophlebitis and paresthesias. The disease most commonly affects the vessels distal to the popliteal artery.[10] However, atypical presentations have been reported in which large intestinal ischemia, splenic and pancreatic infarct, intrarenal arterial stenosis, stroke, and coronary involvement occur.[11–15] In addition, TAO typically occurs with an extensive smoking history, though some cases reported symptom onset after only 2 years of tobacco use.[16] The relatively low incidence of TAO in the African American population and the historically higher incidence in males vs. females is of note.[17] While no definitive histological criteria are established, acute phase TAO is associated with inflammatory occlusive thrombi of the afflicted vessel lumen with less extensive inflammation of the vessel wall. The patient described in this case had punch and excisional biopsies that failed to reveal inflammatory occlusions.[17,18] Laboratory markers are non-specific, though in contrast with the elevated acute phase reactants seen in this case, TAO classically presents with normal serum CRP and ESR.[17]

Two notable diagnostic criteria for TAO have been identified in the literature. The previous criteria, Shionoya Criteria (1998), includes smoking history; onset before age 50; infrapopliteal arterial occlusions; either arm involvement/phlebitis migrans and absence of atherosclerotic risk factors other than smoking.[19] Contrasted with the Olin Criteria (2000) which includes age under 45; current/history of smoking; the presence of distal extremity ischemia; exclusion of autoimmune disease, hypercoagulable states or diabetes; exclusion of proximal source of thrombi, and consistent arteriography findings.[20] Our patient does meet the older Shionoya Criteria; however, fails to meet the diagnostic criteria set forth by Olin.

The patient's condition failed to resolve following hospitalization, anti-coagulation therapy, and smoking cessation prompting the search for additional prothrombotic factors, including Lp(a). The prevalence of elevated Lp(a) in the population is estimated as high as 35.0%.[21] While our lab uses 70 nmol/L as the cut off for elevated Lp(a), the literature suggests that the cut off for African Americans should be as low as 30 nmol/L, much lower than the 391 nmol/L observed in our African-American patient.[22] The pathophysiology has been well described to include anti-thrombolytic properties attributed to the conserved amino acid segment most similar to plasminogen.[1–3,5] We posit that her elevated Lp(a) contributed to an endogenous prothrombotic state that was aggravated by cigarette smoking and occupational immobility. In the literature, the lipoprotein-associated prothrobotic state has been highlighted as a risk factor for arterial and venous thrombosis.[23–27] While thrombosis was not demonstrated histologically, we suspected, the biopsies were obtained after weeks of anti-coagulation therapy. There has been one previous case report of TAO associated with elevated Lp(a) levels. However, our patient's presentation would be atypical for this in the setting of her relatively short 4-pack-year smoking history, race, gender and concurrent extensive DVTs. An independent Lp(a) thromboembolic disease process is further supported by evidence of distal extremity microvascular ischemia without histopathological evidence of inflammatory occlusions or vasculitis.

The pathogenesis of Lp(a) is an expanding field of research with unknown implications on future patient care. It continues to be a promising potential indicator of future cardiovascular disease and thrombotic disease. Patients presenting with dry gangrene and persistent thromboembolic disease involving multiple organ systems may have less common etiologies of such manifestations. These patients should be evaluated for Lp(a)-associated accelerated thromboangiitis, a potentially treatable etiology.

4. Conclusion

Lp(a)-associated thromboangiitis should be considered in patients presenting with thrombotic phenomena and microvascular disease of unknown etiology.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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