Delayed Diagnosis of Paget-Schroetter Syndrome in a Patient with COVID-19

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ABSTRACT

Paget-Schroetter Syndrome (PSS), a subtype of thoracic outlet syndrome, is a rare condition defined as thrombosis of the axillosubclavian vein secondary to anatomical abnormalities or repetitive injury to vessel endothelium from exertion. In the setting of the COVID-19 pandemic, venous thrombosis in COVID-positive patients may be attributed to the well-described hypercoagulability associated with the viral syndrome, increasing the rate of misdiagnosis of PSS and delaying definitive treatment. We report a case of PSS in a 19-year-old male who presented to multiple health care providers with an upper extremity thrombus and was found to be SARS-CoV-2 positive on hospitalization. In his case, his COVID status likely contributed to a delay in diagnosis of Paget-Schroetter syndrome, with the patient missing the window for the standard treatment protocol.

KEYWORDS: Paget Schroetter Syndrome, COVID-19, hypercoagulability, deep vein thrombosis

INTRODUCTION

Paget-Schroetter syndrome (PSS), alternatively referred to as effort thrombosis, is a subcategory of the venous thoracic outlet syndromes, defined as primary thrombosis of the axillo-subclavian vein.[1,2] The thoracic outlet syndrome subcategories also include neurogenic and arterial syndromes, with neurogenic making up over 95% of thoracic outlet syndromes. Only 3-5% of thoracic outlet syndromes are venous in etiology.[3] PSS was first described in 1875 by Sir James Paget[4] as spontaneous thrombosis of the axillo-subclavian vein, with later postulation from von Schroetter that venous damage resulted from activity involving muscular strain.[5] Despite being a well-established condition, it is commonly overlooked as a diagnosis, likely due to its relatively low incidence of one to two per 100,000 cases per year.[1]

A number of case reports have been published detailing various presentations of PSS and the inciting activities. However, very few have been published detailing the diagnosis of PSS in the context of the COVID-19 pandemic, with no reports, to our knowledge, of cases with initial misdiagnosis of PSS as a thrombotic sequelae of COVID-19.[6,7]

We describe a case of a 19-year-old male with PSS who tested positive for SARS-CoV-2 on hospital admission for upper extremity thrombus, after presenting to multiple outside providers for associated symptoms. Clinical diagnosis of PSS was delayed, ultimately placing this patient outside of the window for standard treatment. This case underscores the importance of raising clinicians' awareness of PSS, how its clinical features are distinct from thrombotic events secondary to COVID-19, and when to promptly initiate its unique treatment protocol.

CASE PRESENTATION

An athletic 19-year-old right-handed male with no significant medical history was admitted with edema, erythema, and pain with abduction of the right upper extremity (RUE). His symptoms began roughly one month prior, following vigorous physical activity, which included cliff jumping and playing basketball. The patient also reported exacerbation of symptoms, with intermittent pain of the entire right extremity, when weightlifting. He denied use of any prescription medications or recent surgeries and reported occasional alcohol and marijuana use. Family history was notable for a lower extremity deep vein thrombosis (DVT) in his father, without clear report of provocation.

He first presented to an urgent care facility, where shoulder x-ray showed no acute abnormalities. He was discharged with instructions to start nonsteroidal anti-inflammatory drugs. Roughly 20 days following his urgent care visit, he presented to an outside emergency department (ED) with dyspnea and worsening RUE pain. CT angiogram (CTA) showed subsegmental pulmonary emboli (PE) in the left lingula and lower lobe of the left lung and duplex ultrasound (US) showed an occlusive thrombus in the right basilic vein. Details of thrombus involvement of more proximal vasculature were not documented. The patient's PEs were treated with heparin and he was discharged on rivaroxaban 15mg, twice daily with hematology follow-up to further assess the etiology of his thrombi. The patient refused COVID-19 testing throughout that hospitalization for unknown reasons and did not exhibit typical symptoms of COVID-19 during his stay.

Ten days following discharge, he presented to outpatient hematology with residual edema and reduced range of

motion due to pain in the RUE, despite reported compliance with rivaroxaban therapy. He was then advised to present to our ED. His vitals were within normal limits, with a temperature of 36.6°C, heart rate of 69 beats per min, blood pressure of 118/58 mmHg, a respiratory rate of 17 breaths per min, and SpO2 of 99%. Physical exam was notable for additional findings of cervical lymphadenopathy and tenderness to palpation of the right axilla and lateral to the cubital fossa. Visible prominence of superficial veins on the affected side, known as Urschel's sign, was not observed. Distal pulses were palpable bilaterally, neurological exam was normal, and a general review of systems was grossly negative.

Duplex US of RUE demonstrated thrombi in the right subclavian, axillary, and basilic veins, concerning for extension or reoccurrence of thrombosis. A repeat CTA was also performed, with no evidence of PE. In the context of palpable cervical lymph nodes and concerns for hypercoagulability associated with malignancy, a CTA of the neck was ordered, which did not demonstrate pathologic lymphadenopathy. Initial laboratory workup was notable for an INR of 1.9, a negative hypercoagulability panel (activated protein C resistance, protein S and protein C activity, lupus anticoagulant, antithrombin III, factor VIII assay, activated partial thromboplastin time mix 1:1, prothrombin time mix 1:1) and detection of SARS-CoV-2 on PCR. Complete blood count and basic metabolic panel were unremarkable.

The patient was admitted on a heparin drip and bridged to warfarin on hospital day two. Both hypercoagulability due to COVID-19 and PSS were considered as potential diagnoses based on his clinical history. Vascular surgery consultants recommended further imaging with MRI/MRA, which was scheduled as an outpatient. The patient was discharged on hospital day five on warfarin.

Outpatient MRI/MRA with and without venous contrast revealed a right subclavian DVT arising near the vein's origin, as it passes ventral to the anterior scalene muscle without any notable anatomical abnormalities on these images. The patient was continued on warfarin, but duplex imaging 3 months later revealed no change in the right subclavian thrombus. Failure of thrombus resolution suggested PSS over COVID-19-associated hypercoagulability, with repetitive physical activity being the most likely trigger.

The patient fell far outside of the standard 14-day window for catheter-directed thrombolysis by the time of final diagnosis. Five months following discharge, the patient underwent first rib resection for decompression of the thoracic outlet. The one-month post-operative RUE duplex US showed complete resolution of the thrombi with wall thickening in the axillary vein. Despite thrombi resolution, the patient continued to report episodes of discoloration and edema of the right arm after upper body exercise but was able to return to full activity.

DISCUSSION

PSS accounts for only 10–20% of all cases of upper extremity deep vein thrombosis, and approximately 1% to 4% of all cases of venous thrombosis in general, making it relatively rare.[1,8] The other 80% of cases of upper extremity thrombosis are secondary to a predisposing factor, such as in-dwelling devices or hypercoagulable states.[8] Our patient reflects the demographics of those usually affected, as it is most common in young male athletes, with the mean age at presentation of roughly 30 years and a male-female ratio of 2:1. It is also more commonly is seen in the right arm, likely reflecting the greater proportion of right-handed individuals in the general population.[1]

Activities that involve repetitive movement of the upper extremity, with extremes of abduction or external rotation, such as throwing sports or overhead lifting, are seen as the inciting factor in 60–80% of cases.[1,9–12] At such extremes of motion, the subclavian vein may be compressed between the clavicle and first rib, even in cases without anatomical abnormalities of the thoracic outlet.[1,2] This chronic compression is thought to incite microtrauma, which progresses to fibrosis of the area and reduced mobility of the vein, predisposing it to further damage with movement, and thrombosis formation.[13]

Symptoms at presentation may vary from intermittent upper extremity edema and pain, aggravated by physical activity, to severe, persistent feelings of heaviness and swelling with erythema or blue discoloration. Patients may also have axillary fullness and tenderness to palpation of the affected arm. Many patients with chronic obstruction also have Urschel's sign, or visibly enlarged collateral veins of the shoulder and chest, on exam.[1,14] In patients with a presentation suspicious for PSS, duplex US is the test of choice, with a sensitivity and specificity of roughly 80%–100%.[15] Once the diagnosis is made, treatment should be initiated as soon as possible.

Although anticoagulation therapy is advised for at least three months, standard treatment also involves catheter-directed thrombolysis (CDT) within the first two weeks of symptoms, followed by correction of the anatomic problem trigger via thoracic outlet surgical decompression.[16,17] This protocol minimizes the long-term morbidity of the condition and the possibility of treatment failure.[18,19] After the standard two-week window, the success rate of thrombolysis drops significantly. Three reports indicate no success in thrombolysis in patients with symptoms for greater than 10 days, while other studies report a success rate of 29% after 2–12 weeks.[1,20] While it is generally supported that surgical treatment follows thrombolytic therapy, the exact timing of surgery is less agreed upon.

Complications associated with limiting treatment to just anticoagulation includes recurrent thrombosis and pulmonary emboli, which is seen in 15% of cases who do not undergo CDT.[1] Approximately 70% of patients will also go

on to develop additional long-term complications with anticoagulation alone, including persistent symptoms or permanent disability, limiting participation in manual labor.[21] Despite eventual surgical treatment with first rib resection, the patient had residual symptoms, including swelling and pain with extremes of motion, that may have been avoided if CDT was administered within the standard treatment window. While there is limited data on the usual timing of diagnosis, a retrospective review of 34 patients with PSS showed that 26 patients underwent CDT treatment after a mean of 5.5 days of symptoms versus eight patients who were managed over one month after symptom onset, indicating that significant delay in treatment is likely common.[22]

In the setting of the COVID-19 pandemic, the diagnosis of upper extremity venous thrombosis is likely further complicated by the well-described thrombotic sequelae of the novel virus. Although conclusive data on the relative venous thrombosis risk remains limited among patients who do not become critically ill with COVID-19, there has been a general increase in thrombotic events seen in hospitalized patients.[23–25] Greater clinician awareness around all causes of venous thrombosis is needed in this climate, along with more conclusive data on coagulation abnormalities seen in non-critically ill patients with COVID-19. Moreover, clinicians should consider PSS whenever a young patient presents with an upper extremity DVT and be advised to take a thorough history to assess for inciting activities. Familiarity with this syndrome has the potential to greatly impact the promptness of diagnosis and patient outcomes.

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