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Case Report

Cavernous Sinus Thrombosis as a Complication of Undiagnosed Protein Losing Enteropathy Secondary to Mixed Connective Tissue Disease: A Case Report

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Abstract

Background: Mixed connective tissue disease is a rare autoimmune disease that can lead to dysfunction in multiple organ systems. It has known prothrombogenic properties that typically spare the vasculature of the central nervous system. Mixed connective tissue disease is also a cause of protein-losing enteropathy, a disorder resulting from gastrointestinal mucosal damage that presents with hypoproteinemia. Cavernous Sinus Thrombosis (CVST) is a rare form of cerebral venous sinus thrombosis, accounting for a small percentage of all CVST cases.

Case Report: A middle-aged woman presented with headache, rash and edema. She had a recent history of an unprovoked portal venous thrombosis but has discontinued her anticoagulation. A magnetic resonance venography demonstrated cavernous sinus thrombosis. A heparin drip was started and because of profound hypoproteinemia, a 24-hour stool alpha-1-antitrypsin was obtained, confirming protein-losing enteropathy. She improved and was discharged on enoxaparin, hydroxychloroquine and a prolonged prednisone taper.

Conclusion: Mixed connective tissue disease can have an insidious onset. In this case it resulted in two severe, reversible, life-threatening disorders. Both protein-losing enteropathy and cavernous sinus thrombosis were caused by the autoimmune disease and occurred concurrently. An earlier diagnosis and treatment may have prevented both complications.

Keywords: Mixed Connective Disease; Protein-Losing Enteropathy; Thrombosis; Cavernous Sinus Thrombus

Introduction

Mixed Connective Tissue Disease (MCTD) is a rare, chronic, relapsing-remitting systemic autoimmune disease [1]. The risk of venous thromboembolism is higher in individuals with MCTD, especially when the disease is clinically active or in the first year of diagnosis [2]. Protein-losing enteropathy is a clinical syndrome characterized by Gastrointestinal (GI) protein wasting as a result of increased permeability in the GI tract mucosa [3]. Autoimmune disorders are known antecedent risk factors for acquired PLE and PLE has even been shown to be a presenting feature of MCTD possibly [4].

Cavernous sinus thrombosis (CST) is a rare form of Cerebral Venous Sinus Thrombosis (CVST), accounting for a small percentage (1-4%) of all CVST cases. MCTD could be a risk factor for CST because of the thrombogenic properties of the autoimmune condition [5]. We present a woman with venous thrombosis and PLE as a result of progressive MCTD.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Case Report

A 34-year-old female with a past medical history of portal vein thrombosis, diagnosed at an outside facility 4 months prior to admission and initially treated with apixaban, presented to the Emergency Department (ED) with several days of a severe frontal headache and photosensitivity. The patient had discontinued the apixaban several weeks earlier and did not know the details of her workup for the portal thrombosis. Upon admission to our ED, Magnetic Resonance Venography (MRV) demonstrated cavernous sinus thrombosis. A heparin drip was started and she was subsequently transferred to a higher level of care facility for neurosurgical evaluation. She denied trauma, drug use and recent travel and reported no recent weight loss. Her family history was not significant. She was not taking oral contraceptives or exogenous estrogen. She denied chills, fever, memory loss or recent antibiotics.

Upon arrival, her physical exam revealed significant periorbital and peripheral edema, including in her hands. A healing rash was noted on the trunk and lower extremities, which the patient described as a pruritic maculopapular rash that first appeared several months prior. An MRV was repeated, documenting a thrombus within the left transverse sinus, left sigmoid sinus and proximal left internal jugular vein (Fig. 1). Blood chemistry showed a total protein level of 4.2 g/dL (grams per deciliter; normal range is between 6.0 and 8.3 g/dL) and an albumin level of 1.5 g/dL (normal range is between 3.4 and 5.4 g/dL). Anti-thrombin III function was measured at 39% (the common range for adults is 80% to 120%), which likely reflected her overall low-protein state rather than an isolated deficiency. Liver function tests, renal function tests, lipid profiles and urinalysis were within normal limits. A review of recent lab work conducted prior to admission to evaluate possible causes of her previous portal vein thrombosis revealed reduced protein S function at 49% (normal protein S activity ranges from 60% to 150%). Protein C activity was preserved at 72% (normal is between 70% and 150%). Factor V mutation, Factor II mutation, anticardiolipin antibody and anti-beta-2 glycoprotein antibodies were found to be negative.

Workup of her hypoproteinaemia revealed some recent appetite suppression, but the patient reported eating a diet high in protein. The patient reported a former alcohol use disorder but had not had any alcohol for a year leading up to her hospitalization. Liver enzymes were not elevated and no cirrhosis was demonstrated on imaging. A 24-hour urine protein study was negative for nephrotic range proteinuria. After a positive anti-nuclear antibody titer, further autoimmune studies revealed anti-U1RNP antibodies >240 U/mL (normal, <10 U/mL) and anti-RNP70 antibodies > 218 /U/mL (normal, 0 to 1 U/mL. Thus, a diagnosis of mixed connective tissue disease was made and PLE was suspected.

A 24-hour stool Alpha-1-Antitrypsin (A1AT) study was conducted and while the volume of stool was not reported, the A1AT stool clearance at 2313 mL/24 h confirmed a diagnosis of protein-losing enteropathy. The gastroenterology service collected endoscopic biopsies revealing normal esophageal, gastric, small intestinal, colonic and rectal mucosa. Therefore, the protein-losing enteropathy was considered a complication of mixed connective tissue disease.

The patient was discharged on enoxaparin, hydroxychloroquine and a prolonged prednisone taper. This combination of medications was prescribed to treat her thrombosis, MCTD and by treating these disorders, her PLE would improve. She did not require intravenous immunoglobulin or plasmapheresis. She has been encouraged to follow up closely with rheumatology but has, so far, not been able to do so due to a lack of proximity to rheumatology services in her hometown. However, during an office visit with another specialist, she presented in a wheelchair because of diffuse joint pain limiting her ambulation. Therefore, we presume that more classic symptoms of MCTD have continued to progress.

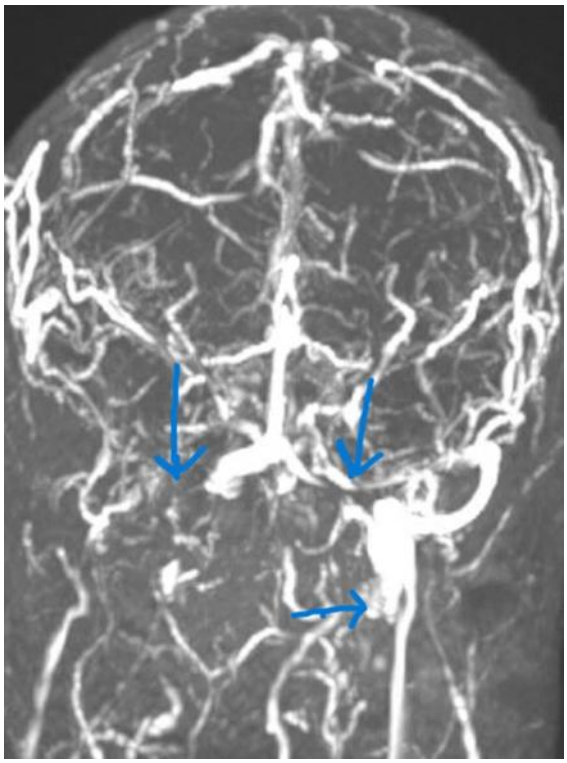

Figure 1: MRV revealing no flow within the left transverse sinus, left sigmoid sinus and proximal left internal jugular vein constituent with thrombosis.

Discussion

This case is important for three reasons. First, this appears to be the first case of MCTD presenting as concurrent PLE and venous thrombosis. Her portal venous thrombosis was initially thought to be unprovoked based on the data available, but we lacked a timeline of her MCTD status until she presented to our facility. Minimal workup was conducted at the portal venous thrombosis admission. She subsequently presented to our healthcare system four months later with a history of rash, edema and headache. MCTD was suspected as the etiology of her thrombosis when her workup revealed her clinical findings, laboratory abnormalities and an MRV demonstrating cavernous sinus thrombosis. Although thrombosis is not a diagnostic component of MCTD, which requires at least two crossover features with other autoimmune diseases [6], the incidence of thrombus formation in MCTD is higher than in the general population [2]. Although, her first thrombotic event occurred in her portal system, she was not diagnosed with MCTD at that time. Her CVT was the initial thrombotic episode when she met all the criteria for MCTD. MCTD presenting as a thrombus in the brain is highly unusual. There are only three previous cases in the literature of MCTD presenting as cerebral venous thrombosis and none of these were identified as cavernous sinus thrombosis [5,7,8].

The second and strong point of this case, especially with regard to treatment, is the intersection of MCTD and PLE in a patient with an active central nervous system thrombosis. Acquired PLE can be a complication of a broad spectrum of disease states [9] and results from lymphatic leakage [10] or the more common capillary leakage. Capillary leakage can be secondary to erosion of the GI mucosa, as seen in inflammatory bowel disease or nonerosive leakage seen in autoimmune disorders, including Mixed Connective Tissue Disease (MCTD). If PLE is secondary to an erosive gastroenteropathy, the necessary anticoagulation treatment for the CST becomes problematic. However, MCTD has only been implicated as a cause of PLE in 8 previous reports. Of the eight, 7 were females and none other than ours were reported to have suffered with a concomitant thrombus [4].

Diagnostic tests for PLE include the Alpha-1-Antitrypsin (A1AT) clearance in a 24-hour stool sample [11] and technetium-99 m human serum albumin scintigraphy [12-15]. In this case, diagnostic workup started with dietary history, investigation of liver synthesis capabilities and urine studies to rule out significant proteinuria. Though PLE is thought to be underrecognized, the ease of obtaining these studies makes them a convenient starting point. The treatment PLE is supportive and treats the underlying cause of the disease.

The third important point of this paper is factoring in patient follow-up with outpatient visits, imaging, consultations and medication. She had three treatable nonmalignant diseases that were life-threatening but potentially reversible with compliance. Her unique living conditions prevented her from following through on all phases of her care and it was not surprising when she ultimately presented for an outpatient visit in a nonambulatory state due to joint pain, suggesting the progression of her autoimmune disease.

Conclusion

MCTD is a rare cause of PLE and CST. It is even more unusual for both disorders to occur simultaneously. Nonetheless, in this case, MCTD was likely the initial disorder that caused the PLE and hypercoagulation that resulted in the CST. Hypercoagulation is worsened by PLE and may have been a factor in the development of the thrombosis. Her edema and rash were two crossover features that were present when she presented with the headache and CST. Whether an earlier workup for autoimmune disease when she had the portal vein thrombosis would have been helpful is only speculative, but this case clearly illustrates that the earlier a diagnosis can be made and treatment started, the more serious complications can be mitigated.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability and Consent of Patient

Patient consent was obtained.

Author's Contribution

All authors had access to the data and a role in writing the manuscript, no disclaimers.

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