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DEEP VEIN THROMBOSIS REVEALING A "SILENT" COELIAC DISEASE

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ABSTRACT

Introduction: We present a clinical case of a 45-year-old man with recurrent deep vein thrombosis (DVT) and multiple hospital admissions due to severe infectious conditions. A newfound hypoalbuminemia raised the suspicion of a protein-losing condition, with an upper endoscopy revealing lesions at the D2 level compatible with coeliac sprue and HLA typing positive for both DQ-2 and DQ-8.
Methods: A gluten free diet was started and apixaban was suspended.
Results: No new complications were reported.
Discussion: Multiple mechanisms are believed to be behind the association between DVT and coeliac disease. However, to this date, no consensus exists regarding the ideal duration of anticoagulation.

KEYWORDS

Venous thromboembolism, coeliac disease

LEARNING POINTS

- Coeliac disease should always be considered a systemic disease.
- Thromboembolism is a possible extraintestinal manifestation of coeliac disease.
- Coeliac disease should be considered as a possible cause of thromboembolism even in the absence of gastrointestinal symptoms, which it can precede by several years.

CASE DESCRIPTION

A 45-year-old man presented to the emergency department with a 2-day history of fever, redness, and oedema in his right leg. His past medical history included epilepsy and recurrent episodes of DVT. Both acquired (malignancy and antiphospholipid syndrome) and inherited causes (factor V of Leiden and prothrombin mutations, deficiency of proteins C, S, and antithrombin III, and hyperhomocysteinemia) were excluded. Also of note were two previous hospital admissions due to a psoas abscess resulting in septic shock and a soft tissue infection by *Streptococcus pyogenes* complicated with sepsis. His chronic medication included eslicarbazepine 800 mg/day, apixaban 10 mg/day, and diosmin 450 mg + hesperidin 50 mg/day.

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METHODS AND PROCEDURES

A physical exam showed an afebrile and hemodynamically stable patient with pronounced inflammatory signs in the entirety of the right leg. Laboratory studies showed leucocytosis of 12.3 x 10^9/l with neutrophilia of 93%, albumin 2.1 g/dl, AST and ALT 116 U/l, and C reactive protein of 31mg/dL. As the Wells score for DVT was 3, the D-dimer levels were also obtained and were below the cut-off value.

A diagnosis of cellulitis was then presumed, and empirical levofloxacin was administered after blood cultures were drawn (which were negative) for a total of 14 days. A right leg CT scan with angiography performed within 24 hours showed an oedematous and diffuse subcutaneous infiltration, confirming the diagnosis. The association of recurrent hospital admissions due to infectious conditions, significant hypoalbuminemia, and previous history of DVT raised the suspicion of a possible nephrotic syndrome or protein-losing enteropathy. On the other hand, proteinuria of only 67 mg in a 24-hour urine collection and a normal lipid profile excluded a diagnosis of nephrotic syndrome.

An investigation of a possible autoimmune disease revealed a deficit of both IgG (410 mg/dl; cut-off 650 mg/dl) and IgM (17 mg/dl; cut-off 50 mg/dl), while IgA was within the reference range. C3 and C4 were both above the higher reference value (192 to 180 mg/dl and 50 to 36 mg/dl, respectively), while HLA-B57, ANA, ANCA, anti-dsDNA, rheumatoid factor, and anti-CCP were all negative. A common variable immunodeficiency was suspected but the robust response to both anti-tetanus and streptococcal vaccines made the diagnosis highly unlikely. Additionally, no changes in lymphocytic subpopulations were noted.

Although the diagnosis of intravascular haemolysis was unlikely given the absence of relevant laboratory findings, a flow cytometry was performed and revealed no decreased CD55 and CD59 expression on either red or white cells. A diagnosis of paroxysmal nocturnal haemoglobinuria was therefore excluded.

Lastly, an etiological study directed at diseases with hepatic involvement was also performed: serologies were compatible with a past infection by cytomegalovirus, but negative for a current infection by HIV, hepatitis B, or hepatitis C; ceruloplasmin and iron profile were within reference ranges, while alpha-1 antitrypsin was elevated (317 mg/dl; cut-off value 200 mg/dl); ASMA, AMA, anti-LKM, anti-SLA/LP, anti-LC-1, anti-actin, anti-endomysium, anti-gliadin, and anti-transglutaminase IgA and IgG were all negative.

As protein-losing enteropathy seemed more probable at this stage, an upper endoscopy was performed, which revealed a nodular mucosa with multiple fissures at the D2 level. Concurrently, ASCA IgA was positive. Considering the patient's propensity for serious infectious events and the newfound hypogammaglobulinemia, the team opted for a single infusion of human intravenous immunoglobulin at a 0.4 g/kg dosage.

At the 3-month follow-up consultation, the biopsy confirmed the presence of a coeliac sprue with mild villous atrophy, crypt hyperplasia and lymphocytic infiltration (Marsh classification 3A). In order to solidify the diagnosis, HLA typing for DQ-2 and DQ-8 was requested and positive for both. The patient was then instructed to initiate a gluten-free diet and apixaban was suspended as the DASH and Vienna prediction model scores were both low.

RESULTS

As of the publication of this article, no new complications were registered and all analytical abnormalities were resolved.

DISCUSSION

A recent systematic review[1] identified 55 published cases of thromboembolism (10 lower-extremity DVT) connected to coeliac disease. In 19 of these, thromboembolism was the first manifestation of the disease.

Multiple mechanisms[1-4] have been suggested to explain this seemingly increased risk, including genetic factors, thrombocytosis, elevated homocysteine levels (vitamin B12 and folic acid malabsorption), diminished protein C and S levels (vitamin K malabsorption), elevated levels of thrombin-activatable fibrinolysis inhibitor, ongoing inflammation and hyperviscosity (high circulating levels of antibodies). A Naranjo score of 2, indicating only a possible correlation, prevents us from completely eliminating chance as the promoter of its coexistence. However, considering the exclusion of other diagnoses, the authors feel this possible association should be considered and addressed in order to reduce the probability of a new thrombotic event.

Another point of discussion relates to the ideal duration of anticoagulation. While some authors prefer lifelong anticoagulation in cases of recurrent DVT[3], others advocate its suspension according to homocysteine levels[5]. In this case, this was not applicable, and a decision was made to use validated tools to assist our clinical approach. As the authors considered the untreated coeliac disease to be the true risk factor for DVT, we decided to suspend anticoagulation and maintain a close follow-up under the assumption that a gluten-free diet would reduce the inflammation to negligible levels.

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