

# Deep vein thrombosis, an unreported first manifestation of polyglandular autoimmune syndrome type III

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## Summary

A 71-year-old woman with severe right lower leg pain, edema and erythema was presented to the Emergency Department and was found to have an extensive deep vein thrombosis (DVT) confirmed by ultrasound. She underwent an extensive evaluation due to her prior history of malignancy and new hypercoagulable state, but no evidence of recurrent disease was detected. Further investigation revealed pernicious anemia (PA), confirmed by the presence of a macrocytic anemia (MCV=115.8 fL/red cell, Hgb=9.0 g/dL), decreased serum B12 levels (56 pg/mL), with resultant increased methylmalonic acid (5303 nmol/L) and hyperhomocysteinemia (131 µmol/L), the presumed etiology of the DVT. The patient also suffered from autoimmune thyroid disease (AITD), and both antithyroglobulin and anti-intrinsic factor antibodies were detected. She responded briskly to anticoagulation with heparin and coumadin and treatment of PA with intramuscular vitamin B12 injections. Our case suggests that a DVT secondary to hyperhomocysteinemia may represent the first sign of polyglandular autoimmune syndrome III-B (PAS III-B), defined as the coexistent autoimmune conditions AITD and PA. It is important to recognize this clinical entity, as patients may not only require acute treatment with vitamin B12 supplementation and prolonged anticoagulation, as in this patient, but may also harbor other autoimmune diseases.

## Learning points:

- A DVT can be the first physical manifestation of a polyglandular autoimmune syndrome.
- Hyperhomocysteinemia secondary to pernicious anemia should be considered as an etiology of an unprovoked DVT in a euthyroid patient with autoimmune thyroid disease.
- Patients with DVT secondary to hyperhomocysteinemia should undergo screening for the presence of co-existent autoimmune diseases in addition to treatment with B12 supplementation and anticoagulation to prevent recurrent thromboembolism.

## Introduction

Polyglandular autoimmune syndromes (PASs) are a heterogeneous group of uncommon diseases defined by the presence of autoantibodies targeting two or more organ systems. Pernicious anemia (PA) was first described in the mid nineteenth century by Thomas Addison who recognized an association between adrenocortical failure and PA (1, 2). PASs were

originally classified into two major types by Neufeld (3) and later extended into three by Eisenbarth and Gottlieb (4, 5).

PAS I, also called autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), involves the presence of two or more of the following three pathologies: chronic mucocutaneous candidiasis,

hypoparathyroidism and Addison's disease, which tends to present in pediatric patients in the order listed. PAS II, also known as Schmidt's syndrome, is more common than PAS I and is defined by the presence of Addison's disease with either autoimmune thyroid disease (AITD) or type 1 diabetes mellitus. PAS III, considered a subtype of PAS II, presents with AITD and one or more other organ-specific autoimmune disease(s), most commonly involving the pancreas, stomach, intestine or skin; the adrenal and parathyroid glands are uninvolved (5, 6).

One common association of AITD is pernicious anemia, defined as anemia caused by vitamin B12 deficiency resulting from autoantibodies targeting the source of intrinsic factor, the parietal cells of the stomach or intrinsic factor itself (7). Vitamin B12 is an essential cofactor in the metabolism of both amino acids and fatty acids (7). Therefore, B12 deficiency can lead to decreased assembly of products necessary for myelination of the corticospinal tracts and the dorsal columns of the spinal cord, a condition known as subacute combined degeneration of the spinal cord, as well as toxic accumulation of metabolic precursors such as homocysteine (8). Hyperhomocysteinemia (HH) has been established as an independent risk factor for cardiovascular disease in causing both atherosclerosis and deep venous thrombosis (DVT) (9). We report a patient diagnosed with PAS III-B after presenting with a DVT, a previously unreported initial manifestation of the disease.

## Case presentation

A 71-year-old Caucasian female was seen in our Emergency Department with a chief complaint of progressive right leg pain, edema and erythema over the course of 1 week (Fig. 1). Her past medical history was significant for hypothyroidism, a DVT in the right leg 6 years prior, and anemia ascribed to both iron deficiency and chronic disease. She was also diagnosed with recurrent stage IV cervical cancer treated with radiation, chemotherapy and pelvic exenteration surgery with urostomy, colostomy and bilateral nephrostomy tube placement. She had no evidence of disease for 5 years. Subsequent to the pelvic surgery, she also developed stage IV chronic kidney disease. Her medications at presentation included 75 µg levothyroxine and 10 mg oxycodone twice a day for chronic pain. She did not smoke or use illicit drugs, and alcohol use was limited to one or two glasses of wine with dinner per week. She denied recent prolonged immobilization and had no recent surgeries. Her family history was not significant for endocrinopathies, autoimmune diseases or coagulopathies.



**Figure 1**  
Lower limb presentation at ED.

At the ED, her vital signs were unremarkable (HR=82, BP=122/72, RR=16, O<sub>2</sub>sat=98% on room air, T=98.7°F). Physical examination was remarkable for a 2×2 cm erythematous, tender, indurated area with a tense vascular spidering on her mid-hypogastrium. Abdominopelvic ostomies with pouches were intact. There was significant edema (4+), diffuse erythema, extreme tenderness and warmth of the right lower extremity from hip to ankle with palpable cord from the popliteal fossa to the common femoral vein. The right foot was cool to touch with dorsalis pedis and posterior tibialis pulses detectable only with Doppler ultrasonography. The patient had minimal range of motion secondary to edema and pain.

A compression ultrasound confirmed both superficial thrombophlebitis of the abdomen and extensive DVT of the right lower extremity extending from the common femoral vein to below the popliteal vein. Laboratory values on admission are shown in Table 1 and were remarkable for: MCV=115.8 fL/red cell; (Normal value (NV): 80–100 fL/red cell), Hgb=9.0 g/dL; (NV 12–16 g/dL). Plasma folate was normal, serum vitamin B12=56 pg/mL; (NV 200–500 pg/mL). Plasma MMA=5303 nmol/L; (NV 0–378 nmol/L) and homocysteine=131.0 µmol/L; (NV 4–15 µmol/L). Peripheral blood smear revealed hypersegmented neutrophils (6 or more per high power field with 5 lobes and macro-ovalocytes) and a normal RDW of 14.5%. Organ-specific autoantibody screening was positive for both anti-intrinsic factor antibodies and antithyroglobulin antibodies. Antitissue transglutaminase, celiac panel and total immunoglobulins, including IgA, were within normal limits. An AM serum cortisol level was normal (26.9 µg/dL; NV 7–28 µg/dL) and antiadrenal

**Table 1** Laboratory values on admission and at 5-month follow-up.

Variable	Admission	5-month follow-up	Normal range
Hematocrit (Hct)	28.2%	36.5%	35–45.5%
Mean corpuscular volume (MCV)	115.8 fL/red cell	85.2 fL/red cell	80–100 fL/red cell
Red cell distribution width (RDW)	14.5%	15.0%	12.0–16.2%
Vitamin B12	56 pg/mL	–	200–500 pg/mL
Homocysteine	131.0 µmol/L	–	4–15 µmol/L
Methylmalonic acid (MMA)	5303 nmol/L	–	0–378 nmol/L
D-dimer	3.19 mg/mL	–	<0.50 mg/mL
INR	–	3.5	2.0–4.5
AM cortisol	26.9 µg/dL	–	7–28 µg/dL

antibodies were not present. A repeat PET/CT with contrast of the thorax, abdomen and pelvis was without evidence of recurrent malignancy.

Hospital course: The patient was diagnosed with a DVT, presumed etiology HH secondary to pernicious anemia, and anticoagulant treatment was started with IV heparin and warfarin. Urgent thrombolysis was not indicated, and limb elevation with compressive dressing as tolerated was initiated. Clinically, the diagnosis of PAS III-B was confirmed with coexistent PA and AITD. Metabolic derangements apart from these were attributed to chronic kidney disease and corrected as appropriate. Intramuscular injections of vitamin B12 (1000 IU/day × 5 days) were initiated. There was rapid resolution of the DVT and the patient was discharged to outpatient care. At follow up 5 months later, the patient was well and the CBC had normalized (Table 1).

## Discussion

DVT is associated with inherited conditions such as antiphospholipid syndrome, factor V Leiden, prothrombin G20210A, deficiencies of antithrombin, protein C or protein S or with acquired conditions such as malignancy, trauma, prolonged immobility, pregnancy, drugs or infections (10). HH, a less well-appreciated etiology of DVT, has been described and may result from congenital disorders such as Imerslund–Grasback syndrome, metabolic derangements, nutritional deficiencies, autoimmune disease, infections, or after surgery, notably gastrectomy or ileal resection (8). HH due to B12 deficiency can develop when this cofactor, essential in pathways involving amino acid synthesis and fatty acid β-oxidation, is lacking. Specifically, B12 is necessary for conversion of the amino acid homocysteine to methionine via methionine synthase and degradation of the branched chain fatty acid MMA via methylmalonyl CoA mutase allowing it to proceed through β-oxidation

(7, 8). In the absence of adequate vitamin B12, serum homocysteine and MMA concentrations increase which can be detected via serum assay and are important diagnostic factors for PA.

In elderly patients such as ours, B12 deficiency is most often due to B12 malabsorption secondary to intestinal pathology (60–70%), dietary deficiency (<5%) or PA (15–20%) (8). The etiology of PA results from either autoantibodies targeting intrinsic factor or an autoimmune gastritis with autoantibodies targeting parietal cells, both of which result in impaired B12 absorption from the terminal ileum (8).

Clinical manifestations of B12 deficiency include both neurological and cardiovascular deficits. From a neurological standpoint, B12 deficiency leads to inability to fully myelinate both the corticospinal tracts and the dorsal columns of the spinal cord via a poorly understood mechanism. This condition is known as subacute combined degeneration of the spinal cord and most often presents with deficits in both vibratory sensation and proprioception leading to gait ataxia, which our patient did not have (8). Cardiovascular consequences of B12 deficiency are specifically related to HH. The mechanism is not clear, but it is theorized that elevation of serum homocysteine causes inflammation leading to endothelial damage that can eventually contribute to both coronary artery disease and thrombus formation (9).

The patient had two important conditions that predisposed her to developing a DVT: her previous history of DVT with possible subsequent vascular damage and hypercoagulability secondary to malignancy. However, in this case, the patient's HH secondary to B12 deficiency was found to be a distinct provocation factor. A review of her medical records revealed that the elevated MCV was long-standing and prior serum B12 levels were markedly decreased. Hypothyroidism secondary to autoimmune disease, the predominant etiology, and PA were confirmed by the presence of

**Table 2** Polyglandular autoimmune syndromes (3, 4, 5, 6).

	PAS I	PAS II (Schmidt's syndrome)	PAS III-A	PAS III-B	PAS III-C
Incidence	<1:100 000/year	1–2:10 000/year		Unknown	
Female:male	4:3	3:1		N/A	
Time of onset	Childhood (3–5years)	Adulthood (peak 30years)	Adulthood (particularly middle aged women)		
Transmission	Autosomal recessive	Polygenic	Polygenic		
Genetic associations	Mutations in <i>AIRE</i> gene; HLA-DR3	HLA-B8, HLA-DR3, HLA-DR4	HLA-B8, HLA-DR3, HLA-DR4		
Phenotype	Chronic mucocutaneous candidiasis with either hypoparathyroidism or Addison's disease	Addison's disease with either AITD or immune-mediated type 1 diabetes (DM, type 1)	AITD DM, type 1	AITD PA	AITD with vitiligo and/or alopecia and/or other organ-specific autoimmune disease

antithyroglobulin and anti-intrinsic factor antibodies, respectively. The presence of both AITD and PA without evidence of Addison's disease, excluded by a normal AM serum cortisol and negative antiadrenal autoantibodies, confirmed the diagnosis of PAS III-B.

Vascular anomalies in autoimmune diseases are well described and include many of the various systemic vasculitides (e.g. granulomatosis with polyangiitis or microscopic polyangiitis), vasospasm or bleeding diatheses that can occur with hyperthyroidism or hypothyroidism, and thromboembolism that can occur with lupus or antiphospholipid syndrome to name a few. On the other hand, similar reports of vascular complications in PAS are much less common. A few case reports have recently found an association between PAS and specific vascular complications such as cutaneous vasculitis, small-vessel vasculitis, serositis with effusive pericarditis leading to cardiac tamponade and stroke, but these are rare and the mechanism by which these events occur has not been studied (11, 12, 13, 14). To our knowledge, there are no specific reports of DVTs in patients with PAS.

While particular genes or HLA markers have been identified for many of the polyglandular syndromes (Table 2), the data regarding PAS III-B are less clear (6). Prudence dictates that all patients presenting with an autoimmune condition receive an evaluation for additional autoimmune conditions; the cost-effectiveness and utility of such an evaluation is unknown.

To our knowledge, this is the first report of a DVT presenting as the first sign of a PAS. The association between AITD and PA is well recognized, as it has been reported that AITD can occur in up to 40% of patients with PA (7). It is, therefore, important to screen patients

with either AITD or PA for the presence of the other autoimmune disease. In addition to PA, AITD has also been associated with HH (8). Though studies have shown that B12 supplementation will effectively lower serum homocysteine levels, the effect of treatment on prevention of future thrombotic events is unproven and further study is indicated (15, 16). Patients with DVT secondary to HH should undergo further screening for the presence of autoimmune disease in addition to treatment with B12 supplementation and anticoagulation to prevent recurrent thromboembolic events.

#### Declaration of interest

The authors declare that there is no conflict of interest with respect to the case written.

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#### Patient consent

Written informed consent was obtained from the patient for publication of this article.

#### Author contribution statement

Michael Horsey, who is a 3rd year medical student at Georgetown University School of Medicine, directly cared for the patient and is the primary author of this case report. Dr Patricia Hogan is an Internal Medicine Resident at Walter Reed National Military Medical Center who directly cared for this patient and contributed to the writing of this case report. Dr Thomas Oliver is an attending Endocrinologist at Walter Reed National Military Medical Center who directly cared for this patient and contributed to the writing of this case report.

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