

A Case of Autoimmune Polyglandular Syndrome Type 3 Complicated by Pulmonary Embolism and Subacute Spinal Cord Degeneration

Alexander W. Jahng MD and Ashwin Ashok MD

Harbor-UCLA Medical Center, Torrance, CA

Introduction

Autoimmune polyglandular syndrome (APS) refers to a heterogeneous group of endocrinopathies driven by autoimmunity. APS Type 3 refers to a combination of autoimmune thyroid disease and another organ specific autoimmune process that does not involve the adrenal axis. In this case report, we present a patient diagnosed with APS type 3b/d. The patient is a 53 year old male with a history of Grave's disease who presented with symptoms of posterior column disease that was attributed to pernicious anemia based on serologic studies. Subsequent work-up for exertional dyspnea revealed a pulmonary embolism with a positive lupus anticoagulant. Based on these observations, the patient was diagnosed with APS type 3b and 3d. We will highlight the complexity of disease processes driven by autoimmunity, and discuss therapeutic modalities.

CASE SUMMARY

The patient is a 53 year-old African-American male with a history of Grave's disease status post radioactive iodine (RAI) therapy 10 years prior, who presented with:

- Two years of slowly ascending bilateral lower extremity pain that began in the feet and now involves the knees
- Two years of progressive gait instability
- One year of exertional dyspnea
- Recent loss of coordination in the bilateral hands

The neurological examination was consistent with posterior column disease:

- Lack of proprioception bilaterally from the knees down
- Loss of sensation to light touch bilaterally from the knees down
- Spastic, feet-slapping gait
- Abnormal Romberg test

Evaluation of this patient led to the following diagnoses:

- **Grave's Disease** based on a history of hyperthyroidism treated with RAI ten years prior and positive thyroid peroxidase antibodies (anti-TPO).
- **Pernicious anemia** with neurologic sequela, based on low vitamin B12 levels associated with an elevated methylmalonic acid level coupled with positive anti-intrinsic factor and anti-parietal cell antibodies. Macrocytic anemia with hypersegmented neutrophils were observed on peripheral smear review (Figure 1).
- **Pulmonary emboli** were diagnosed on CT angiogram of the chest (Figure 2). It was thought to be chronic based on clinical and radiologic data. Ultrasound failed to reveal deep venous thrombosis in lower extremities.
- **Antiphospholipid Syndrome** was tentatively diagnosed based on a prolonged Partial Thromboplastin Time(PTT) and after a work-up for a hypercoagulable state yielded a positive lupus anticoagulant. Confirmatory tests are pending.
- Hyper-homocysteinemia, which was secondary to Vitamin B12 deficiency.
- Non-ischemic dilated cardiomyopathy was diagnosed via echocardiogram and cardiac catheterization.

Autoimmune polyglandular syndrome type 3 is diagnosed at this time, based on the history of Grave's disease with the new diagnosis of pernicious anemia (type 3b), along with tentative diagnosis of antiphospholipid syndrome (type 3d).

DIAGNOSTIC DATA

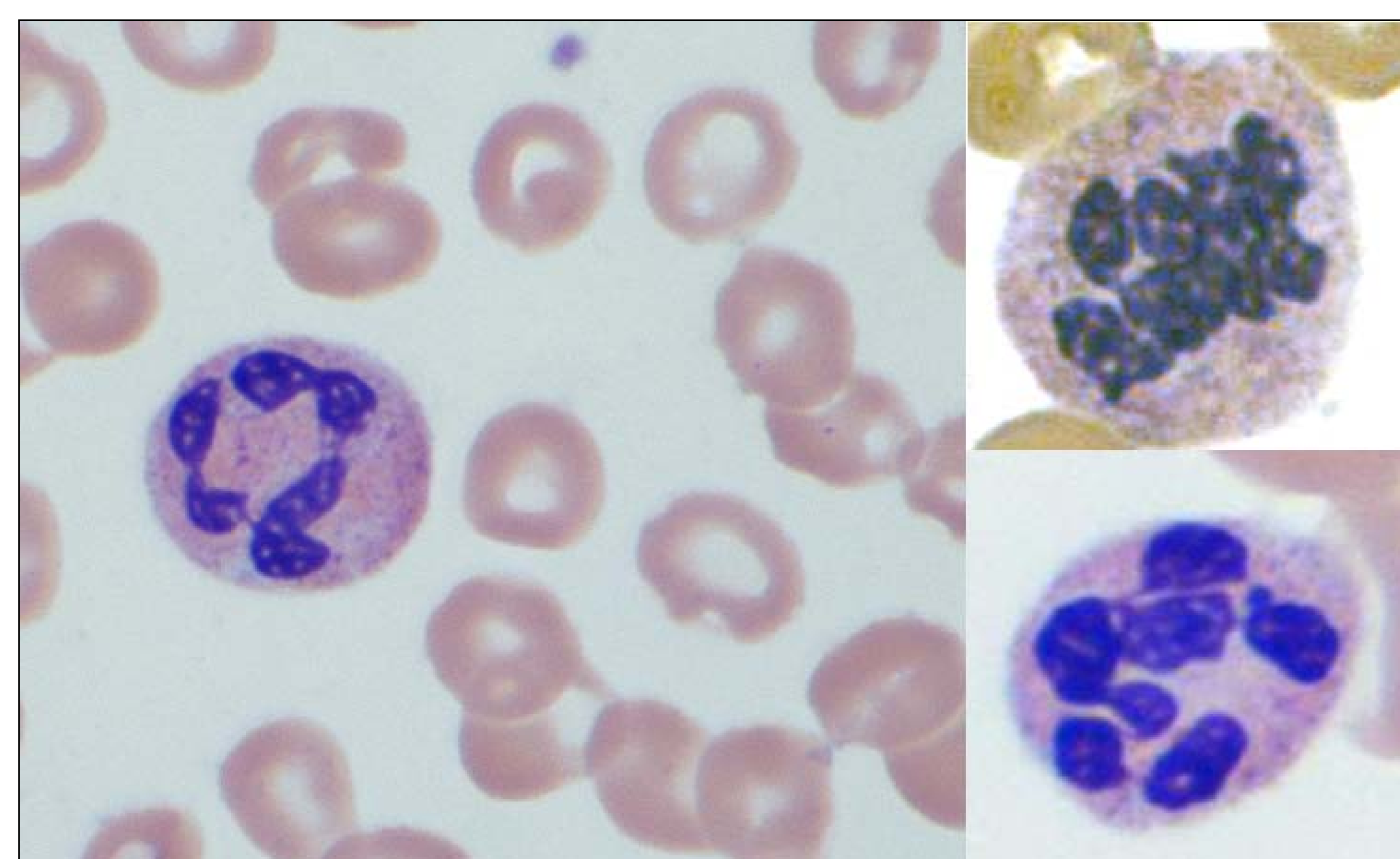


Figure 1. Hypersegmented neutrophils and macrocytic erythrocytes on light microscopy of the peripheral smear.



Figure 2. CT angiogram of the chest demonstrating extensive pulmonary embolism. Filling defects were noted in the distal right main pulmonary artery, extending both into the lower lobe branches, and into the left main artery as a linear strand. Additional thrombi is noted on the left upper lobe and descending pulmonary arteries, extending into basilar branches.

Laboratory tests (selected)	Result
Vitamin B12	44 pg/mL
RBC-folate	380 ng/mL
Methylmalonic acid	88269 nmol/L
Homocysteine	>50 micromol/L
Anti-intrinsic factor Ab	Positive
Anti-parietal cell Ab	57.9 Units
Thyroid stimulating hormone	5.04 IU/mL
Free T4	1.08 ng/dL
Thyroid stimulating immunoglobulin	110%
Anti-thyroid peroxidase Ab	132 IU/mL
Lupus anticoagulant	Positive
Partial thromboplastin time	47.9 seconds
Hexagonal phase phospholipid test	Positive
Diluted Russel viper venom test	Negative

References

1. Borch-Johnsen K. Update on autoimmune polyglandular syndrome (APS). *Acta Dermatol.* 2013 Apr;74(1):3-13.
2. Amato P, Toporoff M, De Ruggieri P, De Rosa C, Varola L, Marzulli M, Di Rocco D, Casella R, Falaschi E, Tassi A. Vitiligo associated with other autoimmune diseases: polyglandular autoimmune syndrome types 3b-C and 4. *Clin Exp Dermatol.* 2008 Jul;33(7):794-5.
3. Aung K, Kaur P. Polyglandular autoimmune syndrome, Type III. *Indian J Dermatol.* 2007; 52(1):11-13.
4. Haddad EB, Sengupta D, Bhatti JC, Gargi S, Lohitharan J. Neurologic aspects of autoimmune polyglandular syndrome type 3. *Indian J Dermatol.* 2011 Jul;56(3):229-31.
5. Kishimoto T, Shimizu A, Hirota M, Shimizu C, Hirose K, Imai M, Schweder B, Takagishi K, Kuroki Y. Hyperhomocysteinemia as a risk factor of recurrent venous thromboembolism. *Thromb Haemostasis.* 1998 Oct;78(4):966-9.
6. Ray JL, Khamis MM, Gonsky R, Laine C, Bhandari S, Prasad S, et al. Homocysteinemia, hyperhomocysteinemia, and risk for venous thromboembolism: a randomized, placebo-controlled trial. *Ann Intern Med.* 2002 Jun 11;136(11):781-7.
7. Jerny A, Lohr A, Gans M, Fritsch M, Straub M. Autoimmune polyglandular syndrome type 3: a clinical review program in patients with pernicious anemia. *Neurogastroenterology.* 2003 Nov;15(5):228-31.
8. Schirmer C, Fuchs M, Gschwend M, Schmitt M, Stieve M. Autoimmune polyglandular syndrome associated with idiopathic giant cell myocarditis. *Eur Clin Endocrinol Diabetes.* 2005 May;11(5):303-5.
9. Klein JE. Pernicious anemia and giant cell myocarditis. *New association.* *Am J Med.* 1991 Feb;79(2):355-60.
10. Kaur A, Mahapatra S, Gangopadhyay S, Kaur A, Kaur A. Giant cell myocarditis without a symptom of heart failure seen in a patient with myasthenia gravis and occulted Hashimoto's disease. *Stratford J Neurology.* 2001 Nov;41(11):813-7.

TREATMENT COURSE

Supplemental intramuscular vitamin B12 and oral folate were started. Anticoagulation was initiated and an inferior vena cava filter was placed for precaution against future events given a large thrombus burden. High dose pyridoxine was added for hyper-homocysteinemia following the diagnosis of pulmonary embolism. Possibility for thrombectomy was discussed, pending repeat pulmonary artery measurements. Figure 3 shows hematologic response over time. No neurologic improvements were noted during this short follow up.

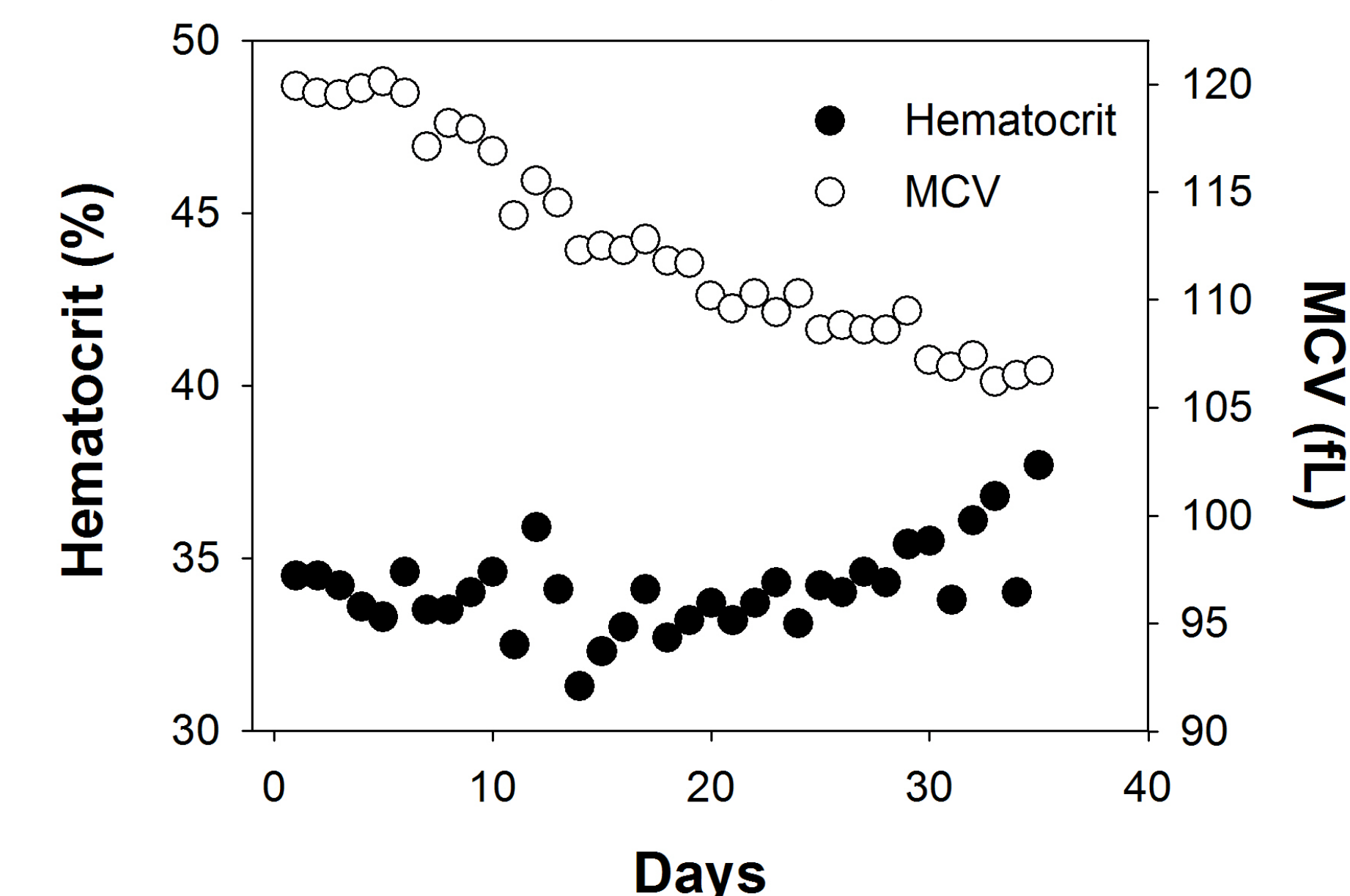


Figure 3. Hematologic response to intramuscular injection of vitamin B12.

DISCUSSION

- Autoimmune polyglandular syndrome (APS) type 3 refers to a syndrome of autoimmune thyroid disease in association with other autoimmune diseases.^{1,2}
- Type 3 is the most common APS diagnosed, ranging in 3% to 4.5% (1.5% in males).
- Multi-genetic involvement distinct to APS type 3, and likely autosomal dominant inheritance with incomplete penetrance have been suggested.³

1. **APS-3b is definitively diagnosed based on the history of Grave's disease and pernicious anemia. The criteria for APS type 3b are: autoimmune thyroid disease and the presence of at least one of the following: atrophic gastritis, pernicious anemia, celiac disease, inflammatory bowel disease, autoimmune hepatitis, primary biliary cirrhosis, or sclerosing cholangitis.**
2. **APS-3d is also tentatively diagnosed based on anti-phospholipid syndrome (positive lupus anticoagulant with elevated partial thromboplastin time, and an unprovoked thromboembolic event). Confirmatory testing is needed in the future.**
3. **In pernicious anemia, the degree of macrocytic anemia may not always correspond to the degree of neurologic deficits.⁴**
4. **The reversibility of sub-acute combined degeneration of spinal cord is dependent on the severity and the duration of symptoms. The chronicity of the patient's symptoms suggests complete reversibility to be unlikely.⁴**
5. **Hyper-homocysteinemia is thought to lower the threshold for thrombotic events. It must be noted that a randomized, placebo-controlled trial for homocysteine-lowering therapy (with vitamin B6, B12 and folate) did not show risk reduction for future thromboembolic events.^{5,6}**
6. **Patients with atrophic gastritis have increased risk for gastric cancers, and screening with endoscopy may be warranted.⁷**
7. **Idiopathic giant cell cardiomyopathy is rarely associated with autoimmune endocrinopathies, but such a case cannot be made for or against this patient at this time lacking biopsy.⁸⁻¹⁰**