Title

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CLINICAL VIGNETTE

A Spotted Zebra: An Unusual Presentation of Autoimmune Polyglandular Syndrome

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Introduction

Autoimmune polyglandular syndrome (APS) is characterized by impairment of multiple endocrine glands due to the loss of immune tolerance. Two predominant subtypes have been described. Type 1 is autosomal recessive and manifests in childhood with two of the three following: hypoparathyroidism, mucocutaneous candidiasis and Addison's disease.[1] Type 2 is more common and can occur throughout life, predominantly in women. Type 2 is typically defined by the presence of Addison's disease along with either type 1 diabetes or autoimmune thyroid disease. Others have proposed that type 1 diabetes and thyroid autoimmunity without adrenal insufficiency represents an important subtype.

Case Report

A 52-year-old woman with a past medical history of latent autoimmune adult diabetes, hypertension, and Hashimoto's thyroiditis presented to the emergency department with nausea, vomiting, fatigue and epigastric pain for 3 days along with diarrhea for 1 month. On exam, her epigastrium was tender with no blood on rectal exam. Her palms, soles and hard palate had numerous brown hyperpigmented macules ranging from 2-7 mm. Her lab work was notable for a hemoglobin of 5.6 with a mean corpuscular volume of 125, a white blood cell count of 3 and platelet count of 80. The patient received 3 u packed red blood cells with an appropriate rise in her hemoglobin. Further lab testing revealed profound vitamin B12 deficiency (<50), normal folate, elevated homocysteine to 113 and methylmalonic acid to 38,980. Labs were also notable for an elevated LDH, low haptoglobin, negative Coomb's test and a hypo proliferative reticulocyte index. Cyanocobalamin repletion was started. Intrinsic factor and parietal cell antibodies later resulted positive confirming a diagnosis of pernicious anemia. Diarrhea evaluation was notable for positive IgG antibodies to anti-tissue transglutaminase but negative IgM. Patient's hemoglobin was stable and she was discharged, after two days.

As an outpatient, she subsequently underwent testing for adrenal insufficiency including AM cortisol, ACTH, 21-hydroxylase antibodies, co-syntropin stimulation test, and immunoglobulin levels all of which were within normal limits. With ongoing treatment with B12, her hyperpigmented lesions and her anemia improved.

Lab Data

Table 1. Laboratory data

Hematology	**Chemistry**	**Diabetology**
Wbc 3.0 k/cumm	Na 137 mmol/L	HbA1c 6.0%
Neutro 22%	K 3.5 mmol/L	GAD 65 Ab 7 IU/mL
Band 4%	Cl 103 mmol/L	Insulin AutoAb <0.4 U/mL
Lymph 74%	CO2 25 mol/L	IA-2 Ab <0.8 U/mL
Rbc 1.31 M/cumm	BUN 10 mg/dL	C peptide 0.87 ng/mL
Hb 5.6 g/dL	Cr 0.77 mg/dL	
Ht 16.4%	Glucose 62 mg/dL	**Endocrinology**
MCV 125.2 fL	Ca 8.6 mg/dL	Cortisol 8.4 mcg/dL
MCH 43.0 pg	Phos 3.0 mg/dL	ACTH stim test
RDW 33.4%	Albumin 3.9 g/dL	Cortisol 0 10.3 mcg/dL
PLT 80 k/cumm		Cortisol 30 17.9 mcg/dL
Retic pct 3.7%	**Immunology:**	Cortisol 60 19.6 mcg/dL
Abs Retic 56.6 x 10^9 / L	Intrinsic factor Ab: +	ACTH 30 pg/mL
Haptoglobin <6 mg/dL	Parietal cell Ab: + 1:160 titer	21-hydroxylase Ab: Negative
LDH 1669 U/L	tTG Ab IgA <1 u/mL	TSH 1.83 uIU/mL
DAT: negative	tTG Ab IgG 7 U/mL	TPO Ab >600 IU/mL
Folate 37.2 ng/mL	IgA 420 mg/dL	
Vitamin B12 < 50 pg/mL	IgG 1430 mg/dL	
Homocysteine 113.3 umol/L	IgM 65 mg/dL	
MMA 38980 nmol/L		

Discussion

The patient's macrocytic anemia, combined with leukopenia and thrombocytopenia, were a result of pernicious anemia. Pernicious anemia is caused by autoantibodies that target intrinsic factor and/or gastric parietal cells resulting in interference with B12 absorption. All formed blood cell lines can be affected as B12 is essential in megaloblastic hematopoiesis.[2] Initial testing involves assessing for either low B12 or high MMA, after which autoantibodies are sent. Intrinsic factor antibodies are highly specific and can confirm the diagnosis.

This patient's pernicious anemia is part of a larger syndrome, specifically type 2 APS. Type 2 APS has been associated with numerous other autoimmune diseases including vitiligo, premature ovarian failure, myasthenia gravis, celiac disease, sarcoidosis, alopecia, IgA deficiency, hepatitis, and hypogonadism.[3,4]

The patient's hyperpigmented rash posed an additional diagnostic dilemma. The improvement of this patient's lesions with repletion of B12 combined with subsequent testing revealing an intact adrenal access, suggests that her hyperpigmentation was likely a consequence of her pernicious anemia.

In conclusion, we presented a women with Type 1 diabetes and Hashimoto's thyroiditis with severe macrocytic anemia, and skin hyperpigmentation, ultimately found to have pernicious anemia resulting in severe B12 deficiency. This case highlights the importance of considering additional autoimmune diseases when following patients with multiple autoimmune endocrinopathies. While this patient had normal adrenal access, undiagnosed autoimmune adrenalitis, presenting as Addisonian crisis, can be potentially fatal. Screening for adrenal insufficiency in patients with multiple features of APS is essential, along with ongoing surveillance.

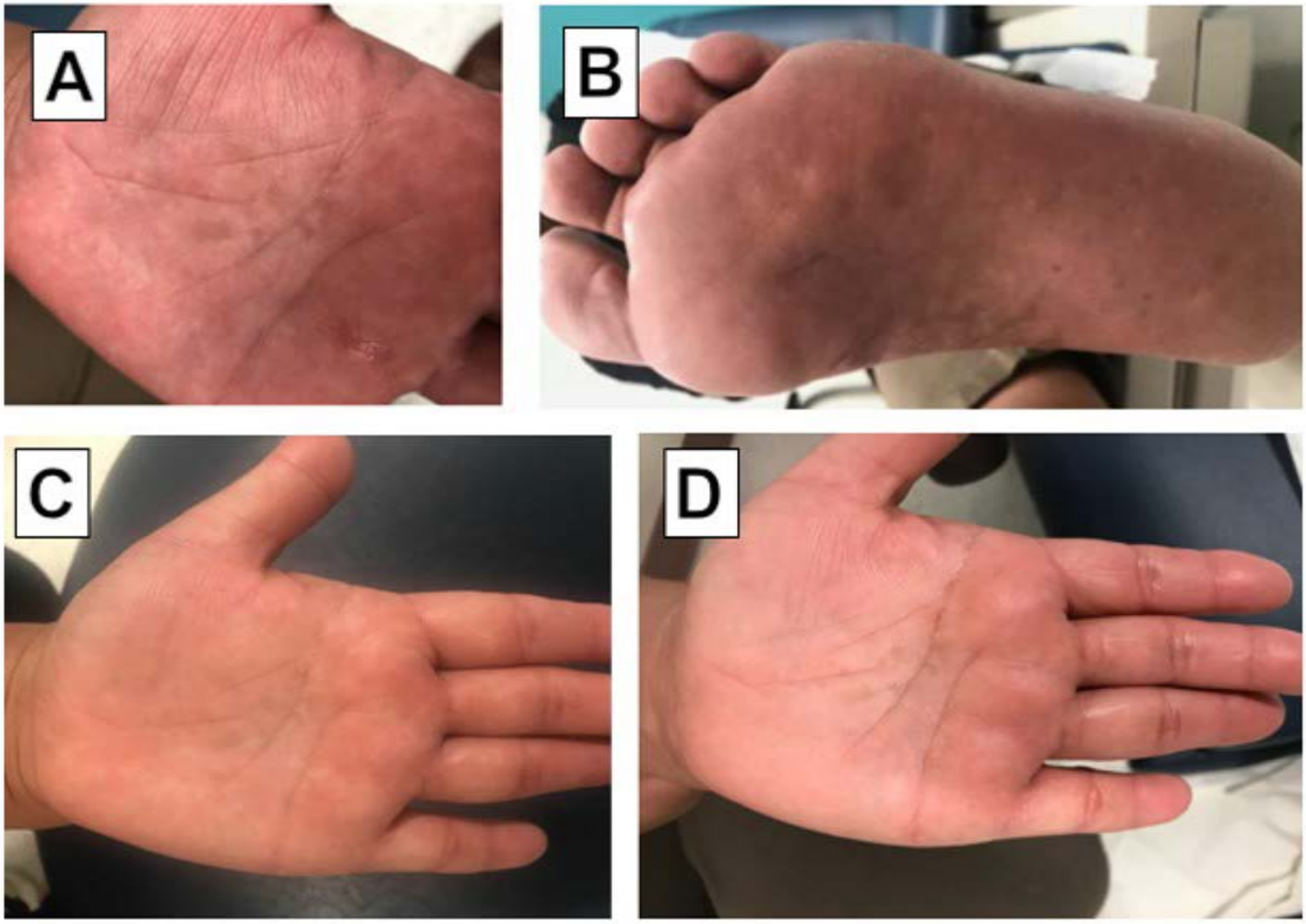

Figure 1. Hyperpigmentation hypothesized to be due to vitamin B12 deficiency. Images A&B are of her hand and foot immediately after hospitalization. C&D are pictures of her hand 8 and 9 months later, respectively, after B12 repletion and resolution of her anemia.

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