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Case Report

Pernicious Anemia in a Pediatric Patient With Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy

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Abstract

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an autosomal recessive disease caused by a monogenic pathogenic mutation in the autoimmune regulator (*AIRE*) gene. *AIRE* is a transcriptional regulatory gene expressed within thymic medullary cells, which play a critical role in developing central immune tolerance. APECED is classically associated with the triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. We report a case of a pediatric patient with a known history of APECED who presented with symptomatic megaloblastic anemia and was found to have vitamin B12 deficiency secondary to the presence of antibodies to intrinsic factors. Interestingly, our patient did not have gastric parietal cell antibodies, which are present in 90% of pernicious anemia cases. Pernicious anemia itself is relatively rare and primarily manifests in the elderly population. There is limited literature involving pernicious anemia within the pediatric population, specifically within the subgroup that has APECED. Screening and early recognition of pernicious anemia in this relatively rare condition is crucial, as it has the potential to be life-threatening if left unaddressed.

Key Words: pernicious anemia, APECED, intrinsic factor, B12 deficiency

Introduction

The *AIRE* gene was first identified through positional cloning in 1997 [1]. Before this discovery, several decades of clinical data had documented a range of autoimmune endocrinopathies associated with the condition. A 1964 report describing a young patient with pernicious anemia, familial Addison disease, idiopathic hypoparathyroidism, and candidiasis was unable to establish a definitive link between pernicious anemia and the other documented endocrinopathies [2]. An earlier case described a family in which Addison disease was present in 3 siblings, 1 of whom also had superficial candidiasis, idiopathic hypoparathyroidism, and pernicious anemia; prior this report, only 6 such cases had been documented in the literature [3].

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autoimmune disease caused by a defect in the *AIRE* gene. The *AIRE* gene is pivotal in autoimmune regulation because it modulates the destruction of reactive T cells that would otherwise escape into peripheral tissue and stimulate autoreactivity [4]. The characteristic findings of APECED include chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. Aside from the classic presentation, APECED can involve multiple endocrine and nonendocrine organs, but most often involves endocrine organs. The clinical spectrum is vast and documented to include pernicious anemia. While APECED can manifest as multiple autoimmune diseases, pernicious anemia occurs infrequently, especially within the pediatric population.

Case Presentation

A 14-year-old male with a history of autism, diffuse alopecia areata, type A vitiligo, and APECED presented to our emergency department at a referral from his primary care doctor for a hemoglobin of 5 g/dL (International System of Units [SI]: 50 g/L) (reference range: 13 g/dL-17 g/dL [SI: 130 g/L-170 g/L]). He was evaluated by a pediatrician earlier in the week for shortness of breath, dizziness, headache, decreased appetite, and fatigue of 3 weeks' duration. The pediatrician performed laboratory tests at that time, which demonstrated a hemoglobin of 5 g/dL (SI: 50 g/L), prompting hospital evaluation. Hemoglobin 6 months prior was 14.1 g/dL (SI: 140 g/L).

Diagnostic Assessment

In the emergency department, the patient endorsed fatigue and headache. On the day prior to presentation, he appeared jaundiced and had dark urine. He also noted that his stools have been darker than normal, and he is usually constipated at baseline. A physical examination was notable for pallor, jaundice, scleral icterus, candidiasis in oral mucous membranes, tachycardia, and diffuse vitiligo. He denied epistaxis, easy bruising, and excessive bleeding. Laboratory evaluation demonstrated macrocytic anemia with hemoglobin 5.2 g/dL (SI: 52 g/L), hematocrit 14.1% (SI: 0.141 L/L) (reference range: 37-48% [SI: (0.37-0.48 L/L]), mean corpuscular volume 110.2 fL (SI: 1.102 $\times 10^{-13}$ L) (reference range: 77-94 fL [SI: 77-94 μm^3]), reticulocyte count 2.12% (reference range:

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Table 1. Laboratory results

Laboratory	Normal range	Patient value
Initial hemoglobin	13 g/dL-17 g/dL (130 g/L-170 g/L)	5.2 g/dL (52 g/L)
Initial hematocrit	37%-48% (0.37-0.48 L/L)	14.1% (0.14 L/L)
Initial mean corpuscular volume	77-94 fL (77-94 μm^3)	110.2 fL (1.102 $\times 10^{-13}$L)
Initial reticulocyte count	0.90%-1.49%	2.12%
Initial B12	200-800 pg/mL (150-600 pmol/L)	150 pg/mL (110.5 pmol/L)
B12 after treatment	200-800 pg/mL (150-600 pmol/L)	>2000 pg/mL
Hemoglobin after treatment	13 g/dL-17 g/dL (130 g/L-170 g/L)	7.3 g/dL (73 g/L)
Hemoglobin at follow up	13 g/dL-17 g/dL (130 g/L-170 g/L)	16.4 g/dL (164 g/L)

0.90-1.49), indirect hyperbilirubinemia, and transaminase elevation (Table 1). Additional results showed a low B12 level at 150 pg/mL (SI: 110.5 pmol/L) (reference range: 200-800 pg/mL [SI: (150-600 pmol/L]), elevated homocysteine, and mild hyponatremia. Abdominal ultrasound was remarkable only for gallbladder sludge.

The patient was admitted to the pediatric intensive care unit, where he underwent cardiorespiratory monitoring while receiving 2 units of packed red blood cells. Further history obtained revealed he had low B12 levels in the past, although the time-point was unknown. While in the pediatric intensive care unit, lactate dehydrogenase levels were found to be elevated. Gastroenterology was consulted due to the presence of hyperbilirubinemia and elevated transaminases and recommended a workup to rule out autoimmune hepatitis in the context of a known genetic disorder, which ultimately returned unremarkable results. Additionally, the patient underwent bone marrow aspirate to rule out hematological causes, including myelodysplastic syndrome.

The continued workup included a negative fecal occult blood. B12 levels were negligible, with an expected elevation of methylmalonic acid and homocysteine. Folate was within normal limits. The coagulation panel and ammonia level performed in the setting of transaminase elevation was unremarkable. Gastric parietal cell antibodies were negative, while intrinsic factor antibodies were positive. Zinc and copper levels were also within normal ranges. Blood smear showed multiple hypersegmented neutrophils and red blood cells with atypical morphology, anisocytosis, tear drop cells, and some red blood cell fragments (Fig. 1). The bone marrow aspirate results were significant for erythroid hyperplasia with megaloblastic changes, no significant dysplasia, no blasts, and erythroid hypercellularity indicative of increased red blood cell production compensating for anemia (Fig. 2). Fluorescence in situ hybridization myelodysplastic syndrome panel and myeloid next-generation sequencing panel were both negative. The clinical signs of jaundice, dark stools, and dark urine indicated the presence of some degree of hemolysis. A direct antiglobulin test was performed for this reason and was negative. While autoimmune hemolysis likely contributed to the patient's presentation, due to its association with APECED, the primary underlying process was B12 deficiency, as evidenced by insufficient reticulocytosis and an elevated mean corpuscular volume.

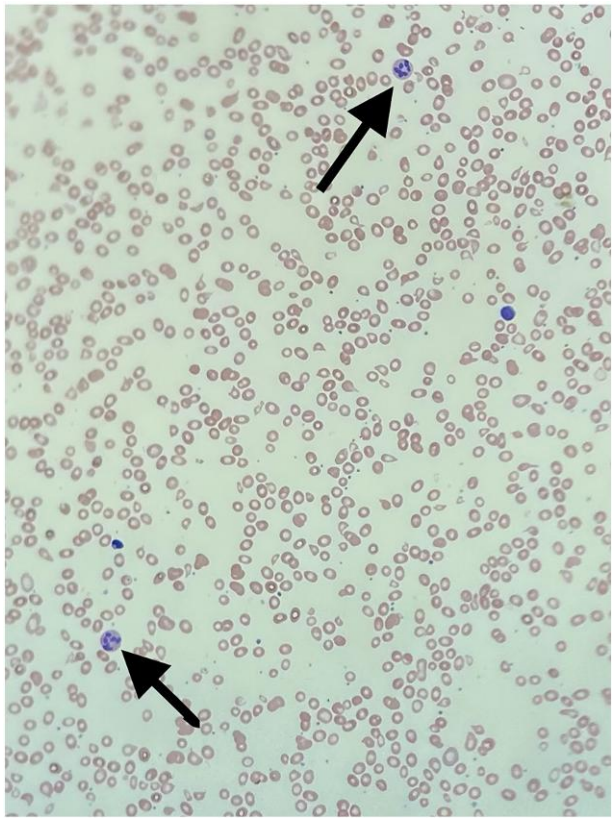

Figure 1. Arrow pointing to hypersegmented neutrophils, which are a classic finding in megaloblastic anemia.

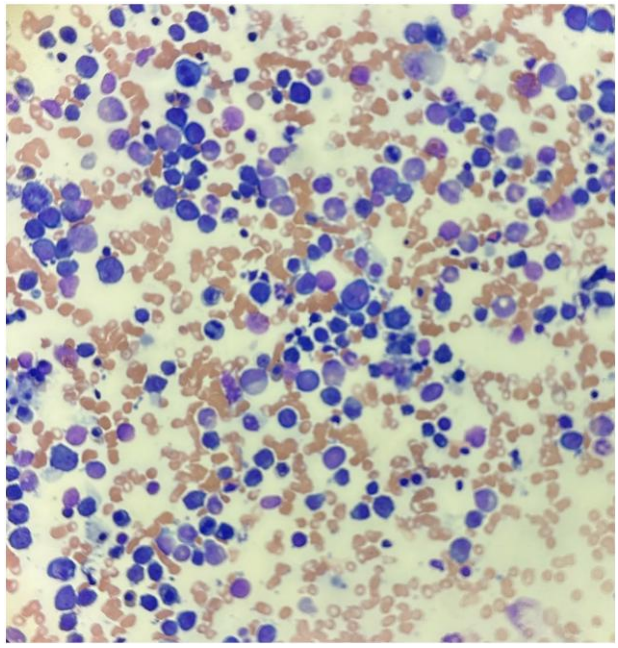

Figure 2. Erythroid hyperplasia with megaloblastic changes, no significant dysplasia, no blasts and erythroid hypercellularity indicative of increased red blood cell production compensating for anemia. A standard Wright-Giemsa stain was performed to evaluate for hematologic malignancies.

Treatment

The patient received three B12 injections of 1000 mcg with significant improvement. The injections were discontinued

inpatient after 3 doses due to B12 levels >2000 pg/mL. On the day of discharge, hemoglobin was stable at 7.3 g/dL (SI: 73 g/L) and the symptomatic anemia resolved.

Outcome and Follow Up

He was discharged with scheduled follow-up appointments in gastroenterology and hematology. Over the course of the year, he has continued to do well with monthly vitamin B12 injections. The most recent hemoglobin level was 16.4 g/dL (SI: 164 g/L). He is evaluated every 3 months in the pediatric hematology clinic for laboratory assessments and check-ups, and every 6 months in the pediatric gastroenterology clinic. A preliminary plan is being considered for the future implementation of screening esophagogastroduodenoscopy.

Discussion

APECED, also referred to as autoimmune polyendocrine syndrome type 1, is a rare autosomal recessive autoimmune disease characterized by a pathogenic variant in the *AIRE* gene [4]. *AIRE* is central in creating immunological tolerance by allowing the adaptive immune system to distinguish between self-constituents and foreign invaders [5]. Within the medullary thymic cells, *AIRE* promotes the expression of tissue-restricted self-antigens [6]. The expression of tissue-specific proteins that are ordinarily confined to organs within the periphery is critical for the negative selection of T-effector cells and generation of T-regulatory cells [7]. The elimination of self-reactive T cells and the creation of T-regulatory cells facilitates immunological tolerance. In the absence of *AIRE*, self-reactive T cells are defectively eliminated, which can then enter the peripheral circulation and target organs [7].

APECED is classically associated with the triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenocortical failure [8]. The disease begins in childhood, with chronic mucocutaneous candidiasis often the first and most frequent presentation [9]. In the absence of AIRE, central immunological tolerance is not present, and organ-specific autoimmunity occurs. APECED tends to affect endocrine organs more predominantly [10], although nonendocrine organs are also affected. In conjunction with the classic symptoms, enamel hypoplasia and enteropathy with chronic diarrhea or constipation is common [11]. Given the lack of central immunity in this disease, theoretically any organ can be affected, and the exact prevalence of the lesser known manifestations within the pediatric population, such as pernicious anemia, is unclear.

Megaloblastic anemia can be caused by multiple etiologies, including nutritional deficiencies such as zinc, folate, B12, and copper deficiency, myelodysplastic syndrome, alcohol, malabsorptive diseases, medications, toxins, and aplastic anemia. Pernicious anemia occurs when there is disruption in the B12 absorption pathway, primarily due to a deficiency of intrinsic factor. Intrinsic factor plays a crucial role in the binding and transportation of vitamin B12, facilitating its absorption in the terminal ileum [12]. Pernicious anemia is typically characterized by the presence of antiparietal antibodies that destroy the parietal cells that produce intrinsic factor and hydrochloric acid [13]. Of the 11% to 13% of patients with pernicious anemia and APECED, most are positive for both parietal cell antibodies and intrinsic factor antibodies [14]. A study conducted by Oliva-Hemker et al described a 12-year-old female presenting with pernicious anemia within the context of APECED. This patient was found to have positive gastrointestinal endocrine cell antibodies but tested negative for antiparietal cell antibodies. Notably, the gastric corpus of this patient exhibited a complete absence of both gastrointestinal endocrine cells and parietal cells, despite the negative result for antiparietal cell antibodies. We concur with the hypothesis that the absence of gastric parietal cells in such cases may be attributed to hypergastrinemia resulting from the loss of gastrin-secreting cells, rather than the immune-mediated destruction of parietal cells typically observed in adults with pernicious anemia and atrophic gastritis [15]. Similarly, our patient did not possess antiparietal cell antibodies but was positive for intrinsic factor antibodies. The exact pathophysiology surrounding the gastrointestinal manifestations within APECED remains poorly understood [16].

New components of the disease can continue to manifest as patients age, with the literature showing emergence of new symptoms in as late as the fifth decade of life [17]. This notion is on par with our patient, who developed pernicious anemia at the age of 14 years. In this patient population, it is important to monitor closely for emergence of new symptoms. In a patient presenting with macrocytic anemia in the setting of APECED, we suggest obtaining the screening antibodies to assess for pernicious anemia, as untreated B12 deficiency can lead to substantial neurological and hematological abnormalities. The association between pernicious anemia and APECED exists and may present within any age.

Learning Points

- The pathophysiological mechanisms underlying pernicious anemia in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) remains poorly understood.
- We recommend screening for pernicious anemia in patients with APECED.
- Pernicious anemia can occur in the absence of antiparietal antibodies.

Contributors

All authors made individual contributions to authorship. K.K. was involved in formulating and submitting the manuscript. M.B., R.D., and M.W. were involved in the diagnosis and management of this patient. All authors reviewed and approved the final draft.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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