COEXISTENCE OF ADDISON'S DISEASE AND PERNICIOUS ANEMIA: IS THE NEW CLASSIFICATION OF AUTOIMMUNE POLYGLANDULAR SYNDROME APPROPRIATE?

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SUMMARY – A case of autoimmune polyglandular syndrome (APS) is presented. A 45-year-old man was admitted due to fatigue, malaise and inappetence. He had a history of primary hypothyroidism and was on levothyroxine substitution therapy. One year before, he was diagnosed with normocytic anemia and vitamin B12 deficiency, which was treated with vitamin B12 substitution therapy. Physical examination revealed hypotension and marked hyperpigmentation. Laboratory testing showed hyponatremia, hyperkaliemia and severe normocytic anemia. Endocrinological evaluation disclosed low morning cortisol and increased adrenocorticotropic hormone levels. Hence, the diagnosis of Addison's disease was established. Additional laboratory workup showed positive parietal cell antibodies. However, his vitamin B12 levels were increased due to vitamin B12 supplementation therapy, which was initiated earlier. Gastroscopy and histopathology of gastric mucosa confirmed atrophic gastritis. Based on prior low serum vitamin B12 levels, positive parietal cell antibodies and atrophic gastritis, the patient was diagnosed with pernicious anemia. Hydrocortisone supplementation therapy was administered and titrated according to urinary-free cortisol levels. Electrolyte disbalance and red blood cell count were normalized. This case report demonstrates rather unique features of pernicious anemia in a patient with Addison's disease. It also highlights the link between type II and type III APS. Not only do they share the same etiological factors, but also overlap in pathophysiological and clinical characteristics. This case report favors older classification of APS, which consolidates all endocrine and other organ-specific autoimmune diseases into one category. This is important since it might help avoid pitfalls in the diagnosis and treatment of patients with APS.

Key words: *Polyendocrinopathies, autoimmune – classification; Anemia, pernicious; Addison's disease; Case reports*

Introduction

Autoimmune polyglandular syndrome (APS) is a group of autoimmune disorders that affect two or more endocrine glands and can include other organ related or non-organ related conditions. The two most distinct subtypes are autoimmune polyendocrine syndrome type I and type II[1-4]. Type I is defined by the presence of mucocutaneous candidiasis, hypoparathyroidism and Addison's disease. It is a very rare condition, specific to certain enclosed populations such as Iranian Jewish, isolated Scandinavian and Sardinian populations. It has an autosomal recessive inheritance pattern associated with AIRE gene mutation and is

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Received May 26, 2014, accepted June 30, 2014

characterized by early onset and equal gender incidence[5-7]. Type II is defined by the presence of thyroid disease, type 1 diabetes mellitus (DM) and Addison's disease, but can also include other autoimmune conditions such as myasthenia gravis and celiac disease. It is a rare condition with a yearly incidence of up to 4.5 *per* 100,000 and a polygenic inheritance pattern. In contrast to type I, type II occurs most often in third or fourth decade and is more common in women[1,8]. Both type I and type II have been associated with vitiligo and alopecia. There is a tendency to further classify APS type II into type III and IV[1-4]. According to Neufeld *et al.*[9], type III is associated with thyroid autoimmunity and other autoimmune diseases, excluding Addison's disease and type 1 DM. Taking into consideration that thyroid autoimmune conditions are the most often autoimmune disorders in general population, it was speculated that APS type III affects up to 4% of the total population, and therefore is the most important and frequent APS[2]. Subclassification of type III includes 3A (autoimmune thyroiditis combined with immune mediated DM), 3B (autoimmune thyroiditis with pernicious anemia) and 3C (autoimmune thyroiditis with vitiligo or alopecia). Type IV is defined as two or more other organ-specific autoimmune diseases[1-4].

In this paper, a patient with autoimmune thyroiditis, Addison's disease and pernicious anemia is presented. The clinical presentation, diagnostic procedures and treatment will be discussed, with special reference to the APS classification issues that arise with the new classification.

Case Report

A 45-year-old male patient was admitted to the hospital due to fatigue, malaise and inappetence. He was diagnosed with autoimmune hypothyroidism (peroxidase antibodies of >600.0 kIU/L, thyroid-stimulating hormone (TSH) 10.5 mIU/L (0.3-3.0 mIU/L) and diffuse goiter on ultrasound) two years earlier, when levothyroxine supplementation therapy was initiated. Additionally, he was diagnosed with moderate normocytic anemia one year prior to current admission. Gastroscopy and fecal occult blood test showed normal findings, but laboratory testing revealed low vitamin B12 level of 87 ng/L (normal range, 200-900 ng/L). Therefore, vitamin B12 supplementation therapy (1000 mcg every four weeks) was administered.

On admission, physical examination showed hypotension (80/50 mm Hg), marked skin hyperpigmentation and low body mass index (19 kg/m^2). Complete blood count showed the following: hemoglobin 88 g/L (13-175 g/L), mean corpuscular volume 93.1 fL (83-97.2 fL), Fe 23.2 μmol/L (11-32 μmol/L), TIBC 33.2 μmol/L (49-72 μmol/L), and UIBC 10.0 μmol/L (25-54 μmol/L). Serum vitamin B12 levels were elevated (1175 ng/L, normal range 200-900 ng/L) due to vitamin B12 supplementation therapy. His electrolyte panel disclosed hyperkaliemia, (potassium 6.8 mmol/L, normal range 3.7-5.2) and hyponatremia (sodium 124 mmol/L, normal range 135-145). Endocrinological evaluation disclosed low morning cortisol (77 nmol/L, normal range 171-536) and aldosterone levels (<49 pmol/L, normal range 190-830 pmol/L), and elevated adrenocorticotropic hormone level (>275 pmol/L, normal range 1.6-13.9). Therefore, the diagnosis of primary adrenal insufficiency (Addison's disease) was established. Replacement therapy with hydrocortisone (200 mg hydrocortisone intravenously divided into four doses over three days, 50 mg orally for five days, then 30 mg daily) and fludrocortisone (0.2 mg three times a week) was initiated.

We performed additional workup due to previously established vitamin B12 deficiency. Parietal cell antibodies were positive. Therefore, we performed upper gastrointestinal endoscopy. Histopathologic analysis of the thin gastric mucosa revealed marked lymphocytic and plasma cell infiltrates, destruction of glandular structures which were replaced by intestinal-type epithelium and fibrous tissue. Based on prior low serum vitamin B12 levels, positive parietal cell antibodies and atrophic gastritis, the patient was diagnosed with pernicious anemia.

There were no clinical signs of other autoimmune diseases. Autoimmune DM was excluded based on normal HbA_{1c} levels and negative glutamic acid decarboxylase and islet antigen 2 antibodies.

Upon adequate hydrocortisone supplementation therapy, the patient's general condition improved and his symptoms withdrew. His hemoglobin level increased to 99 g/L and his sodium and potassium levels normalized. Three months later, the patient gained

10 kg and had normal electrolyte and complete blood count panel.

Discussion

This case report demonstrates rather unique features of pernicious anemia in a patient with Addison's disease. To the best of our knowledge, we found no reports on the coexistence of pernicious anemia and Addison's disease. Pernicious anemia is most often caused by atrophic gastritis. It is an autoimmune disorder in which the gastric parietal cells are destroyed, with consequent intrinsic factor deficiency. Insufficient hematopoiesis subsequently leads to the production of immature, large and fragile red blood cells, which is the main characteristic of pernicious anemia. However, our patient with pernicious anemia had normal mean corpuscular volume. This can be explained by the superimposed glucocorticoid deficiency, which causes anemia of chronic disease. Additionally, one can assume that cortisol has a more pronounced effect than vitamin B12 in this setting, since vitamin B12 supplementation therapy in our patient had no effect on erythropoiesis. Nevertheless, our case demonstrates that patients with normocytic anemia and Addison's disease can also have pernicious anemia, and *vice versa*. However, this brings up a problem concerning screening of patients with APS type II. A novel classification of APS defines APS type II as the presence of autoimmune thyroid disease and Addison's disease or type 1 DM. On the other hand, APS type III B, which consists of autoimmune thyroid disease and pernicious anemia, excludes the presence of Addison's disease. This excludes the possibility of coexistence of Addison's disease and pernicious anemia. APS type II and recently more emphasized APS type III are attributed to the synergistic effects of genetic and environmental factors. They are strongly associated with HLA class II genes, with different alleles being characteristic of each of the autoimmune conditions (for example, HLA-DRB1-DQA1-DQB1 with Addison's disease, HLA-DRB1*04/DQA1*0301/DQB1*0302 and DM, HLA-DQB1*0301 with autoimmune thyroiditis, and HLA-DRB1*13 with vitiligo)[2]. As for the clinical difference among these entities, type II combines autoimmune thyroiditis and Addison's disease or type 1 DM[1-4]. Type III APS is defined by the presence of autoimmune thyroid conditions (Hashimoto's thyroiditis, idiopathic myxedema, asymptomatic thyroiditis, Graves' disease) and another autoimmune disease, excluding type 1 DM or Addison's disease[1-4]. The most comprehensive description and subclassification of type III APS was proposed by Betterle and Zanchetta in 2001[2]. Type 3A combines thyroid conditions with type 1 DM and premature ovarian failure, lymphocytic hypophysitis or neurohypophysitis. Type 3B combines thyroid autoimmune diseases with gastrointestinal apparatus syndromes (atrophic gastritis, celiac disease, chronic inflammatory bowel disease, autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis). Type 3C combines thyroid conditions with vitiligo, alopecia, autoimmune thrombocytopenia, autoimmune hemolytic anemia, antiphospholipid syndrome, myasthenia gravis or multiple sclerosis. Type 3D combines thyroid conditions and collagen diseases and vasculitis[2]. APS IV is the rarest syndrome, consisting of combinations of autoimmune disorders not classified within the previous three groups[2].

Our case report highlights the link between type II and type III APS. Not only do they share the same etiologic factors, but also overlap in pathophysiological and clinical characteristics, and therefore a logical question arises whether these two are separate disorders. When making a diagnosis of APS, it is important to recognize all the autoimmune disorders the patient has. We believe that older classification, which divides APS into type I and II, is more appropriate. Our case report emphasizes that the combination of all autoimmune diseases in APS type II is possible. This might help avoid pitfalls in the diagnosis and treatment of patients with APS.

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Sažetak

BOLESNIK S ADRENALNOM INSUFICIJENCIJOM I PERNICIOZNOM ANEMIJOM: JE LI NOVA PODJELA AUTOIMUNOG POLIGLANDULARNOG SINDROMA PRIMJERENA?

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Prikazujemo slučaj bolesnika s autoimunim poliglandularnim sindromom (APS). Muškarac u dobi od 45 godina hospitaliziran je zbog opće slabosti i malaksalosti. Od ranije je bolovao od primarne hipotireoze i uzimao je nadomjesnu terapiju levotiroksinom. Jednu godinu ranije otkrivena je normocitna anemija i deficit vitamina B12, zbog čega je liječen nadomjesnom terapijom vitaminom B12. Pri fizikalnom pregledu nađena je hipotenzija i naglašena hiperpigmentacija kože. U laboratorijskim nalazima nađena je hiponatremija, hiperkalemija i teška normocitna anemija. Endokrinološkom obradom nađen je snižen jutarnji kortizol te povišen ACTH, nakon čega je postavljena dijagnoza Addisonove bolesti. Dodatnom laboratorijskom obradom nađena su i pozitivna protutijela na parijetalne stanice uz povišenu koncentraciju vitamina B12 posljedično nadomjesnoj terapiji. Nalaz gastroskopije i patohistološke analize sluznice upućivao je na atrofični gastritis te je stoga postavljena dijagnoza perniciozne anemije. Započeta je nadomjesna terapija hidrokortizonom i titrirana prema ciljnim vrijednostima slobodnog kortizola u 24-satnoj mokraći. Elektrolitski disbalans i anemija su se normalizirali. Ovaj prikaz slučaja je opisao karakteristike perniciozne anemije u bolesnika s Addisonovom bolešću te naglašava vezu između APS tip II. i III. Ova dva sindroma dijele istu etiologiju te se njihove komponente često preklapaju. Slučaj našega bolesnika daje prednost starijoj klasifikaciji APS koja dopušta kombinacije svih primarnih endokrinih insufucijencija i drugih za organ specifičnih bolesti. Poštivajući staru podjelu APS mogu se izbjeći potencijalne zamke u dijagnostici i liječenju.

Ključne riječi: *Poliendokrinopatije, autoimune – klasifikacija; Anemija, perniciozna; Addisonova bolest; Prikazi slučaja*