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Small-duct Primary Sclerosing Cholangitis associated with type IIIb Autoimmune Polyglandular Syndrome: A rare combination

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ABSTRACT: *Objective:* To report an uncommon presentation of a rare case of autoimmune polyglandular syndrome type IIIb in a patient presenting as well with Small Duct Primary Sclerosing Cholangitis. *Clinical Presentation and Intervention:* A 42-year-old man presented with jaundice and intermittent fever. Blood tests showed macrocytic anaemia due to vitamin B 12 deficiency compatible with Biermer's disease. A thyroid function test was consistent with hyperthyroidism compatible with Basedow's disease. And Liver biopsy revealed signs compatible with Small Duct Sclerosing Cholangitis. A final diagnosis of Small Duct Sclerosing Cholangitis with Biermer's disease and Basedow's disease, which constituted autoimmune polyglandular syndrome type IIIb, was made and the patient was treated with L-thyroxine, vitamin B 12 injection and Ursodeoxycholic acid with a impressive improvement during his follow up. *Conclusion:* This case showed a rare combination between APS type IIIb and Small Duct Sclerosing Cholangitis and that the presence of one autoimmune endocrine disease should prompt clinicians to look for other coexisting autoimmune diseases which may be asymptomatic.

KEYWORDS: Small-duct, Sclerosing Cholangitis, type IIIb, Autoimmune, Polyglandular, Syndrome.

1 INTRODUCTION

Autoimmune polyglandular syndrome (APS) is a rare form of autoimmune disorder involving at least two glandular autoimmune-mediated diseases [1].

The APS is an association of endocrine and non-endocrine organ-specific autoimmune diseases [2], and is divided into four types:

a) APS I, characterized by the presence of at least two of the following situations: Addison's disease, chronic hypoparathyroidism and chronic candidiasis;
b) APS II, associating Addison's disease with autoimmune thyroiditis and/or diabetes mellitus 1;
c) APS III, associating an autoimmune thyroiditis with other autoimmune diseases (such as diabetes mellitus 1, atrophic gastritis and pernicious anemia, vitiligo, alopecia and myasthenia gravis), except for Addison's disease and/or hypoparathyroidism;
d) APS IV, characterized by the combination of autoimmune diseases that do not fall into the categories already mentioned [3].

The APS III, can be subdivided according to the associated autoimmune disease: APS III (a), when the patient has diabetes mellitus 1; APS III (b), characterized by the presence of atrophic gastritis and pernicious anemia and APS III (c) when there is vitiligo, severe alopecia or myasthenia [4].

Autoimmunity, environmental factors, and genetic are the 3 major factors that should be considered in the physiopathology of APS III.

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We report the case of a patient presenting with an extremely rare combination of APS III (b) associated with Primary Sclerosing Cholangitis.

2 CASE REPORT

A 42 years old male patient presented to the Gastoenterology unit with symptoms of jaundice and intermittent fever. He had a personal history of Ag Hbe negative chronic HBV infection. No endocrine or autoimmune diseases were mentioned in his family. Physical examination revealed palor, tachycardia, jaundice and pedal edema. Laboratory tests found macrocytic anemia with hemoglobin at 5.2 g/dl and VGM at 103 fl, a lymphopenia, and thrombocytopenia. The patient had a low reticulocyte rate estimated at 12000/ul and a low rate of VitB12. His oesophagoduodenoscopy showed no abnormalities except duodenal lymphangiectasis. Histological features found atrophic gastritis compatible with Biermer's disease.

The patient had elevated liver enzymes and prothrombin level was at 67%. Abdominal ultrasonography showed a cirrhosis liver without ascites or hepatocellular carcinoma nodules. Viral serologies B and C, autoimmune hepatitis and storage disorders tests were negative.

Liver biopsy revealed portal areas with essentially mononucleated leukocyte infiltrate almost completely erasing the bile ducts that are not individualized after immunolabeling by the anticytokeratin antibody 7.

These histologic features were compatible with a Small Bile Ducts Primary Sclerosing Cholangitis (PSC).

The rectosigmoidoscopy examination found no evidence of chronic inflammatory bowel disease.

Their thyroid profile revealed a high free T4 level and very low thyroid-stimulating hormone level. The thyroperoxidase antibody and thyroid receptor antibody were detected. Thyroid gland ultrasonography revealed a small homogeneous diffuse goiter.

The electrocardiogram found sinus tachycardia with electrical left ventricular hypertrophy. Trans-thoracic ultrasound found an atrial disease secondary to thyrotoxycosis.

The oesophagoduodenoscopy showed no abnormalities except duodenal lymphangiectasis but on the other hand histological features found compatible signs with Biermer's disease.

Based on these results, the patient was diagnosed as having Graves' disease, Biermer's disease, and PSC. Treatment with 30 mg per day of carbimazole and propanolol was started for Grave's disease.

Ursodeoxycholic acid with increasing doses was started for the PSC and Intramuscular injections of Hydroxocobalamin for the Biermer disease.

During their follow-up, the patient's thyroid hormones, liver enzymes and B12 levels improved gradually and returned to the normal range afterwards.

Hence, long-term follow-up and screening for other possible glandular involvements is necessary for the patient.

3 DISCUSSION

Autoimmune polyglandular syndrome as a group of autoimmune diseases in which multiple endocrine organs are targets was first described by Addison in 1855 in a patient with idiopathic adrenal insufficiency, pernicious anemia and vitiligo [5].

Subsequently the association between diseases in APS was noted not to be at random but in particular combinations and that some non-endocrine autoimmune diseases were also part of the syndromes. Therefore in 1980 and after clinical observations, Neufeld and Blizzard suggested a classification of APS, based on clinical criteria only, and described four main types summerized in Table1 [6]:

Table 1. Classification of the APS

APS-1 Chronic candidiasis, chronic hypoparathyroidism, Addison's disease *(*at least two present*)*
APS-2 Addison's disease *(*always present*)* + autoimmune thyroid diseases and/or type 1 diabetes mellitus
APS-3 Autoimmune thyroid diseases associated with other autoimmune diseases *(*excluding Addison's disease and/or hypoparathyroidism*)*
APS-4 Combinations not included in the previous groups

In APS III patients, Addison's disease is absent, while autoimmune thyroiditis is an essential element. APS III can be complicated by type 1 diabetes, pernicious anemia and autoimmune hepatitis [7,8].

As described, the findings of the present case are compatible with a diagnosis of APS III.

By reviewing the literature, and to the best of knowledge we confirm that this is a rare combination that has never been reported.

The prevalence of APS type IIIb is unknown. It is more often met in middle-aged women but it can occur in people of any age [9].

This article reports the case of a previously healthy young patient, who presents with hepatitic manifestations leading to the diagnosis of Primary Sclerosing Cholangitis. Afterwards they were diagnosed with pernicious anemia and Grave's disease, which is consistent with the diagnosis of APS type III (b).

Primary sclerosing cholangitis (PSC) is a chronic immune-mediated disease of intra-and extrahepatic bile ducts, primarily affecting large ducts. Its insidious course related to progressive fibrostenotic structuring of the biliary tree causes important clinical sequelae, including liver cirrhosis, portal hypertension, and end-stage liver disease. Unlike primary biliary cholangitis (PBC), which affects small bile ducts and predominantly occurs in females, PSC effects more often males, with a median age of presentation of ~40 years [10]. PSC is associated with a range of autoimmune conditions, such as Autoimmune thyroiditis, Celiac disease and Inflammatory bowel disease. [10, 11, 12] and by detecting many autoantibodies in the sera of patients, suggesting a possible role of immunological abnormalities in the etiology of this disease.

The detection of antibodies is sufficient for the diagnosis of autoimmune disease of the thyroid. Positive Anti-thyroid peroxidase antibody (anti-TPO) are strongly indicative markers of autoimmune thyroiditis and are present in 90% of disease cases and currently used to define the existence of an autoimmune thyroiditis. Thyroid stimulating hormone receptor antibody (TRAb) are present in 20 to 50% of patient [13]. The presence of positive anti- TPO and TRAb, associated with low levels of Thyroid-stimulating hormone were enough for diagnosis of autoimmune thyroiditis type Grave's disease in the case presented.

Pernicious anaemia is a sequela of autoimmune chronic atrophic gastritis that involves the fundic glands and is characterized by severe gland atrophy [12]. Almost 90% of patients have antibodies directed against the parietal cells [14]. As a result, pernicious anaemia leads to vitamin B 12 malabsorption and subsequently B 12 deficiency. This patient had both anti-gastric parietal cell and anti-intrinsic factor antibodies negative but the diagnosis was based on a low rate of VitB12 and histological features compatible with Biermer's disease.

Gastrinaemia wasn't measured but hypergastrinaemia is a known complication of long-standing achlorrhydria due to a lack of acid secretion by the parietal cells of the stomach. The pronounced hypergastrinaemia (>1,000 pg/ml) likely leads to subsequent hyperplasia of gastric enterochromaffin-like cells which predisposes to gastric malignancy [15]. Close monitoring for detection of gastric carcinoid tumours, which have been reported in 3–5% of patients with hyperplasia of gastric enterochromaffin-like cells, should also be performed [15]. Furthermore, pernicious anaemia is also associated with an increased risk of gastric cancer [16].

The treatment of APS depends on the organ involved and the accompanying hormonal deficiencies. This patient was treated with ursodeoxycholic acid associated with Carbimazole as well as intramuscular vitamin B 12 injections which he will require as lifelong therapy.

However, it is important to highlight that autoimmune adrenalitis with accompanying adrenal insufficiency must be excluded before commencement of treatment with l-thyroxine in patient with autoimmune hypothyroidism [17].

Thus, regular and long-term glandular function monitoring seems necessary. This is important because early recognition and appropriate therapy can be lifesaving, particularly when the glandular failure involves the adrenal glands. Although the

gland involvement in APS type III is usually limited to 2 or 3 glands, extensive involvement of up to 7 autoimmune diseases with extensive circulating antibodies including anti-glutamic acid decarboxylase antibodies and islet cell antibodies has been reported [18].

4 CONCLUSION

This patient with APS type IIIb represents an exceptional autoimmune association with PSC. The clustering of these organ-specific autoimmune disorders suggests an underlying defect toward autoimmunity, which may be relevant for further understanding of the pathogenesis of PSC.

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