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Multiple Autoimmune Syndrome (MAIS): About Two Cases

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Abstract

MAIS is a rare entity, characterised by a combination of several autoimmune disorders. It is divided into three groups. Biermer disease (BD) belongs to MAIS 3 and is an autoimmune atrophic gastritis causing vitamin B12 deficiency, often associated with autoimmune diseases. The most frequently described are endocrinopathies, dominated by autoimmune thyroiditis followed by type 1 diabetes. Others have been reported, such as vitiligo, Gougerot-Sjögren syndrome and systemic lupus erythematosus. The coexistence of Biermer disease, AHAI or Biermer disease, primary biliary cirrhosis (PCB) and immunological thrombocytopenicpurpura (ITP) is rare. The diagnosis of Biermer's disease therefore requires systematic screening for other autoimmunedisorders.

Keywords: multiple autoimmune syndrome, Biermer disease, autoimmunity, atrophicgastritis, replacement therapy.

Introduction

The occurrence of three or more autoimmune diseases in the same person is an uncommon and unusual situation. It defines the multiple autoimmune syndrome (MAIS) [1]. According to Humbert and Dupon, there are three types of MAIS, depending on the associated diseases [2]. Biermer disease (BD) is one of the fundamental pillars of MAIS due to its frequency [3].

The aim of this paper is to recall the frequent association of Biermer's disease with other autoimmune disorders, through two observations of MAIS 3 and MAIS grouping types 2 and 3, in which the cascade of different autoimmune disorders occurred simultaneously and over several years respectively.

Case Report

Case report 1:

The patient was Mrs Y.I, aged 26, with no previous pathological history of note. The patient consulted the emergency department for an anaemic syndrome that had been evolving for 2 months. On admission, the patient was found to be haemodynamically stable, apyretic and subicteric. The rest of the somatic examination was unremarkable. The initial work-up showed pancytopenia (anaemia with macrocytic aregeneration at 3.7g/dl, MCV at 115fL, with thrombocytopenia at 51000/mm^3 and neutropenia at 640/mm^3), with anisocytosis on the blood smear. TSH was 6.91mUI/l with positive anti-TPO. Vitamin levels showed vitamin B12 deficiency at 50pg/ml (with positive antiintrinsic factor antibodies) and the myelogram showed megaloblastosis. A FOGD performed with biopsies was in favour of Biermer's disease. The haemolysis work-up showed an increase in serum free bilirubin to 17mg/L, a collapsed haptoglobin <0.08g/L, an LDH 2392U/L, with a positive coombs test (warm anti IgG+C3d antibodies). The rest of the work-up was normal (NAA negative, reactionalosteomedullary biopsy with no suspicious elements, cervico-thoraco-abdomino-pelvic CT scan with no abnormalities). The patient was put on vitamin B12 supplementation. The anaemia persisted despite the replacement therapy. The diagnosis of MAIS type 3, combining Biermer's disease, autoimmune haemolyticanaemia (AHAI) and autoimmune thyroiditis (AIT) was established. The course was favourable after corticosteroid therapy was combined with replacement therapy.

Case report 2:

Mrs Z. F, aged 63, with a history of type 1 diabetes on insulin therapy and primary biliary cirrhosis for 5 years on Ursodesoxycholic. Referred from the gastroenterology department for assessment of the aetiology of a bicytopenia (normocytic normochromic anaemia with an aegerative value of 8.3 g/dl and thrombocytopenia of 79,000/mm^3). Vitamin B12 deficiency was suspected and confirmed by a vitamin assay with the presence of megaloblastosis on myelogram and atrophic gastritis on FOGD. As the thrombocytopenia did not improve (platelets 95,000/mm^3) under vitamin B12 replacement therapy, a myelogram was performed,

confirming the peripheral origin of the thrombocytopenia (megakaryocytes were present and maturing), an NAA assay and liver serologies were performed, with negative results. The diagnosis of MAIS, comprising biermer's disease associated with primary biliary cirrhosis (PCB), type 1 diabetes and immunological thrombocytopenic purpura (ITP), was accepted.

Discussion

MAIS is a rare entity. In 1988, the number of cases described in the literature was 87 [4]. Since then, around twenty cases have been reported [3]. Humbert and Dupon have proposed a classification of MAIS into 3 groups, according to the associated pathologies. MAIS type 1 includes autoimmune myasthenia, thymoma, polymyositis and autoimmune myocarditis. MAIS type 2 includes Gougerot-Sjögren's syndrome, rheumatoid arthritis, primary biliary cirrhosis, scleroderma and autoimmune thyroiditis. MAIS type 3 includes autoimmune thyroiditis, myasthenia gravis, thymoma, Gougerot-Sjögren syndrome, Biermer disease (BD), immunological thombopenicpurpura (ITP), Addison's disease, diabetes type 1, vitiligo, autoimmune haemolyticanaemia, lupus and dermatitis herpetiformis [2].

Our case in the first observation is compatible with a MAIS type 3, in which the simultaneous occurrence of the three diseases (BD, AHAI and AIT) is certainly not fortuitous. On the other hand, in the second case, the MAIS had developed over several years, combining PBC, which is part of MAIS type 2, with MAIS type 3, which makes our case exceptional and difficult to classify. In addition to the diversity of similarities between BD, CBP, type 1 diabetes and ITP, in terms of age of onset, sex, genetic background, histological lesions (BD and PCB) and disturbances in cellular and humoral immunity, there is a definite pathophysiological interest.

Analysis of the two cases shows that BD is the common feature. BD is an autoimmune disorder characterised by the presence of autoimmune atrophic gastritis, predominantly in the fundus, and accompanied by reversible vitamin B12 malabsorption in the presence of intrinsic factor [5]. It accounts for more than 25% of the causes of vitamin B12 deficiency in adults [6]. It is often associated with autoimmune diseases [7]. The prevalence of autoimmune diseases in BD appears to be higher (34.2%) [8] Than in the general population (5%) [9], justifying systematic screening.

Classically, BD is suspected in the presence of macrocytic anaemia, a fortiori when associated with a neurological syndrome and/or an epithelial syndrome (Hunter's glossitis). However, although this is the most common presentation, it may be missed in certain highly atypical and often acute cases [10]. The main atypical presentations of BD are pseudo-TMA, haemolyticanaemia, cerebellar syndrome, involvement of the cranial pairs and sphincter disorders [11, 12]. The definitive diagnosis of MB is based on the presence of antiintrinsic factor antibodies and anti-parietal cell antibodies, as well as anatomopathological features that differentiate autoimmune fundial gastritis from H. Pylori gastritis, in particular the inflammatory infiltrate of mononuclear cells, which is characteristic in the early stages due to its aggressiveness towards the epithelium of the glands, leading to focal destruction and replacement by pyloric or intestinal metaplasia [13].

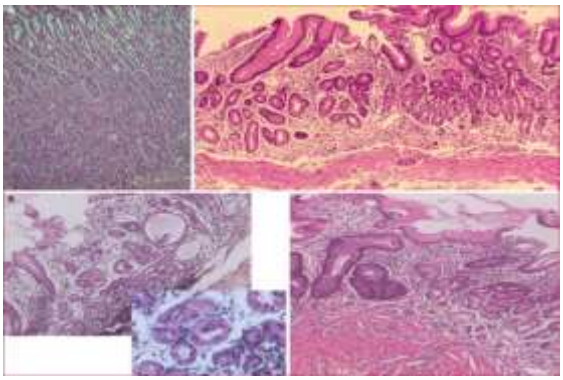

Figure 1: Pathological aspects of Biermer's disease. A) On the left, normal fundus. On the right, complete atrophy of the fundic mucosa. B) Autoimmune atrophic gastritis in its early stages. C) Autoimmuneatrophicgastritis in the atrophic stage [13].

The frequent association of BD with other autoimmune diseases, in particular endocrinopathies, dominated by AIT (50%) and type 1 diabetes, can be explained by the existence of a genetic predisposition for BD (classically HLA B8 DR3 for Caucasians) [3]; the association of BD with new genes predisposing in particular to MAIS, such as the AIRE gene [14,15], remains to be studied.On the other hand, the diagnosis of PCB, on the basis of anicteric hepatic cholestasis and the presence of anti-mitochondrial antibodies, during the course of BD and vice versa, is an exceptional case, since only seven observations have been recorded in the literature. The treatment and course of the two conditions are usually independent, and the pathophysiology of this association remains uncertain, leading to hypotheses of autoimmunity [16]. ITP during BD has also been described, but it is very rare and the causal link remains unknown [2].

AHAI is an anaemia caused by the destruction of red blood cells by antibodies directed against the patient's own unmodified red blood cell membrane antigens [5]. It was defined by the following criteria: a haemoglobin level of < 12g/dl, associated with biological signs of haemolysis (haptoglobin < 0.3g/l), and evidence of an anti-erythrocyte antibody by a direct/indirect Coombs test or the presence of cold agglutinins at a significant level (≥1/500). A negative Coombs test was not a criterion for exclusion after eliminating other causes of constitutional or acquired haemolysis [17]. Clinically, haemolysis is essentially expressed by an anaemic syndrome in 63.4% of cases, and the biological markers of haemolysis are mainly disturbed, particularly haptoglobin, which is decreased and constitutes the most sensitive marker [18].

Depending on the immunochemical properties of the autoantibody in question, a distinction is made between: AHAI with "hot" autoantibodies, antibodies which exert their maximum haemolytic activity at temperatures close to 37°C. The direct Coombs test is most often positive for IgG or IgG+ complement (anti-C3); this is the most common type of AHAI. AHAI with "cold" autoantibodies, antibodies (called "cold agglutinins") whose haemolytic activity is exerted at temperatures < 37°C, with a thermal optimum at + 4°C. In this case, the direct coombs test is usually positive for isolated complement (anti-C3d). The cold agglutin test is positive at a significant titre (positivity threshold > 1/64, rate usually ≥ 1/500) [19].

The coexistence of BD and AHAI with two different mechanisms of haemolysis: ineffective erythropoiesis and immunological haemolysis; is a rare situation [20]. It was first described by Rubio in 1953 [5]. A direct Coombs test may be positive in untreated biermer's disease, making the diagnosis

of associated AHAI sometimes difficult [21]. Generally, the diagnosis is suspected when the reticulocyte count is increased before treatment with vitamin B12 and the Coombs test remains positive despite replacement therapy [20]. The discovery of an AHAI with warm antibodies, as in our first case, requires an aetiological investigation to look for a systemic autoimmune disease, a lymphoid haemopathy, an immune deficiency or an associated cancer [5]. Treatment of warm antibody AHAI is based on 1st line corticosteroid therapy at a dose of 1 to 2mg/Kg/d. Other treatments include splenectomy, anti-CD20 antibodies (Rituximab) and immunosuppressants [19]. In our 1st observation, the etiological assessment found an associated IAT, and the corticosteroid treatment allowed normalization of the Hb level within 2 weeks. The coombs test was always positive.

Our observations show the importance of looking for associated autoimmune disorders in adults with BD. In the absence of a consensus, however, it seems necessary to carry out an annual autoimmune check-up as part of the follow-up of these patients. The treatment of BD in the context of MAIS remains vitamin therapy, combined with specific treatment for other conditions.

Conclusion

The incidence of autoimmune diseases appears to be higher in patients with Biermer disease than in the general population. The diagnosis of Biermer disease warrants systematic screening for other autoimmune disorders, both at the time of diagnosis and during patient follow-up.

Conflicts of interest

The authors declare no conflict of interest.

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