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Immunodeficiencies and autoimmune diseases: Common variable immunodeficiency and Crohn-like

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ABSTRACT

Common variable immunodeficiency (CVI) gives a major risk of principally respiratory and digestive infections. It is associated with autoimmune diseases, granulomatous process and neoplasias. The digestive clinic is common, in 10% of patients it is the only symptom, and 60 % present chronic diarrhea. Clinically it can be confused and related with other pathologies such as inflammatory bowel disease which is infrequent (2-13%). We present the case of a patient with CVI with digestive symptoms being diagnosed of Crohn-like disease with extent ileal affectation. The main treatment of these patients is the same as classical Crohn disease although in the most severe cases, as this one, the use of immunosupresors is necessary. At this time the patient remains on clinical remmision with infliximab. She presented a previous adverse reaction with adalimumab. The few case series in this pathology makes the treatment with immunomodulators in this immunodeficiency a real diagnostic and therapeutic challenge.

Key words: Common variable immunodeficiency. Inflammatory bowel disease. Anti-TNF.

CASE REPORT

We present the case of a 50-year-old woman diagnosed with common variable immunodeficiency (CVI). The patient receives substitute treatment with intravenous immunoglobulines every 3 weeks and presents ferropenic anemia due to gynecological problems in treatment with parenteral iron. She comes to admission because of 3-4 months of evolution of general syndrome with asthenia, anorexia, and weight loss, approximately 10 kg. She presents oral ulcers (not previously) for which she has taken antibiotic treatment with moxifloxacin and partial improvement. Febricula with occasional fever up to 38 °C. She refers daily diarrheic stools, although they have increased in the last 1-2 months. The patient presents neither arthritis, phlebitis, genital ulcers, cutaneous injuries nor associate visual alterations. Not another associate symptomatology.

Previous treatments: Immunoglobulines in hematology day hospital every 3 weeks.

To the physical examination, she presents blood pressure 100/70 mmHg, pulse 74 beats per minute, temperature 36.4 °C, 99% oxygen saturation and weight 48.8 Kg.

Good general condition: cardio-pulmonary auscultation without significant pathological alterations. Right axillary adenopathy. The abdomen is depressible, without masses or visceromegalies. No other finding on exploration.

At admission, radiological study by abdominal computed tomography (CT) is performed, identifying a diffuse and homogeneous thickening of bowel walls corresponding to the ileum, without any affectation of the terminal ileum; some ganglionar images in the root of the mesentery and a small quantity of intraperitoneal free liquid are found (Fig. 1).

The differential diagnose is made between infectious, inflammatory or tumor process so that an enteroscopy is carried out without any macroscopic damage. The biopsies are compatible with granulomatous enteritis of small bowel (SB).

The study is completed by an endoscopic capsule identifying in duodenum and jejunum small isolated ulcerations, edematous creases of inflammatory aspect, some

of them covered with fibrin (Fig. 2).

The findings are compatible with Crohn-like granulomatous enteritis. Infectious complications and lymphoma are discarded. Corticosteroids infusion is started with a light improvement of the fever, but the patient begins with episodes of profuse bleeding with secondary anemization, so new endoscopic studies are made (anterograde enteroscopy, colonoscopy and angio-CT), identifying ulcerations with diffuse bleeding and without a concrete localization.

The colonoscopy shows several minimal aphthoid lesions in descending colon and some erythematous areas in proximal sigma (Fig. 3). Biopsy shows absence of plasmatic cells, without any other alterations.

The patient requires politransfusion and endovenous iron supplements. Corticosteroids therapy at 1 mg/kg dose is administered without response. Because of the torpid evolution it is decided to intensify the treatment of the Crohn-like disease in order to have a better control of the inflammation and to evaluate the digestive hemorrhage. Subcutaneous treatment with adalimumab is started with induction dose of 160 mg. Thanks to the intensification of the treatment a gradual clinical improvement is achieved with cessation of the bleeding. Later on a severe aplasia of three series is settled. She also presents hemorrhoid bleeding. We consult the Hematology department who attributes the pancytopenia to adalimumab.

For this reason, the second infusion of adalimumab is stopped. In later blood test, there is a progressive improvement of the aplasia so bone marrow stimulant treatment is not needed. At that time, the use of azathioprine, mercaptopurine and metrotexate was evaluated.

In relation to the pancytopenia that appears to be secondary to the anti-TNF α , a bibliographical search is made with scarce evidence on the strategy to follow, for what we comment our clinical case with other reference hospitals supporting the option to begin the treatment with infliximab with good clinical answer. At this time, the patient remains on remission of the intestinal affectation with infliximab infusion at dose of 5 mg/Kg (325 mg) every 8 weeks.

As a result of the hereditary predisposition to infections in addition to the use of biological treatment that leads to more immunosuppression status, the patient is at

high risk for infections. She remains on gastrointestinal clinical remission with blood tests controls without alterations of the three series. Not associated or opportunists infections have been documented.

DISCUSSION

Common variable immunodeficiency (CVI) or acquired hypogammaglobulinemia is the most common symptomatic primary immunodeficiency (1/25,000-1/50,000) in which the antibody deficient production is predominant (1-4).

The diagnose is based on the determination of two serologic immunoglobulins (Igs) (IgG and IgA and/or IgM) with a decrease in at least two standard deviations under the limit assigned by age as well as a deterioration of the production of antibodies against vaccination (principally tetanus toxoid or diphtheria, haemophilus influenzae type B, flu, mumps, measles and polyssacaridic pneumococcus) or a recent infection (5).

In addition to the Igs decrease, it is associated with acquired immunity alterations at other levels: a wrong differentiation of the lymphocytes B (LB) to plasmatic cells as well as a number of lymphocytes T (LT) or normal LB or lightly decreased. The most recent studies have demonstrated an important alteration of the LT mediated immunity stablishing 4 genes whose mutations give place to a wide percentage of the CVI: ICOS (inducible costimulator), TACI (that is found in 10% of patients), CD19 and BAFF-R (receptor of the T cells activator) (6). TACI is expressed in peripheral LB and is a member of the family of TNF-like receptors that transduce signs related to the cellular survival, the isotopic change or the apoptosis (6).

This immunity alteration entails a major risk of principally respiratory and digestive infections with predominance of encapsulated bacteria (1). It is associated with autoimmune diseases, chronic inflammation and granulomatous process as well as neoplasias (lymphoma, gastric adenocarcinoma, melanoma, squamous carcinoma of head and neck, meningioma and renal large cells lymphoma) (6). It has been described the association with granulomatous diseases (8-22%) as well as with inflammatory processes including nodular lymphocytic hyperplasia, aphthous stomatitis, autoimmune atrophic chronic gastritis, pernicious anemia, sarcoidosis, scleroderma, chronic enteritis, inflammatory bowel disease (IBD) and chronic hepatitis among

others (6,7). It turns to be controversial the relation between an antibodies primary immunodeficiency coexisting with an autoimmune illness (2).

It is not known when this pathology develops, but the clinical manifestations appear in the adolescence or 3rd-4th decade of life without predominance between sexes. Most cases are sporadic (19-22% are hereditary) (6).

The digestive clinic is common. In 10% of patients, it is the only symptom and 60% of the patients can present chronic diarrhea (1,3,5). Another related clinic is the loss of weight or malabsorption (10%), being the most frequent cause of this clinic infections like giardiasis and the bacterial overgrowth in the small bowel (7). In some cases, the digestive clinic is the first and only manifestation of the CVI (1).

Clinically, it can be confused with lymphocytic colitis, collagen colitis, coeliac disease, lymphocytic gastritis, granulomatous disease and the IBD (6).

The relation between CVI and IBD is rare with a wide variation in series with a range of 2-13% (1). In Spain, the prevalence of IBD in CVI is 3.2% (2).

The Crohn-like illness is the appearance of an intestinal inflammatory process compatible with Crohn's disease as a result of another underlying pathology.

There are two described types of enteropathy, one that affects exclusively the large intestine and another one that involves predominantly small intestine with malabsorption. The intestinal involvement secondary to infections can be explained as an inappropriate inflammatory reaction of the LT that produces cytokines, particularly the TNF-alpha, from a part of the CD8 cells, increasing the permeability of the large intestine (2).

The association between these two illnesses appears on the basis of an immune dysregulation: one of the basics on the etiopathogenesis of the IBD is the misbalance of the immune response on the intestinal barrier. The alteration in the luminal antigens presentation bears a disproportionate inflammatory response initiating a cytokine cascade, which is an etiological foundation and base of the directed-treatment in this illness (immunosuppressors and inhibiting these cytokines). Being the gastrointestinal tract one of the more extensive secondary lymphoid organs with a large number of lymphocytes, it is necessary to consider that this immune deficiency in this first step barrier might lead to different digestive manifestations that overlap IBD.

In Crohn's disease and colitis, there are more proinflammatory cytokines and in the CVI there is an imbalance of these (principally IL-2, IL-10 and TNF α). In a sub-group of patients with CVI, there has been described the persistent activation of the TNF α (2), being these patients those who present major Crohn-like proportion (7).

Biopsies usually show an intense intraepithelial or subepithelial lymphocytosis, apoptosis, granulomas, distortion of the crypts and the most outstanding thing, the absence of plasmatic cells in the lamina propria (4,5).

The treatment of choice of CVI is based on the therapy with intravenous or subcutaneous administered human antibodies. The treatment is safe although allergic reactions (6) have been documented. The biggest problem in these patients is the handling of the post-infectious consequences or the damage due to the associate illnesses (IBD, endocrinopathy, etc.) (6,8). In the group of patients with IBD-like the treatment is the same that the primary enteropathy including corticosteroids, 5 aminosalicylate, 6-mercaptopurin and azathioprine.

In relation to the immunosuppressor therapy, it is necessary to have in mind that many patients with CVI have functional alterations of the LT and that the treatment with azathioprine would produce a severe malfunction of the T cells. Although in IBD the treatment with anti-TNF α contributes to a major risk of infections, particularly mycobacteria, it has been seen that patients with CVI are resistant to this type of infections for a regulation (up-regulation) of the interleukin 12 and the interferon gamma (2,9). For the rest of microorganisms, the risk remains the same.

Anti-TNFs as infliximab are used in the most severe cases paying special attention to opportunist infections and monitoring mainly fungoid infections (5).

There is still little experience in the use of these drugs in the CVI although their use in other related illnesses endorses their efficacy and the absence of significant side effects (4,8,9). During the infusion, it is recommended to determine levels of antibodies (5,9).

Few series of patients still exist for the management of this pathology that appears in such an unspecific way with digestive clinic. The communication of new cases and the experience in clinical practice will provide us with more enlightening information.

We must continue with a close monitoring of these patients.

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Fig. 1. Computerized tomography of the abdomen showing a diffuse homogenous thickening of the small bowel walls corresponding to the ileum.

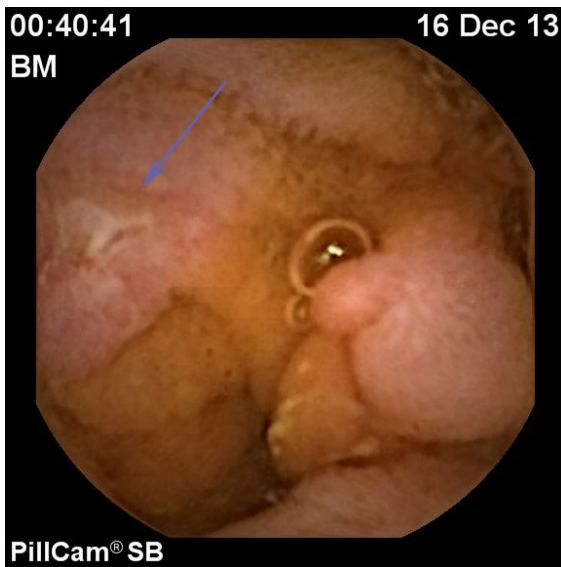


Fig. 2. Endoscopic capsule showing isolated ulcerations, edematous creases of inflammatory aspect, some of them covered with fibrin, in jejunum.

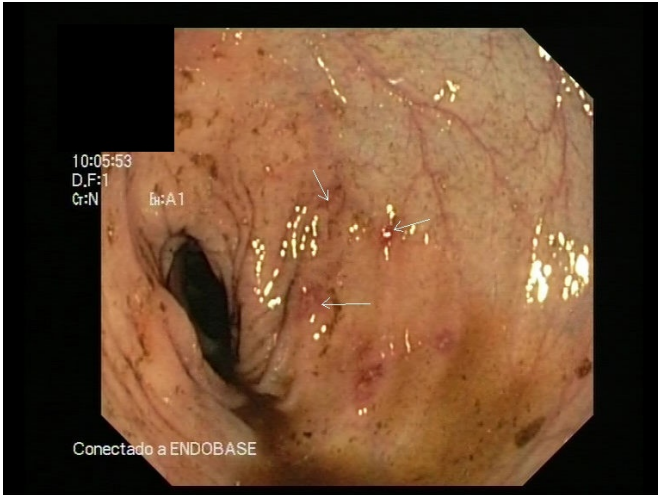


Fig. 3. Colonoscopy showing in descending colon several minimal aphthoid lesions and some erythematous areas in proximal sigma.