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CASE REPORT

PARTICULAR DIAGNOSIS AND TREATMENT FEATURES OF A CASE OF COMMON VARIABLE IMMUNOGLOBULIN DEFICIENCY ASSOCIATED WITH GLUTEN INTOLERANCE AND SEVERE MALABSORPTION SYNDROME

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Abstract. The authors present the case of a Common variable immunoglobulin deficiency (CVID) patient who has hypogammaglobulinemia, bowel involvement and severe malabsorption syndrome. Various problems related to positive and differential diagnosis are discussed within the framework of a very severe progression due to malabsorption syndrome with cachexia, numerous intercurrent pulmonary, intestinal, genital and skin infections and thrombophilia secondary to malabsorption. Eventually the course of disease is favourable partially thanks to the multidisciplinary approach undertaken.
Keywords: immunodeficiency, enteropathy, gluten, malabsorption, thrombophilia

Introduction

Specific to the common variable immunoglobulin deficiency syndrome (CVID) is the low level of serum immunoglobulins despite the normal number and morphology of the B lymphocytes. The incidence of the disease varies widely between 1:10,000 and 1:200,000, having an equal distribution among sexes [1, 2]. The late onset of intercurrent infections, usually in adolescence lead to the term "acquired hypogammaglobulinemia" although the conditions seems to have genetic origins causing altered lymphocyte B functionality [1,3]. Besides recurrent infections, oftentimes with opportunistic germs, the disease can involve various organs and systems; it can be associated with numerous autoimmune and granulomatous conditions and is quite often seen together with cancers of the hematopoietic system and the digestive tract, thus creating difficult differential diagnosis problems [4,5]. In spite of severe infections and organ complications, the diagnosis is established late most of the times, 1-10 years after the initial symptoms [5]. A multidisciplinary approach is necessary in order to diagnose and treat these patients in an effective manner [1].

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Case report

Male patient, aged 32, presented with serious weight loss over the last year (10 kg) and diarrheic, liquid stools. No immunodeficiency or celiac sprue was present in family members. The patient suffered from viral hepatitis A one year ago, and repeated respiratory infections over the last years in the absence of smoking or alcohol as risk factors.

The physical examination showed a cachectic patient (Body mass index - BMI 12.7), hyperpigmentation of the skin, missing subcutaneous adipose tissue, calf oedema, no peripheral adenomegaly palpable liver and spleen.

The initial biological evaluation showed light anaemia, (hemoglobinemia: 121 g/L), with low serum iron levels (6.26 μmol/L) but normal mean cell volume (MVC 91.3 fL), white blood cell count 8420/mm^3 with a normal leukocyte formula, normal morphology on the peripheral blood smear test, thrombocytes 153,000/mm^3, low levels for the serum immunoglobulins: IgG 20 UI/ml, IgM 16 UI/ml, IgA undetectable. Immunophenotyping the leukocytes in peripheral blood flow shows no decrease of B: CD19+ 8%, CD56+ 2%, CD3+ 88% (30% Th, 58%Tc; Th/Tc 0.58), CD4 34.50%, CD4/

CD8 0.67. Immunology: endomisium IgA Ab, IgG negative, tissue transglutaminase Ab negative, HLA DQ typing: DQ alpha 1 negative, DQ beta 1 negative, lack of anticentromere antibodies, SCL 70, SSA, SSB, ADN2C, RNP. Biology: serum albumin 3.1 g%, cholesterol 78 mg%, triglycerides 45 mg%, GOT 65 Ul, GPT 55 Ul, GGT 67 Ul, ALP 299 Ul, normal levels of plasma cortisol. Virology: Ac HIV1,2 negative, HIV PCR undetectable, HBV DNA undetectable, HCV ARN undetectable. Bacteriology and parasitology: normal on routine urine examination, sterile urine culture, stools very rich in neutral fats, cellulose, steatocrit 49g/24 hours, Giardia lamblia found on stool parasite test, normal flora on stool culture test. No Helicobacter pylori faecal antigen was found.

The abdominal echography revealed hepatomegaly and splenomegaly. The superior digestive tract endoscopy revealed DII and DIII mucosa with a nodular aspect. No Helicobacter pylori found on gastric biopsy. The colonoscopy showed normal findings, the same for serial biopsies of the colon mucosa. Using the endocapsule inside the small-bowel we found slight changes resembling a tiled pattern.

Chest X-ray was normal. There were no pathological adenomegaly on the abdominal scans.

The combined occurrence of a severe immunoglobulin G deficit with normal lymphocyte B morphology and recurring infections is suggestive of a common variable immunoglobulin deficit. The bowel mucosa aspect combined with diarrhoea and malabsorption seemed to indicate a celiac disease.

The differential diagnosis of the immune deficit focused on selective IgA deficit (which could precede CVID) [6], X-linked agammaglobulinemia (decrease in number of lack of peripheral B cells, light hypogammaglobulinemia) [1,7], hyper IgM syndrome (increase of IgM, lymphocyte B alterations) [8,9].

The patient was soon started on iv immunoglobulin until the low end of the range was reached, then maintained for 6 months; metronidazole to treat the Giardia lamblia infestation, without improvement – malabsorption syndrome and diarrhoea were still present. Then we considered gluten enteropathy as a possibility, making the change to a gluten free diet without any obvious subjective improvement over the following 6 months but with a slight histological one. Given the lack of response to therapy for the celiac disease and the bowel autoimmune manifestations caused by CVID the patient was given oral corticotherapy, Prednisone 15mg/day. The evolution was positive, an improvement of the diarrheic syndrome and nutrition overall aggravated by recurrent respiratory infections.

The low compliance to gluten free diet led after 2 years of steady progress to deterioration in the nutritional status and repeated respiratory infections, the most common agents that were isolated being Haemophilus influenzae, Pseudomonas aeruginosa, Klebsiella pneumoniae. The antibiotic therapy worked well, no secondary bronchiectasis developed. Other infectious episodes included orchiepididymitis, otitis media, leg skin infections suggesting a streptococcal agent, enteric infections caused by Giardia lamblia each time.

With a background of malabsorption and thrombophilia (protein S activity 33%, protein C and antithrombin III normal) the patient later developed bilateral iliofemoral deep vein thrombosis with a good response to anticoagulants but with secondary necrosis in the right leg, possibly Coumadin necrosis. The necrosis eventually led to loss of skin covering the entire lower limb and repeated surgery, immune and nutritional reanimation and skin grafts with a favourable evolution – the limb recovered its skin and function. The patient was put on low molecular weight heparin for lack of other options with an almost complete repermeabilization of the deep veins in the lower limbs.

The current treatment consists of a hyperproteic, hypercaloric gluten free diet, postural drainage of the lower limbs and kinesiotherapy. The most important therapeutic ingredient is intravenous human immunoglobulin IgG (substitution therapy), the minimal required dose in order to maintain their serum level above the laboratory baseline being 20 grams per month, delivered on a fortnight basis. The patient follows an immunosuppressive treatment with prednisone 10 mg/day and anticoagulants – LMW heparins (enoxaparin 2x6000 UI/day). As a side effect of heparins and corticotherapy, osteoporotic lesions were noted that are currently treated with bisphosphonates (ibandronic acid 3 mg IV every 3 months), combined with alpha D3 1 μg/day and 1000 mg calcium salts. The anti-infective treatment is customized to meet the severity of the infection, its localization and the exact nature of the agent when identified. We don't use antibiotic prophylaxis. Tianeptine in a dosage of 2x12.5 mg is our antidepressant of choice. Active immunoprophylaxis is not indicated due to insufficient antibody. Psychological counselling is crucial to maintain compliance to diet and treatment, to accept prolonged hospital stays, motor, social, professional and family disabilities and to allow for an increase in the overall quality of life. The difficulties associated with getting a good peripheral and central venous access force us to consider a totally implanted device for long term intravenous therapy in the near future.

Discussions

Our nosological framework was not accurate

since we couldn't rule out a selective IgA deficit prior to CVID or an X-linked lymphoprolipherative syndrome and we couldn't explore the Epstein Barr infection given the lack of antibodies and the SH2D1A expression [6, 7]. We had no data to confirm gluten enteropathy, the microscopy showing lymphoid nodular hyperplasia and villi alterations without the typical findings of the celiac sprue. Glandular crypt hypertrophy and villous atrophy were to be expected in such a severe malabsorption syndrome [10]. Moreover the genetic tests for celiac disease were negative but cannot rule out the condition. The good response to a gluten free diet strongly suggested the coexistence of CVID and gluten intolerance, extensively reported in medical literature [1, 2, 7].

A particular feature of the case is the severity of the malabsorption syndrome and of the diarrheic syndrome, responding quite well to corticotherapy and gluten free diet. The paradoxical good response to corticotherapy can be explained by the autoimmune involvement of the bowel [1, 3]. Any attempt to do without the corticotherapy led to an immediate aggravation of the condition, especially diarrhoea and malabsorption.

Despite countless infectious episodes, the response to antibiotics has always been very good. The most serious complication was the coumarinic necrosis with a serious risk of losing the lower limb. We want to underline the fact that despite massive skin loss we managed to avoid infection and local suppuration by using isolation measures, asepsis, antisepsis, targeted antibiotic treatment and using the best known reparatory and reconstructive surgical techniques.

Among technical problems we should mention the very difficult IV access, the osteoporosis leading to motor inabilities and teeth loss making certain diets problematic.

Oncological monitoring was another challenge, the risk for lymphoma being 400 times bigger than in general population, and the risk for digestive cancer being also very high [1,7]. We practiced endoscopies and biopsies followed by immunophenotyping each year, also peripheral flow cytometry as often as needed and abdominal echography twice a year. We determined CA 19-9, CA 15-3,CA 72-4, AFP, CEA, tPSA on a yearly basis; in 2011 we recorded a moderate increase in CEA, CA 15-3 and CA 19-9 levels, but cannot confirm an oncologic pathology.

We consider short term prognosis to be good but the long term one remains reserved [4]. The potentially unfavourable evolution leads to suggesting biological therapy with anti TNF alpha antibodies as an option [1, 4, 7].

Conclusions

The common variable immunoglobulin deficit has a wide range of clinical manifestations including various organs and systems. There are real difficulties both regarding the positive diagnosis and treatment which has to be customized to meet the specific needs of the patient. A multidisciplinary approach is crucial in this respect. A great deal of effort is required to increase the quality of life due to the multisystem involvement caused either by disease or by therapy.

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