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Efficacy of subcutaneous immunoglobulins in primary immunodeficiency with Crohn's-like phenotype: report of a case

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Abstract. – Common variable immune deficiency (CVID) is the most frequent primary immunodeficiency in adults. In CVID, the prevalence of gastrointestinal manifestations ranges between 2 and 50% with a complication-related morbidity second only to that of the respiratory tract. In some cases, clinical and endoscopic features are undistinguishable from those of inflammatory bowel disease (IBD). We describe the case of a 28-year-old man in which a diagnosis of Crohn's disease was firstly suspected. Subsequently, a diagnosis of Crohn's-like disease in a patient with CVID was made and a replacement therapy with human normal immunoglobulin intravenously was started. Unfortunately, serum IgG levels remained below 2.0 g/l in pre-infusional controls with persistence of gastrointestinal symptoms and malnutrition despite anti-inflammatory therapy (mesalazine, corticosteroids). Then, the patient began treatment with human normal immunoglobulins administered subcutaneously. The follow-up visits showed a progressive increase in serum IgG. Moreover, the patient reported improvement of gastrointestinal symptoms with reduction of diarrhoea, and laboratory tests showed a progressive and significant improvement.

We confirm that therapy with subcutaneously administered immunoglobulins is safe and effective. In addition, our observations indicate that, for patients with CVID and enteropathic complications, replacement therapy with subcutaneous IgG may be the treatment of choice.

Key Words:
Subcutaneous immunoglobulins, Primary immunodeficiency, Common variable immune deficiency, Crohn's disease, Inflammatory bowel disease.

Introduction

Common variable immune deficiency (CVID) is the most frequent primary immunodeficiency in adults. It is usually diagnosed between the second and fourth decade (earlier and later onset forms have also been reported) based on the finding of reduced serum levels of at least two classes of immunoglobulins, associated with an increased susceptibility to infections[1,2]. The genetic basis of CVID are largely unknown. Mutations in four genes have been associated with the disease: ICOS[3], TNFRSF-138 (TACI)[4], TNFRSF13C (BAFF-R)[5], and CD19[6].

The clinical history of CVID patients is generally characterized by recurrent bacterial infections especially of the respiratory tract. However, more than 40% of patients develop gastrointestinal, lymphoproliferative, autoimmune and granulomatous diseases. Recent analyses of large cohorts of CVID patients identified six phenotypic classes: absence of complications, autoimmunity, enteropathy, polyclonal lymphocytic infiltration, tumours, and pulmonary complications[7,8]. The prevalence of gastrointestinal manifestations ranges between 2 and 50% with a complication-related morbidity second only to that of the respiratory tract. The gastrointestinal manifestations associated with CVID may include infectious, inflammatory, neoplastic or autoimmune diseases. Chronic diarrhoea is the most common manifestation of the gastrointestinal tract[9]. In about one half of patients with chronic diarrhoea, clinical and endoscopic features are often undistinguish-

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able from those of inflammatory bowel disease (IBD)[10]. In these cases, hypogammaglobulinemia with a reduced number or absence of mucosal plasma cells on histology is strongly suggestive of a primary immunodeficiency[11].

Case Report

We describe the case of a 28-year-old man referred to our Hospital in September 2009. The patient was admitted to the Gastroenterology Unit for chronic diarrhoea, unintentional weight loss, iron-deficiency anaemia and low serum albumin levels (2.9 g/dL). Nutritional evaluation showed a malnutrition status: body mass index (BMI) 16.9 kg/m^2, mid upper arm muscle area (AMA) 28.3 cm^2, fat mass (FM) 12%. Intestinal ultrasound showed terminal ileal thickness and mesenteric lymphadenopathy. Colonoscopy showed linear ulcers in terminal ileum, ileocaecal valve, cecum and descending colon (Figure 1). Biopsy examination revealed chronic active inflammation in ileal specimens and chronic active inflammation and neutrophilic cryptitis in colonic specimens (Figure 2). Magnetic resonance (MR) enterography demonstrated marked thickening, abnormal high signal and intense contrast-enhancement involving a terminal ileum segment measuring 15 cm in length (Figure 3). A radioisotope-labelled white cell scan showed increased uptake in the terminal ileum and in the entire colon. A diagnosis of Crohn's disease was suspected and treatment with oral prednisone at a dosage of 40 mg daily and mesalazine was started. On the other hand, laboratory data of the patient, who had suffered from hypogammaglobulinemia from the age of 16 years, revealed panipogammaglobulinemia (IgG levels < 0.08 g/l, IgA < 0.063 g/l, IgM < 0.054 g/l). For this reason, an immunology consult was required. Flow cytometric analysis on peripheral blood lymphocytes showed 1% of CD19$^+$ lymphocytes (normal value 10-25%). All these data led to the diagnosis of Crohn's-like disease in a patient with CVID and a replacement therapy with human normal immunoglobulin intravenously (i.v.) at a dose of 400 mg/kg every 21 days was started. Unfortunately, the therapy did not prove beneficial. In

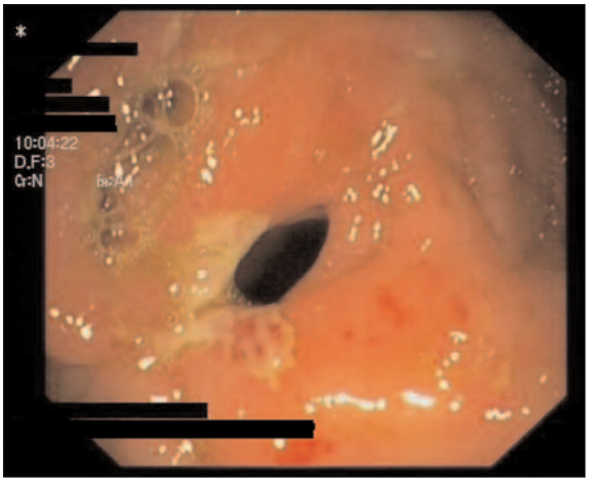

Figure 1. Endoscopic view of ulcerated ileocaecal valve mimicking Crohn's disease.

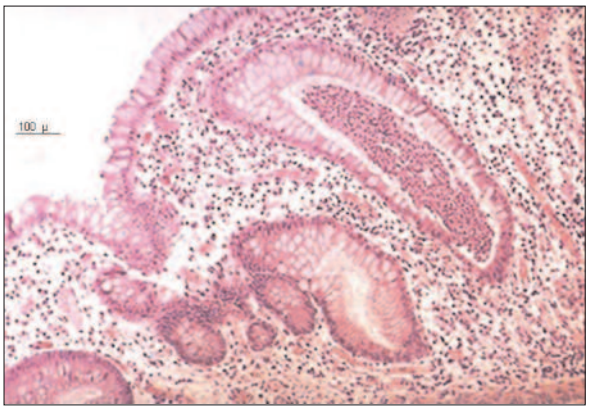

Figure 2. Microscopic findings of left colon showing chronic active inflammation and neutrophilic cryptitis. Hematoxylin and eosin staining.

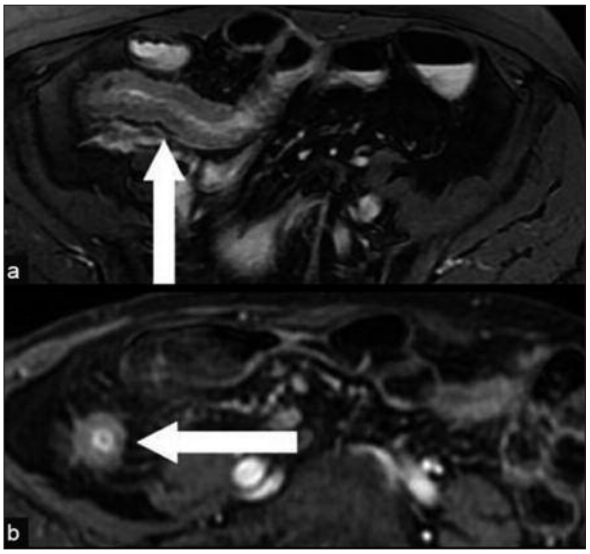

Figure 3. Magnetic resonance (MR) enterography showed active inflammation of terminal ileum. Marked thickening, abnormal high signal ***(a)***. High enhancement in T1-weighted sequences after intravenous administration of paramagnetic contrast medium ***(b)***.

fact, serum IgG levels remained low in pre-infusional controls with persistence of gastrointestinal symptoms and malnutrition despite frequent anti-inflammatory therapy (mesalazine, oral budesonide at a dosage of 9 mg/day) and antibiotic prophylaxis. Given the persistence of low serum albumin (2.8 g/dL) and IgG levels, suggesting protein-losing enteropathy, in April 2010, the patient began treatment with human normal immunoglobulin administered subcutaneously at a dose of 3.2 g twice a week. The follow-up visits showed a progressive increase in serum IgG (2.2 g/l at T0, 3.31 g/l at 6 months, 4.01 g/l at 12 months, 4.56 g/l at 18 months, and 5.5 g/l at 2 years) (Figure 4).

Clinically, the patient reported amelioration of gastrointestinal symptoms with reduction of diarrhoea and abdominal pain. Nutritional status improved: BMI 19.2 kg/m^2, AMA 37.1 cm^2, FM 16%. Laboratory tests showed a progressive and significant improvement, with normal serum albumin levels (3.5 g/dL). The patient reported an overall improvement in his general health and quality of life (no lost work days and better personal activities) even in the absence of anti-inflammatory therapy. Because of the patient's weight gain, the weekly dose of IgG was increased, which resulted in a corresponding increase in serum IgG levels. At endoscopy, the inflammation of colon and terminal ileum mucosa was slightly improved compared with the previous endoscopic findings.

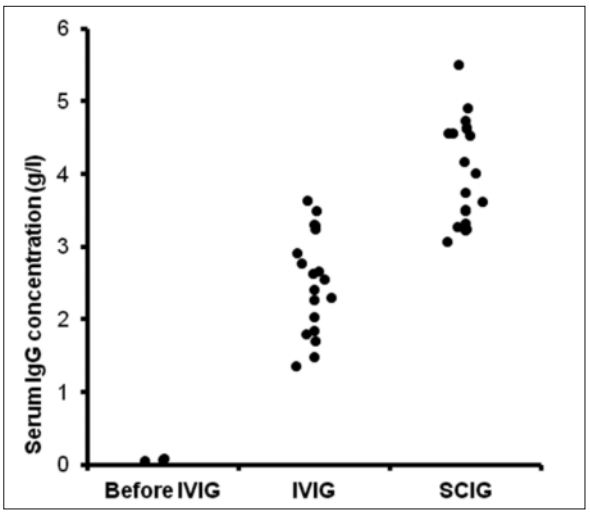

Figure 4. Serum IgG concentration before human normal immunoglobulin intravenously (IVIG) and during 54-weeks follow up of IVIG or human normal immunoglobulin administered subcutaneously (SCIG) therapy. Serum IgG concentration was assessed every three weeks.

Discussion

We have described, for the first time, a case of CVID with Crohn's-like phenotype in which the subcutaneous administration of replacement therapy with human normal IgG determined a significant improvement of intestinal symptoms, laboratory tests and nutritional status.

The main clinical manifestations presented by patients with Crohn's-like disease in a CVID context are chronic diarrhoea, weight loss and malabsorption, as in our patient. Occasionally gastrointestinal symptoms may develop before the underlying immunodeficiency is discovered. Various clinical manifestations of CVID suggest that the pathogenesis of this disorder is complex, with autoimmune alterations appearing in multiple pathways. Identification of immunological parameters associated with this subgroup of patients may allow early diagnosis and help to establish more specific and targeted treatments[12].

A dysregulated immune system is thought to be pivotal in the pathogenesis of Crohn's disease[13]. It is, then, not surprising that CVID may affect the gastrointestinal tract in a manner similar to Crohn's disease. Intestinal inflammation in CVID patients with IBD-like disease may be mediated by abnormal cytokine production through a T-cell receptor-mediated pathway. Moreover, intestinal microbiota could play a role in the pathogenesis of IBD-like alterations[14]. *Giardia lamblia, Cryptosporidium parvum*, *Cytomegalovirus*, *Salmonella species*, *Clostridium difficile*, and *Campylobacter jejuni* have also been implicated as a cause of intestinal symptoms in these patients. Very frequent is bacterial overgrowth, which might be related to decreased luminal antibody (specifically IgA) in the small bowel[9]. The management of CVID with IBD-like phenotype is generally the same as for IBD patients, although gut inflammation in patients with CVID might be more difficult to control. Antibiotics, such as metronidazole or ciprofloxacin; anti-inflammatory agents, such as 5-aminosalicylic acid; and rapidly metabolized steroids (budesonide) or suppositories can be used. Immunomodulators, such as azathioprine/6-mercaptopurine, can be used safely given the fact that the doses used are too low to affect T- and B-cell function. Several groups have demonstrated improvement by using Infliximab or Adalimumab[9,15-18].

Some studies have demonstrated that i.v. Ig supplementation had no effect on the course of diarrhoea, malabsorption, or mucosal damages in patients with CVID with IBD-like disease[19,20].

These findings are in contrast with the efficacy of i.v. Ig in the prevention of respiratory tract infections, which has been ascribed to the transudation of i.v. Ig in the lung alveolar epithelia[21]. The unmodified course of intestinal infections, despite residual serum levels of gammaglobulins of 6 g/l known to be sufficient to prevent respiratory tract infections, pleads against efficient delivery of IgG in the intestinal lumen, even if theoretically possible, through the neonatal Fc receptor[22]. Various hypotheses can be evoked to explain the response to subcutaneous IgG replacement therapy. It is conceivable that the kinetics of IgG distribution depend on the route of administration. In fact, when administered subcutaneously, IgG are slowly absorbed and redistributed during concentration-dependent catabolism, thereby reducing the inflammatory component of intestinal infection that results from an inadequate barrier antibody and/or dysregulation of the T-cell compartment. In addition, traces of IgA may be found in preparations of immunoglobulin for subcutaneous infusion, unlike preparations for intravenous infusion, thereby, leading to reduced susceptibility to intestinal infections[23,24].

Conclusions

We confirm that the administration of replacement therapy with subcutaneously administered immunoglobulins is safe and effective. In addition, our observations indicate that for patients with CVID and enteropathic complications, replacement therapy with subcutaneous IgG may be the treatment of choice. Lastly, patients affected by protein-losing enteropathy and hypogammaglobulinemia might be considered candidates for therapy with subcutaneously administered normal human IgG.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999; 93: 190-197.
2) Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br J Haematol 2009; 145: 709-727.
3) Salzer U, Maul-Pavicic A, Cunningham-Rundles C, Urschel S, Belohradsky BH, Litzman J, Holm A, Franco JL, Plebani A, Hammarstrom L, Skrabl A, Schwinger W, Grimbacher B. ICOS deficiency in patients with common variable immunodeficiency. Clin Immunol 2004; 113: 234-244.
4) Salzer U, Chapel HM, Webster AD, Pan-Hammarström Q, Schmitt-Graeff A, Schlesier M, Peter HH, Rockstroh JK, Schneider P, Schäffer AA, Hammarström L, Grimbacher B. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet 2005; 37: 820-828.
5) Warnatz K, Salzer U, Gutenberger S, Bossaller L, Schlesier M, Grimbacher B. Finally found: Human BAFF-R deficiency causes CVID. XIth Meeting for the European Society for Immunodeficiencies; Versailles. 2004, October. (Abstr. B. 72)
6) Kanegane H, Agematsu K, Futatani T, Sira MM, Suga K, Sekiguchi T, van Zelm MC, Miyawaki T. Novel mutations in a Japanese patient with CD19 deficiency. Genes Immun 2007; 8: 663-670.
7) Cunningham-Rundles C. How I treat common variable immune deficiency. Blood 2010; 116: 7-15.
8) Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, Fieschi C, Thon V, Abedi MR, Hammarstrom L. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood 2008; 112: 277-286.
9) Agarwal S, Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. J Allergy Clin Immunol 2009; 124: 658-664.
10) Liesch Z, Hanck C, Werth B, Kuhn M, Liesch M, Reinhart WH. Diarrhea and weight loss in common variable immunodeficiency. Z Gastroenterol 2004; 42: 599-603.
11) Kalha I, Sellin JH. Common variable immunodeficiency and the gastrointestinal tract. Curr Gastroenterol Rep 2004; 6: 377-383.
12) Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007; 31: 1800-1812.
13) Neurath MF, Finotto S, Glimcher LH. The role of Th1/Th2 polarization in mucosal immunity. Nat Med 2002; 8: 567-573.
14) Agarwal S, Smereka P, Harpaz N, Cunningham-Rundles C, Mayer L. Characterization of immunologic defects in patients with common variable immunodeficiency (CVID) with intestinal disease. Inflamm Bowel Dis 2011; 17: 251-259.
15) Elnachef N, McMorris M, Chey WD. Successful treatment of common variable immunodeficiency disorder-associated diarrhea with budesonide: a

case report. Am J Gastroenterol 2007; 102: 1322-1325.

16) Aukrust P, Lien E, Kristoffersen AK, Müller F, Haug CJ, Espevik T, Frøland SS. Persistent activation of the tumor necrosis factor system in a subgroup of patients with common variable immunodeficiency--possible immunologic and clinical consequences. Blood 1996; 87: 674-681.

17) Chua I, Standish R, Lear S, Harbord M, Eren E, Raeiszadeh M, Workman S, Webster D. Anti-tumour necrosis factor-alpha therapy for severe enteropathy in patients with common variable immunodeficiency (CVID). Clin Exp Immunol 2007; 150: 306-311.

18) Vázquez-Morón JM, Pallarés-Manrique H, Martín-Suárez IJ, Benítez-Rodríguez B, Ramos-Lora M. Crohn´s-like disease in a patient with common variable immunodeficiency treated with azathioprine and adalimumab. Rev Esp Enferm Dig 2013; 105: 299-302.

19) Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999; 92: 34-48.

20) Malamut G, Verkarre V, Suarez F, Viallard JF, Lascaux AS, Cosnes J, Bouhnik Y, Lambotte O, Béchade D, Ziol M, Lavergne A, Hermine O, Cerf-Bensussan N, Cellier C. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. Am J Gastroenterol 2010; 105: 2262-2275.

21) de Gracia J, Vendrell M, Alvarez A, Pallisa E, Rodrigo MJ, de la Rosa D, Mata F, Andreu J, Morell F. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. Int Immunopharmacol 2004; 4: 745-753.

22) He W, Ladinsky MS, Huey-Tubman KE, Jensen GJ, McIntosh JR, Björkman PJ. FcRn-mediated antibody transport across epithelial cells revealed by electron tomography. Nature 2008; 455: 542-546.

23) Bonilla FA. Pharmacokinetics of immunoglobulin administered via intravenous or subcoutaneous routes. Immunol Allergy Clin North Am 2008; 28: 803-819.

24) Holmgren J, Czerkinsky C, Lycke N, Svennerholm AM. Mucosal immunity: implications for vaccine development. Immunobiology 1992; 184: 157-179.