Arab Journal of Gastroenterology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Arab Journal of Gastroenterology

journal homepage: www.elsevier.com/locate/ajg

Case report

A difficult diagnosis of coeliac disease: Repeat duodenal histology increases diagnostic yield in patients with concomitant causes of villous atrophy

Gaetano Cristian Morreale [a,*], Luigi Maria Montalbano [b], Maria Cappello [a], Emanuele Sinagra [c], Aroldo Rizzo [d], Antonio Carroccio [e]

[a] Gastroenterology and Hepatology Section, DIBIMIS, University of Palermo, Italy
[b] Endoscopic Unit, Ospedali Riuniti Villa Sofia-Cervello Palermo, Italy
[c] Gastroenterology and Endoscopy Unit, Fondazione Istituto San Raffaele Giglio, Cefalù, Italy
[d] Pathology Unit, Ospedali Riuniti Villa Sofia-Cervello Palermo, Italy
[e] Internal Medicine Section, DIBIMIS, University of Palermo, Italy

ARTICLE INFO

Article history:
Received 30 October 2016
Accepted 17 September 2017
Available online xxxx

Keywords:
Coeliac disease
Villous atrophy
Common variable immunodeficiency
Giardia lamblia infection
Intestinal histology

ABSTRACT

Villous atrophy in absence of coeliac disease (CD)-specific antibodies represents a diagnostic dilemma. We report a case of a woman with anaemia, weight loss and diarrhoea with an initial diagnosis of seronegative CD and a histological documented villous atrophy who did not improve on gluten-free diet due to the concomitant presence of common variable immunodeficiency (CVID) and Giardia lamblia infection. This case report confirms that CD diagnosis in CVID patients is difficult; the combination of anti-endomysial antibodies (EmA-IgA), anti-tissue transglutaminase antibodies (tTG-IgAb) antibodies and total IgA is obligatory in basic diagnostic of CD but in CVID are negative. Furthermore, the typical histological aspects of the intestinal mucosa in CVID (absence of plasma cells and switch to the IgD immunoglobulins), cannot rule out a concomitant CD diagnosis. HLA typing in this setting has a low positive predictive value but should be considered. Histological response to a gluten-free diet on repeat biopsy and the concomitant treatment of other causes of villous atrophy leads to a definite diagnosis of CD.

Introduction

Duodenal villous atrophy in absence of the positivity of the coeliac disease (CD)-associated serum antibodies (anti-tissue transglutaminase: anti-tTG- and/or anti-endomysial: EmA-) can be defined as sero-negative villous atrophy (SNVA). Although SNVA can be part of the clinical spectrum of coeliac disease (CD) with a prevalence up to 39% [1], many other causes must to be considered and excluded before to making a diagnosis of CD. In this paper we show the case of a "difficult diagnosis" of sero-negative CD as multiple causes of SNVA concurred in the same patient and suggest a diagnostic approach based on repeated intestinal histology evaluation.

Case report

A 40 years old woman with a ten-years clinical history of autoimmune thyroiditis, and iron deficiency anaemia treated with oral iron courses and folic acid supplementation without clinical recovery, was referred to our hospital, a tertiary gastroenterology center, because of chronic diarrhoea. She reported 5 bowel motions per day of liquid stools without blood, and weight loss of 8 kg in the last 2 months.

Two years before (January 2013), the patient had been hospitalized elsewhere for the same reason and had received a diagnosis of CD, based on the following histological characteristics: Marked chronic inflammation with glandular epithelial lymphocytosis and severe flattening of the villi – grade B2 according to Corazza and Villanacci classification. [2] However, CD serologic markers (anti-tTG IgA and IgG and EmA Ig A antibodies) were negative. Accordingly, she had started gluten free diet (GFD) but, for the persistence of the gastrointestinal symptoms despite GFD, a medical reassessment was performed in January 2014. Stool cultures and

* Corresponding author.
E-mail address: dottgaetanocmorreale@gmail.com (G.C. Morreale).

https://doi.org/10.1016/j.ajg.2017.09.011
1687-1979/

search for ova and parasites were negative; laboratory examinations showed persistent negative CD markers, but also low serum levels of all the immunoglobulin (Ig) classes: immunoglobulin IgA < 6.67 mg/dl (ref. 9–450 mg/dl), IgG 119 mg/dl (ref. 751–1560 mg/dl), IgM < 4.17 mg/dl (ref. 40–274 mg/dl).

Abdominal ultrasound examination demonstrated only mild splenomegaly (Dt max 13 cm). The oesophagogastroduodenoscopy (EGDS) showed on the duodenal mucosa, nodules of various sizes, up to 5 mm. Duodenal histology confirmed the persistence of severe villous atrophy, nodular lymphoid infiltration of the lamina propria, no evidence of plasma cells, and showed also the presence of many spheroidal morphology forms compatible with Giardia lamblia (GI) (Fig. 1A and B); CD5, CD3 and CD38 glycoprotein expression were positive (as a markers of intraepithelial T lymphocytes), (Fig. 2A–D) whereas CD20 glycoprotein expression was negative (B-lymphocytes absent) (Fig. 2E); there was also a switch on

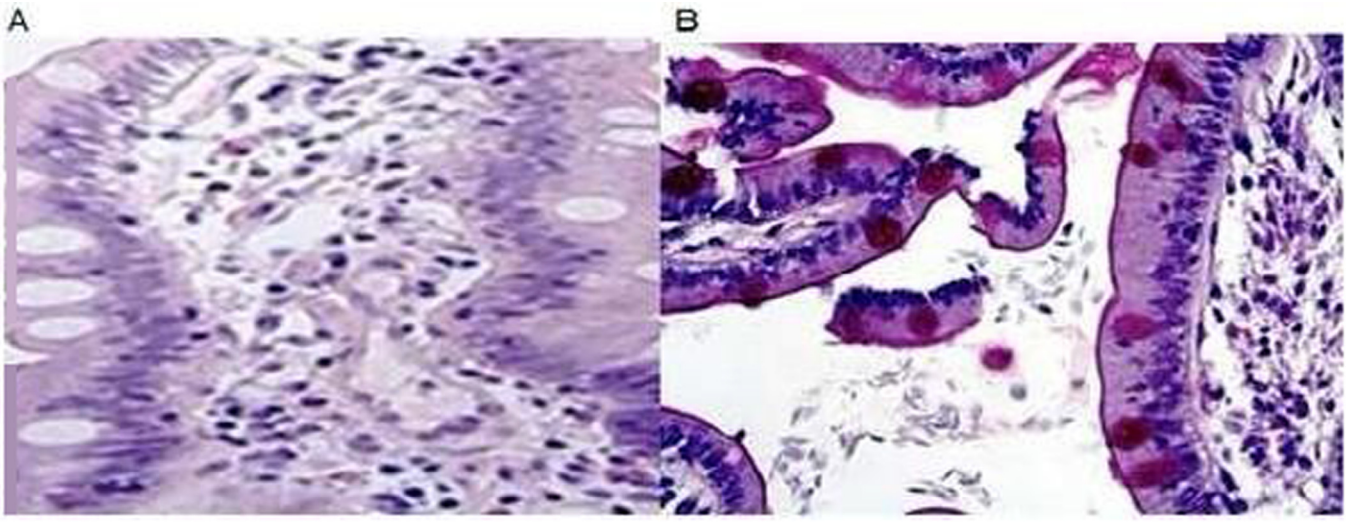

Fig. 1. A. Giardia lamblia, haematoxylin and eosin (×25), B. Giardia lamblia, PAS (×40).

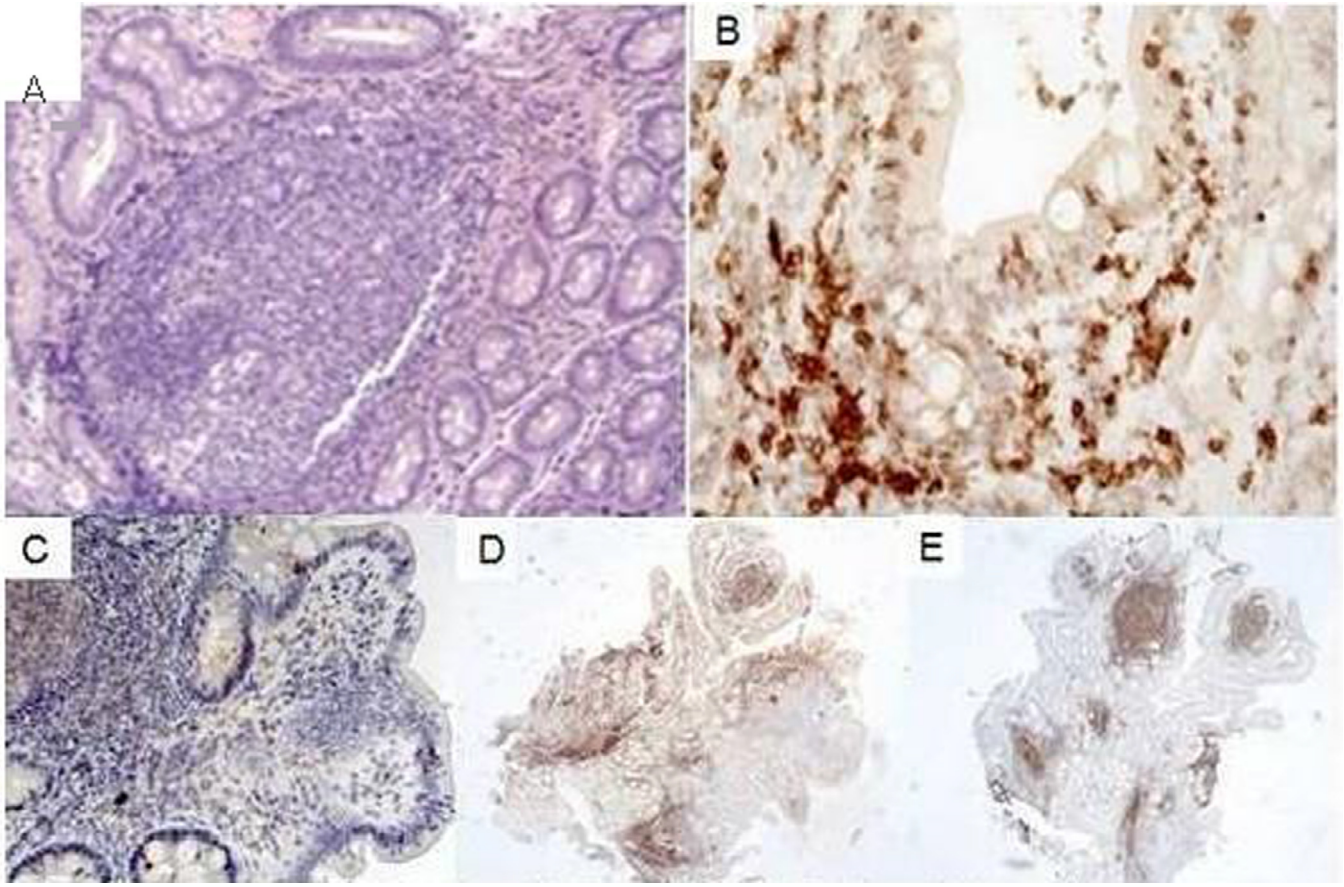

Fig. 2. A. Haematoxylin and eosin (×10), B. CD3 (×25), C. CD38 (×25), D. CD5 (Original magnification ×4), E. CD20 (×4).

Please cite this article in press as: Morreale GC et al. A difficult diagnosis of coeliac disease: Repeat duodenal histology increases diagnostic yield in patients with concomitant causes of villous atrophy. Arab J Gastroenterol (2018), https://doi.org/10.1016/j.ajg.2017.09.011

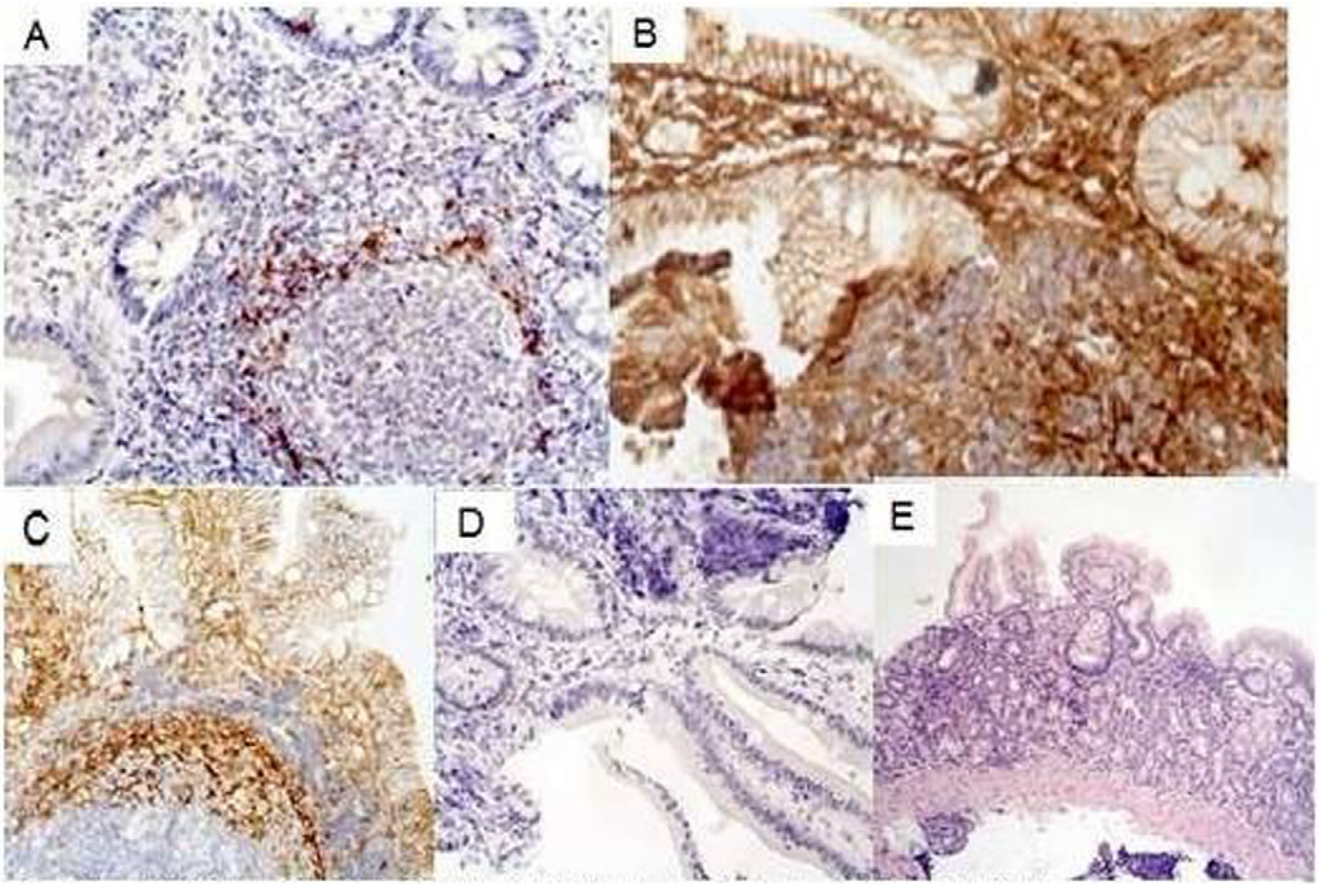

Fig. 3. A. IgD (×25), B. IgG (×25), C. IgM (×25), D. IgA (×25), E. Gastric atrophy (×10).

D-Immunoglobulin (IgD) for absence of other classes of Immunoglobulin (Fig. 3A–D). A gastric biopsy showed also gastric atrophy (Fig. 3E). On this basis, common variable immunodeficiency (CVID) complicated by gastrointestinal infection by Giardia lamblia was diagnosed and the patient started antibiotic therapy with metronidazole. Thus, at this stage, CD was excluded for the persistence of total villous atrophy after one year on GFD and due to the evidence of other known causes of SNVA. Consequently, the patient abandoned GFD. In the following months, the patient had an increase in weight but diarrhoea and anaemia did not resolve.

On January 2015, the patient was referred to our Gastroenterology Unit. She again underwent EGDS with duodenal histology study: B2 lesions were again observed, without evidence of Giardia lamblia. Furthermore, a genetic test for HLA haplotypes was performed and showed a DQ2.5 heterodimer. On the evidence of this result, we proposed to restart GFD for 12 months. The patient had a resolution of diarrhoea and anaemia; another EGDS with duodenal histology, performed on December 2015, showed a normal duodenum mucosa. Histological examination confirmed no villous atrophy (grade A histology). Coeliac disease diagnosis was consequently confirmed.

Discussion

CVID is a frequent primary antibody deficiency syndrome, characterized by recurrent infections and autoimmune phenomena, often linked to the occurrence of lymphoproliferative diseases [3]. Gastrointestinal symptoms or intestinal lesions are frequently seen (up to 50%) in patients with CVID [4,12], diarrhoea, abdominal pain, weight loss and anaemia being the most common [5–8]. In 30% of cases, gastrointestinal involvement was demonstrated to be the result of infestations with *Giardia lamblia*, a protozoan parasite whose presence in the small intestine of these patients is facilitated by the absence of secretory immunoglobulin (Ig) A, a hallmark in most patients with CVID. [5,7]. In a significant percentage of patients, however, intestinal lesions are not caused by infectious/parasitic agents. [7,8]. In particular, Crohn's disease–like lesions [7–9,13] and lymphoid nodular hyperplasia [5,6,10,11,13] have been described, as well as a condition atrophy of the duodenal mucosa characterized by villous atrophy, crypt hypertrophy, and an increase of T-lymphocyte infiltrate [5–8,13,14]. This finding is similar to the histopathologic alterations found in untreated CD; however in CD patients, a variable degree of villous atrophy is usually associated with highly sensitive and specific serum antibodies, as anti-endomysial, and anti- tissue transglutaminase antibodies. The real diagnostic dilemma is represented by the patients showing concomitant villous atrophy and seronegative antibodies (SNVA) as they remain in a grey area and many diagnoses other than CD must be considered (Table 1) [15,16]. The combination of the following antibodies EmA-IgA, tTG-IgAb and total IgA is obligatory in basic diagnostic of CD; in the case we reported, both anti-tTg and EmA antibodies were repeatedly assayed, but they were not reliable because of the antibody deficiency in CVID. Indeed, these patients may have false negative test results because they cannot have an appropriate antibody response. Consequently, in patients with CVID an alteration of duodenal mucosa poses a difficult differential diagnosis that includes CD. This problem is not only because the specific antibodies for CD have no diagnostic role in patients with CVID, but also because these conditions can be associated in the same patient [17,18]. In fact, Biagi et al. [19]

Please cite this article in press as: Morreale GC et al. A difficult diagnosis of coeliac disease: Repeat duodenal histology increases diagnostic yield in patients with concomitant causes of villous atrophy. Arab J Gastroenterol (2018), https://doi.org/10.1016/j.ajg.2017.09.011

Table 1
List of possible diagnoses in patients with SNVA.

Coeliac disease	Unclassified sprue
Autoimmune enteropathy	Peptic duodenitis
Collagenous sprue	Eosinophilic enteritis
CD4 T-cell lymphoma	Food hypersensitivity
Common variable immunodeficiency	Radiation enteritis
Enteropathy-associated T-cell lymphoma	Crohn disease
Gastric metaplasia	Systemic immune-mediated disease (Rheumatoid artritis, Sjogren syndrome, SLE, etc)
Medication-related villous atrophy	AIDS
Small intestinal bacterial overgrowth	Infection (including Helicobacter Pilori, Giardiasis, Tuberculosis, Whipple's disease, etc)
Tropical sprue	Glycogen storage disease
Abetalipoproteinaemia	Refractory CD type 2

demonstrated that in eleven adult patients with duodenal mucosa atrophy and CVID diagnosis, CD was present in 27% of the cases (3/11) and in the other cases (5/11, 46%), the diagnosis of CD could neither be confirmed nor definitely excluded. Some authors have indicated a series of histopathologic aspects characterizing mucosal histology. In CVID. [8,11,20–24], such as the absence of plasma cells and the presence of a polymorphonuclear infiltrate (PMNI) and graft-versus-host disease–like lesions (GVHDL).

Although these histopathologic aspects help in differentiating between a flat mucosa in CVID and a flat mucosa in CD, it is not yet clear whether finding these lesions in the flat duodenal mucosa of patients with CVID can exclude the concomitant presence of CD. Our case suggests that only the histology response to a gluten-free diet allowed the diagnosis of CD and remains the only diagnostic criteria for CD in these patients, after having treated possible concomitant causes of villous atrophy such as Giardia Lamblia infection [25].

In a such difficult diagnosis, HLA phenotyping has also a diagnostic role as in our patient we found the DQ2.5 heterodimer; however, in a previous large study 70% of 72 SNVA patients showed the HLA DQ2 and/or DQ8 and only 20 of the 72 patients were coeliacs [15]. Furthermore, the largest study on seronegative villous atrophy showed a positive predictive value of 51% for HLA DQ2/DQ8 genotyping [16]. This confirms that also in the setting of SNVA the HLA assay doesn't carry a high positive predictive value. The histologic response of a flat mucosa to GFD therefore represents the only diagnostic criterion for establishing whether the patients with CVID also have CD. A potential pitfall of this approach could be the absence of histological recovery at a given point since mucosal healing occurs late in adult-onset CD and the differential diagnosis of refractory CD can be challenging and require multiple follow-up biopsies. [13].

Our case report demonstrates that in a patient with negative CD serology and a known cause of villous atrophy, CVID complicated by Giardia Lamblia, CD can still coexist and only the histological response to GFD after the concomitant treatment of the associated causes, confirmed CD.

Repeat histology remains the most reliable diagnostic strategy.

References

[1] Rostami K, Kerckhaert J, Tiemessen R, et al. Sensitivity of antiendomysium and antigliadin antibodies in untreated coeliac disease: disappointing in clinical practice. Am J Gastroenterol 1999;94:888–94.
[2] Corazza GR, Villanacci V. Coeliac Disease. J Clin Pathol 2005;58:573–4.
[3] Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Curr Allergy Asthma Rep 2009;9(347):2.
[4] Teahon K, Webster AD, Price AB, Weston J, Bjarnason I. Studies on the enteropathy associated with primary hypogammaglobulinaemia. Gut 1994;35:1244–9.
[5] Kalha I, Sellin JH. Common variable immunodeficiency and the gastrointestinal tract. Curr Gastroenterol Rep 2004;6:374–7.
[6] Luzi G, Zullo A, Iebba F, et al. Duodenal pathology and clinical-immunological implications in common variable immunodeficiency patients. Am J Gastroenterol 2003;98:118–21.
[7] Agarwal S, Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. J Allergy Clin Immunol 2009;124:658–64.
[8] Daniels JA, Lederman HM, Maitra A, et al. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007;31:1800–12.
[9] Mannon PJ, Fuss IJ, Dill S, et al. Excess IL-12 but not IL-23 accompanies the inflammatory bowel disease associated with common variable immunodeficiency. Gastroenterology 2006;131:748–56.
[10] Bästlein C, Burlefinger R, Holzberg E, et al. Common variable immunodeficiency syndrome and nodular lymphoid hyperplasia in the small intestine. Endoscopy 1988;20:272–5.
[11] Washington K, Stenzel TT, Buckley RH, et al. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am J Surg Pathol 1996;20:1240–52.
[12] Khodadad A, Aghamohammadi A, Parvaneh N, et al. Gastrointestinal manifestations in patients with common variable immunodeficiency. Dig Dis Sci 2007;52:2977–83.
[13] Teahon K, Webster AD, Price AB, et al. Studies on the enteropathy associated with primary hypogammaglobulinaemia. Gut 1994;35:1244–9.
[14] Martucci S, Biagi F, Di Sabatino A, et al. Coeliac disease. Dig Liver Dis 2002;34 (suppl 2):S150–3.
[15] De Gaetani M, Tennyson CA, Lebwohl B, et al. Villous Atrophy and Negative Coeliac Serology: A Diagnostic and Therapeutic Dilemma. Am J Gastroenterol 2013;108:647.
[16] Aziz I, Peerally MF, Barnes J-H et al. The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000–2015). Gut doi:10.1136/gutjnl-2016-312271.
[17] Heneghan MA, Stevens FM, Cryan EM, et al. Coeliac sprue and immunodeficiency states: a 25-year review. J Clin Gastroenterol 1997;25:421–5.
[18] Webster AD, Slavin G, Shiner M, et al. Coeliac disease with severe hypogammaglobulinaemia. Gut 1981;22:153–7.
[19] Biagi F, Bianchi P, Zilli A, et al. The Significance of Duodenal Mucosal Atrophy in Patients With Common Variable Immunodeficiency A Clinical and Histopathologic Study. Am J Clin Pathol 2012;138(185–189):18.
[20] Shah VH, Rotterdam H, Kotler DP, Fasano A, Green PH. All that scallops is not coeliac disease. Gastrointest Endosc 2000 Jun;51(6):717–20.
[21] Kuitunen P, Kosnai I, Savilahti E. Morphometric study of the jejunal mucosa in various childhood enteropathies with special reference to intraepithelial lymphocytes. J Pediatr Gastroenterol Nutr 1982;1(4):525–31.
[22] Lai Ping So A, Mayer L. Gastrointestinal manifestations of primary immunodeficiency disorders. Semin Gastrointest Dis 1997;8:22–32.
[23] Herbst EW, Armbruster M, Rump JA, et al. Intestinal B cell defects in common variable immunodeficiency. Clin Exp Immunol 1994;95:215–21.
[24] Malamut G, Verkarre V, Suarez F, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with coeliac disease. Am J Gastroenterol 2010;105:2262–75.
[25] Carroccio A, Cavataio F, Montalto G, Paparo F, Troncone R, Iacono G. Treatment of giardiasis reverses active coeliac disease to latent coeliac disease. Eur J Gastroenterol Hepatol 2001;13:1101–5.

Please cite this article in press as: Morreale GC et al. A difficult diagnosis of coeliac disease: Repeat duodenal histology increases diagnostic yield in patients with concomitant causes of villous atrophy. Arab J Gastroenterol (2018), https://doi.org/10.1016/j.ajg.2017.09.011