Features and Progression of Potential Celiac Disease in Adults

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BACKGROUND & AIMS: **Individuals with potential celiac disease have serologic and genetic markers of the disease with little or no damage to the small intestinal mucosa. We performed a prospective study to learn more about disease progression in these people.**

METHODS: **We collected data from 77 adults (59 female; median age, 33 years) diagnosed with potential celiac disease (on the basis of serology and HLA type) at Bologna University in Italy from 2004 through 2013. The subjects had normal or slight inflammation of the small intestinal mucosa. Clinical, laboratory, and histologic parameters were evaluated at diagnosis and during a 3-year follow-up period.**

RESULTS: **Sixty-one patients (46 female; median age, 36 years) showed intestinal and extraintestinal symptoms, whereas the remaining 16 (13 female; median age, 21 years) were completely asymptomatic at diagnosis. All subjects tested positive for immunoglobulin A endomysial antibody and tissue transglutaminase antibody, except for 1 patient with immunoglobulin A deficiency; 95% of patients were carriers of HLA-DQ2. Duodenal biopsies from 26% patients had a Marsh score of 0, and 74% had a Marsh score of 1. A higher proportion of symptomatic patients had autoimmune disorders (36%) and antinuclear antibodies (41%) than asymptomatic patients (5% and 12.5%, respectively), and symptomatic patients were of older age at diagnosis ($P < .05$). Gluten withdrawal led to significant clinical improvement in all 61 symptomatic patients. The 16 asymptomatic patients continued on gluten-containing diets, and only 1 developed mucosal flattening; levels of anti-endomysial and tissue transglutaminase antibodies fluctuated in 5 of these patients or became undetectable.**

CONCLUSIONS: **In a 3-year study of adults with potential celiac disease, we found most to have symptoms, but these improved on gluten withdrawal. Conversely, we do not recommend a gluten-free diet for asymptomatic adults with potential celiac disease because they do not tend to develop villous atrophy.**

Keywords: EmA; tTGA; Autoimmunity; Wheat.

See editorial on page 694.

Celiac disease (CD) is an immune-mediated gluten-dependent systemic disorder characterized by a well-established serologic and genetic profile along with small intestinal damage.[1] In most cases the enteropathy displays the classic celiac hallmark, ie, villous atrophy consistent with active CD (ACD). However, an increasing number of patients show antibodies and genetic alleles as the only markers of the disease in the presence of a relatively normal or slightly inflamed non-atrophic small intestinal mucosa.[2] Potential CD (PCD) is the term coined for the non-atrophic variant of gluten-sensitive enteropathy,[3] which is characterized by serum endomysial (EmAs) and tissue transglutaminase antibodies (tTGAs) and a positive HLA-DQ2 and/or HLA-DQ8 genotype. EmAs are more specific than tTGAs because an isolated positivity for tTGA at low titer can be also found in conditions other than CD.[4,5] In patients with PCD the intestinal mucosa may present a normal histology (Marsh 0) or an increased number of intraepithelial lymphocytes (IELs) (Marsh 1).[2] Regardless of the status of the small intestinal mucosa, PCD patients can

Abbreviations used in this paper: **ACD, active celiac disease; ANA, antinuclear antibody; AU, arbitrary units; CD, celiac disease; EmA, endomysial antibody; GCD, gluten-containing diet; GFD, gluten-free diet; IBS, irritable bowel syndrome; IEL, intraepithelial lymphocyte; Ig, immunoglobulin; PCD, potential celiac disease; TG2, tranglutaminase 2; tTGA, tissue transglutaminase antibody.**

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display both gastrointestinal and extraintestinal symptoms or can be completely asymptomatic.[6]

Although diagnostic criteria are well-established, PCD is still a gray area with many unsettled issues. So far, few studies dealing with PCD in children and adults have been published, and conflicting results have been reported.[7–12] In children, more than 80% of PCD patients are asymptomatic, and the remaining symptomatic patients display intestinal manifestations (eg, malabsorption, chronic diarrhea, recurrent abdominal pain) more frequently than extraintestinal ones (anemia, raised transaminase levels, and short stature).[8,12] In contrast, the symptomatic phenotype was found to be prevalent in adults with more prominent extraintestinal symptoms.[7,10,11] It is unknown whether PCD patients kept on a gluten-containing diet (GCD) will develop an overt gluten-dependent enteropathy over time.[7–12] Therefore, the need for a gluten-free diet (GFD) remains questionable in these patients, although the scientific community is eager to suggest GFD for symptomatic PCD patients. Asymptomatic patients are usually left on a GCD, with a close clinical, serologic, and histologic follow-up.[7–12] Previous studies have reported a possible fluctuation of serologic markers over time in both pediatric and adult PCD patients left on a GCD, with variable progression to villous atrophy.[8,9,11–13]

On the basis of the controversial data regarding the natural history of PCD, the present study was designed to provide a prospective analysis of clinical, serologic, and histologic features of adult PCD. Moreover, asymptomatic PCD patients were followed up to establish the percentage of patients progressing to villous atrophy consistent with ACD.

Methods

Study Protocol

In this prospective cohort study 77 adult patients (59 female; median age, 33 years; range, 14–66 years) with PCD diagnosed at the Celiac Disease Center of Bologna University from 2004 to 2013 were investigated. The diagnosis of PCD relied on the positivity of serology (EmA and tTGA), HLA typing (DQ2 and/or DQ8), and normal or slightly inflamed small intestinal mucosa (lesions 0–1 according to the Marsh-Oberhüber classification). Total serum immunoglobulin (Ig)A was normal in all but 1 patient with selective IgA deficiency (serum IgA <5 mg/dL) who showed positivity for EmA and tTGA of IgG class. To determine the prevalence of PCD in the whole spectrum of CD, we calculated the total number of PCD and ACD patients diagnosed in our Center in the study period. CD cases diagnosed in other Centers and referred to our outpatient clinic were not enrolled.

PCD patients were subdivided into symptomatic and asymptomatic subgroups. Antibody prevalence with

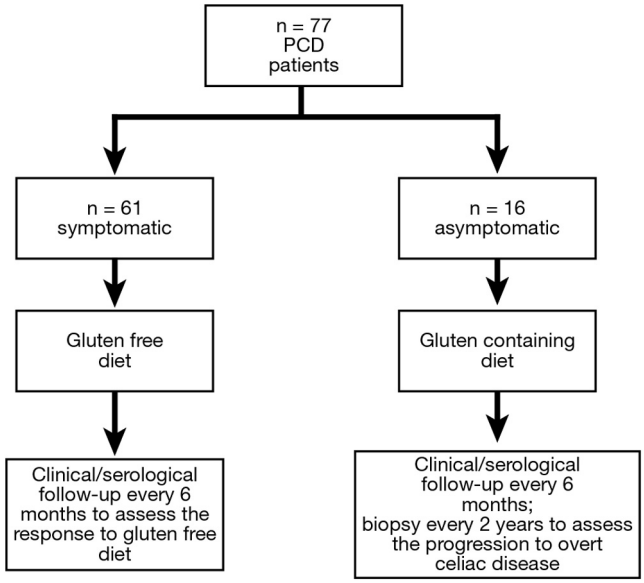

Figure 1. Management of 77 PCD patients enrolled in the study. Symptomatic PCD (n = 61) patients commenced a GFD, with clinical and serologic follow-up every 6 months to assess the response to GFD. Asymptomatic PCD (n = 16) patients were left on a GCD, with clinical and serologic follow-up every 6 months and histologic evaluation every 2 years to assess the progression to ACD.

relative titers/activities of EmA and tTGA, HLA-DQ2 and/or HLA-DQ8 genotype, duodenal histology, associated autoimmune disorders, and markers of autoimmunity (antinuclear antibodies [ANAs] detected by immunofluorescence on HEp-2 cells) as well as familiarity for CD were compared between symptomatic and asymptomatic PCD patients. PCD symptomatic patients were put on a GFD and underwent periodic follow-up to assess their clinical and serologic response to GFD. Patients without symptoms were left on a GCD and followed up every 6 months with a clinical and serologic assessment and every 2 years with histologic evaluation. A thorough dietary survey was performed at each control visit to verify that asymptomatic PCD patients were still on GCD. Also, the asymptomatic PCD patients decided to adhere to a GCD, and doctors checked that they actually continued to consume gluten in their diet. The follow-up of PCD patients lasted from 1 to 10 years (mean follow-up, 3 years) (Figure 1).

Endomysial and Tissue Transglutaminase Antibodies

Serum IgA EmAs were measured by indirect immunofluorescence on 5-μm-thick frozen sections of human umbilical cord. A fluorescein-conjugated anti-human IgA (Dako, Copenhagen, Denmark) was used as a secondary antibody. Immunolabeling was assessed by a thin fluorescent network around smooth muscle fibers in the wall of the umbilical artery and vein. Sera were tested at an initial dilution of 1:5 and, when positive, were titered up

to the end point. IgA tTGAs were assessed with an enzyme-linked immunosorbent assay kit, which was based on human recombinant tranglutaminase 2 (TG2) antigen (Eurospital, Trieste, Italy). A cutoff value of 16 arbitrary units (AU) was used. In the case of IgA deficiency, EmAs and tTGAs of the IgG class were detected.[5] All antibody tests were performed in our certified immunology laboratory.

HLA Typing

HLA typing was performed at the laboratory of Immunogenetics of the St Orsola-Malpighi Hospital. All 77 patients included in the present study were genotyped for HLA DQA1 and DQB1 alleles.[14] HLA-DQ2 and HLA-DQ8 positivities were based on DQB1*02 and DQA1*05 and DQB1*0302 findings, respectively.

Duodenal Biopsy

Six well-oriented duodenal biopsies (2 from the duodenal bulb and 4 from the distal duodenum) were taken during gastroduodenoscopy from all patients at the time of PCD diagnosis and during follow-up. Morphometric evaluation was performed by using a careful orientation of the biopsies. IELs were counted by using CD3 immunostaining and the worst average of the villous height/crypt depth ratio was also assessed. Biopsies were evaluated by 2 pathologists who were blinded to the clinical history of the patients and were graded according to Marsh-Oberhüber.[15]

Immunoglobulin A Anti-transglutaminase 2 Intestinal Deposits

In 20 of the 77 PCD cases, IgA anti-TG2 intestinal deposits were determined at PCD diagnosis on frozen small intestinal biopsies.[16]

Statistics

The 2-tailed Fisher exact test was used to compare the prevalence of antibodies, genetic markers, duodenal histology, and associated autoimmune disorders between symptomatic and asymptomatic PCD. The Mann-Whitney U test was used to evaluate statistically significant difference between symptomatic and asymptomatic PCD according to age of onset. The level of significance was set at $P < .05$.

Ethics

The study protocol (119/2012/U/Tess) was approved by the Institutional Review Board of St Orsola-Malpighi Hospital. All PCD and ACD patients signed an informed consent to enter the study.

Results

Prevalence and Clinical Features of Potential Celiac Disease

Of the 735 consecutively diagnosed CD patients, 77 (10.5%) fulfilled the diagnostic criteria for PCD, with an increasing prevalence of this clinical variant over years. PCD increased from 5% of the total number of CD diagnoses in 2004 to 18% in 2013. Both PCD and ACD were more frequent in the female than male gender (3.2 and 3.5, respectively), but PCD showed a slightly younger median age at diagnosis compared with ACD (33 vs 36 years). Fourteen of PCD patients (18%) were first-degree relatives of CD patients.

Of the 77 PCD patients, 61 (47 female; median age, 36 years) (79%) were symptomatic, whereas the remaining 16 (12 female; median age, 21 years) (21%) did not complain of any symptom. Asymptomatic PCD differed from symptomatic PCD with a significantly younger age at onset ($P < .05$) (Table 1). Among the 61 symptomatic cases, 10 (16%) had the classic phenotype characterized by diarrhea and weight loss, whereas the other 51 symptomatic PCD patients showed the non-classic phenotype characterized by the occurrence of iron deficiency anemia (more frequently than folic acid deficiency anemia), osteopenia, aphthous stomatitis, irritable bowel syndrome

Table 1. Comparison Between Symptomatic and Asymptomatic PCD

	Symptomatic PCD (61 cases)	Asymptomatic PCD (16 cases)	*P* value
Age at diagnosis, *y* (median, range)	36 (14–66)	21 (14–58)	<.05
Female gender	46 (75%)	13 (81%)	NS
EmA IgA	60 (98%)[a]	16 (100%)	NS
tTGA IgA	60 (98%)[a]	16 (100%)	NS
HLA			
DQ2	59 (95%)	15 (94%)	NS
DQ8	2 (5%)	1 (6%)	NS
Duodenal biopsy			
M0	15 (25%)	5 (31%)	NS
M1	46 (75%)	11 (69%)	NS
First-degree CD relatives	11 (18%)	3 (19%)	NS
Autoimmune disorders[b]	22 (36%)	1 (5%)	<.05
ANA (HEp-2)[c]	25 (41%)	2 (12.5%)	<.05

NOTE. EmA titer: mean, 1:20; range, 1:5–1:40; tTGA activities: mean, 1.5 × cutoff; range, 1.0–3.0 × cutoff.
Statistical analysis: Mann-Whitney *U* test, 2-tailed Fisher exact test.
[a]One symptomatic PCD with IgA deficiency positive for EmA and tTGA of IgG class.
[b]Autoimmune disorders including Hashimoto thyroiditis, alopecia areata, psoriasis, type 1 diabetes mellitus.
[c]ANA titer: mean, 1:160; range, 1:80–1:640; predominant speckled pattern.

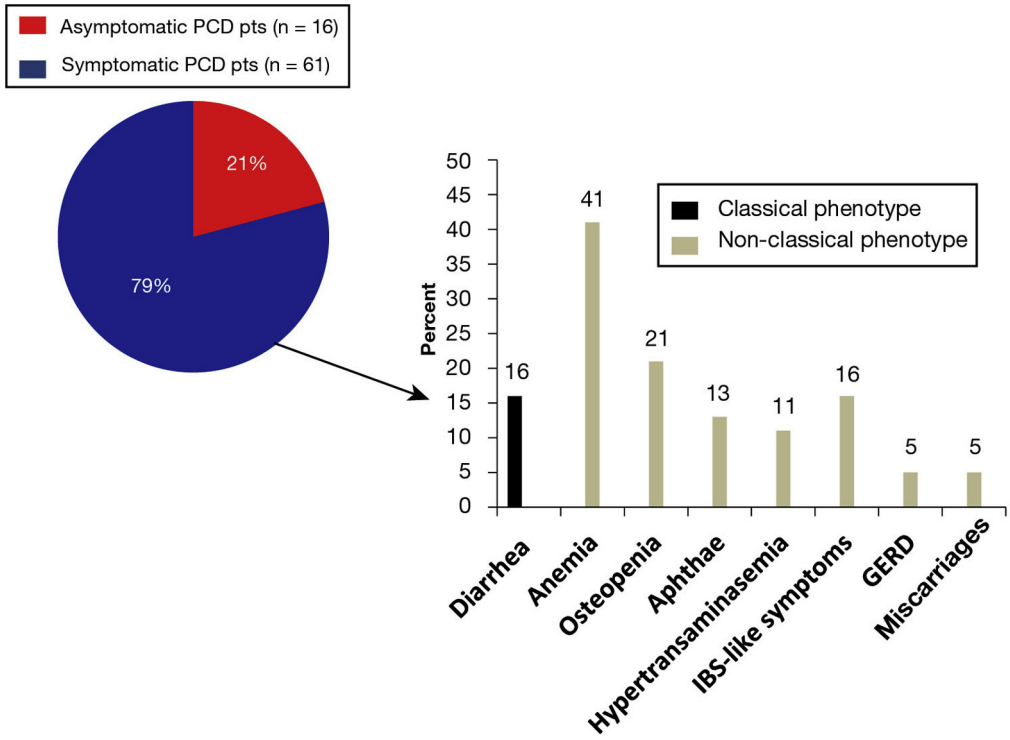

Figure 2. Clinical features of PCD. Sixty-one of 77 patients (79%) with PCD were symptomatic, whereas the remaining 16 (21%) were asymptomatic. Of the symptomatic patients, only 16% showed the classic phenotype (diarrhea and weight loss), whereas the majority (84%) had the non-classic phenotype characterized by anemia, osteopenia, aphthous stomatitis, hypertransaminasemia, IBS-like symptoms, gastroesophageal reflux disease (GERD), and recurrent miscarriages.

(IBS)-like symptoms, gastroesophageal reflux disease, and recurrent miscarriages (Figure 2).

Serology, Genetics, Duodenal Histology, Autoimmunity, and Celiac Disease Familiarity in Symptomatic and Asymptomatic Potential Celiac Disease

No significant difference was found between symptomatic and asymptomatic PCD patients for serology, genetics, duodenal histology, and CD familiarity (Table 1). EmA and tTGA of IgA class were positive in all PCD cases except from 1 symptomatic patient with IgA deficiency who was positive for EmA and tTGA of IgG class. EmA titers and enzyme-linked immunosorbent assay activities were both very low. Most of both symptomatic (95%) and asymptomatic (94%) PCD patients were HLA-DQ2+, with only 3 patients (2 symptomatic and 1 asymptomatic) being HLA-DQ8+. As for duodenal histology, symptomatic and asymptomatic PCD patients showed a higher prevalence of type 1 lesion (75% and 69%, respectively) vs type 0 (25% vs 31%, respectively). Eleven of the 61 PCD patients (18%) with symptoms and 3 of the 16 (19%) without symptoms had a first-degree relative with CD. Conversely, the prevalence of autoimmune disorders (ie, Hashimoto thyroiditis, alopecia, psoriasis, and type 1 diabetes mellitus) was significantly higher in symptomatic PCD (36%) than in asymptomatic PCD (5%) ($P < .05$). In addition, ANAs were more frequently detected in symptomatic than in asymptomatic PCD patients (41% vs 12.5%, $P < .05$).

Follow-up

Potential celiac disease patients put on a gluten-free diet. Sixty-one of the 77 adult PCD patients (79%) began a GFD because of symptoms (Figure 1). All the patients on GFD became negative for antibodies, showing a significant clinical improvement. After gluten withdrawal the 25 patients with low levels of ferritin, with or without folic acid deficiency, normalized hemoglobin and oligo-elements. Liver enzymes reverted to normal in 7 patients with hypertransaminasemia after 3–6 months of GFD. Three women with PCD and recurrent miscarriages improved dramatically and carried pregnancy to term after GFD. Patients with diarrhea and malabsorption (10 cases) showed a very good response to GFD as confirmed by a marked increase in body weight. Aphthous stomatitis disappeared very quickly after GFD. Despite a partial improvement, the symptoms that periodically recurred in PCD patients on a GFD were those related to IBS and gastroesophageal reflux disease. Overall, patients with symptomatic PCD experienced significant relief of their symptoms after GFD.

PCD patients left on a gluten-containing diet. Sixteen of the 77 PCD patients (21%) on a GCD remained asymptomatic. All of them were followed up from 1 to 10 years (mean 3-year follow-up). They received a clinical and serologic evaluation every 6 months, and in cases with fluctuating or permanent antibody positivity, duodenal biopsies were taken every 2 years (Figure 3). Only 1 of the 16 PCD patients on GCD became symptomatic after 2-year follow-up, developing iron deficiency anemia and diarrhea associated with significant increase in antibody titer (1:160 for EmA and >100 AU for tTGA). A small

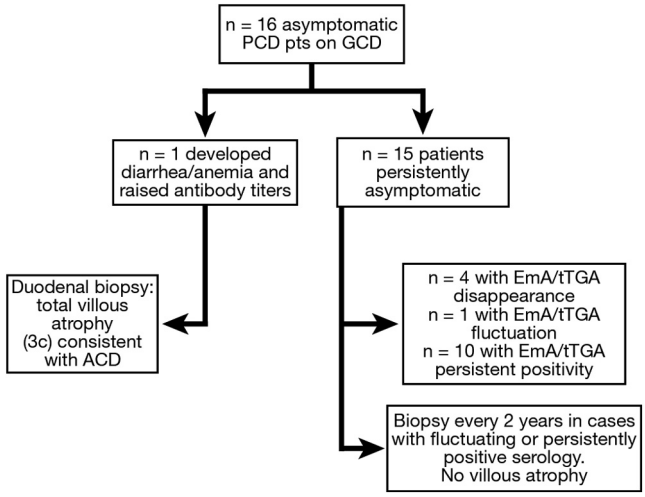

Figure 3. Follow-up of 16 cases with asymptomatic PCD left on a GCD (3-year mean follow-up). One patient developed symptoms and raised antibody titers, with duodenal biopsy confirming ACD. The remaining 15 patients remained asymptomatic; 4 of them had antibody disappearance, 1 showed antibody fluctuation, and 10 had stable antibody positivity. Repeated duodenal biopsies, performed every 2 years in cases with antibody persistence and fluctuation, did not reveal any progression to ACD.

intestinal biopsy showed subtotal villous atrophy, confirming that the patient (a 43-year-old woman) progressed to ACD. No CD-related symptoms were observed in the other 15 patients during follow-up. EmAs and tTGAs disappeared in 4 patients in the first 6 months. At diagnosis these 4 patients had very low EmA titer (1:5 or 1:10) as well as tTGA activities (<2 times the cutoff). Another PCD patient displayed a marked serologic fluctuation, ie, alternating antibody positivity (EmA, 1:40; tTGA, >2 times the cutoff) with negativization. In the remaining 10 PCD cases antibody titers/activities remained stable over time. EmA and tTGA variations in PCD patients on GCD during follow-up are reported in Figure 4. Small intestinal biopsy was repeated every 2 years in 10 of the 11 PCD patients with persistent or fluctuating antibody positivity (1 patient was not rebiopsied because of late enrollment in the study). No significant histologic changes were observed in the duodenal biopsies repeated during the follow-up.

IgA anti-TG2 intestinal deposits were tested in 20 of the 77 PCD cases, resulting as positive in 12 (60%). Six PCD cases positive for IgA anti-TG2 intestinal deposits were asymptomatic (Figure 5 and Supplementary Figure 1). None of them had developed villous atrophy at follow-up.

Discussion

The scant and conflicting information on adult PCD prompted us to plan this prospective cohort study that aimed to shed light on the natural history of this nosologic variant of CD and to determine the best approach for its management.[7,10,11,17]

The first evidence emerging from our study is that the diagnosis of PCD has significantly increased in recent years as a result of common CD antibody screening applied to the general population.[18] The number of patients diagnosed as having PCD is becoming sizeable, because this condition is currently estimated to represent about one-fifth of the total number of CD diagnoses. Although previous studies have shown that PCD in childhood is asymptomatic in about 80% of cases,[8,12] our study clearly highlights that the majority of adult PCD patients are predominantly symptomatic, showing both gastrointestinal and extraintestinal manifestations. Notably, the mean age of the few adult asymptomatic PCD patients was significantly lower than that observed in the larger group of symptomatic patients. Also, a significantly higher prevalence of associated autoimmune disorders and autoimmune markers (eg, ANA) was seen in symptomatic than in asymptomatic PCD patients. In contrast, serology, genetics, duodenal histology, and familiarity for CD did not differ in symptomatic and asymptomatic patients. EmA

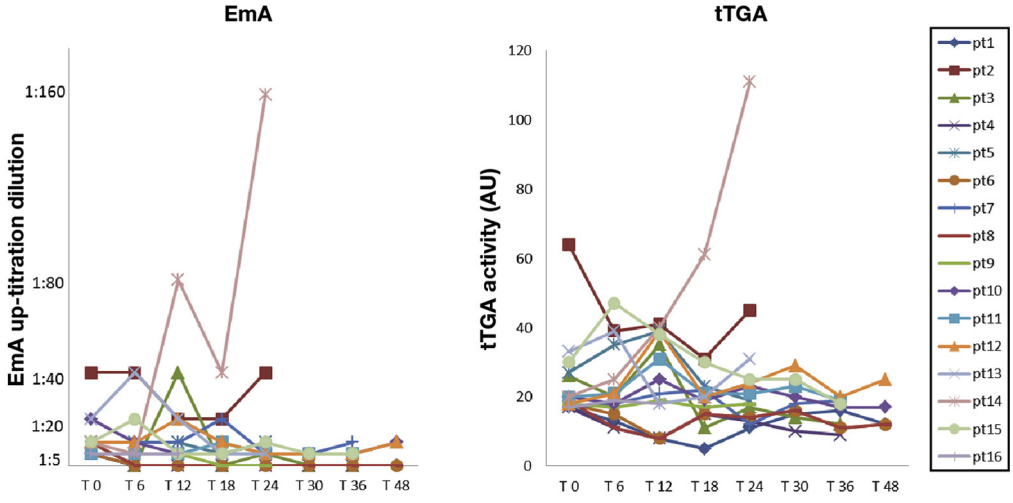

Figure 4. Variation of anti-EmA titer and anti-tTGA activity during mean follow-up of 3 years in 16 adults with PCD on GCD.

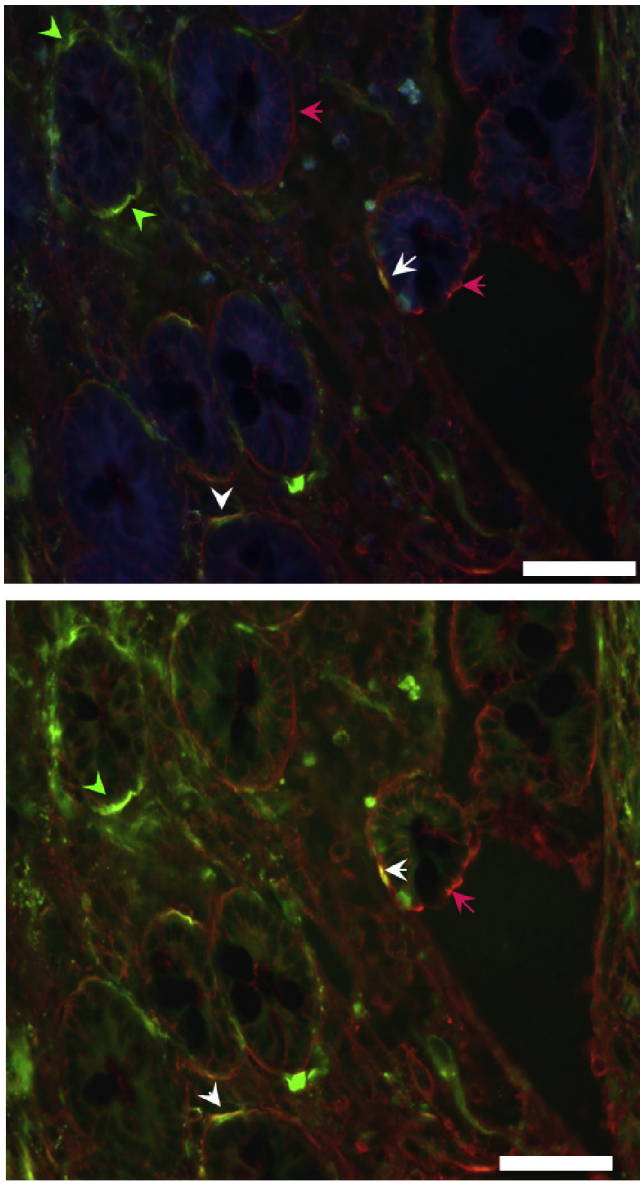

Figure 5. Representative photomicrographs illustrating IgA anti-TG2 intestinal deposits in 2 cases of asymptomatic PCD. Positivity of such deposits is indicated by *white arrows* in both pictures. *Green arrows* show the presence of TG2, and *red arrows* indicate positivity for IgA. Calibration bars = 50 μm.

and tTGA tested positive in PCD, although with lower titers/activities than in ACD.[6,19,20] There was no difference in terms of HLA-DQ2 and HLA-DQ8 genotype in PCD and ACD, suggesting that although these conditions are apparently distinct, they can be viewed as 2 variants of the same disease. From a histopathologic standpoint, the most common pattern of PCD was characterized by an increased number of IELs (Marsh 1) prevailing over normal mucosa (Marsh 0) in both symptomatic and asymptomatic PCD patients. In our series, the increased IELs were not an indicator of progression of PCD to ACD. Finally, familiarity for CD was a remarkable feature commonly identified in our cases of PCD, confirming previous data.[21] However, our data did not show any difference between symptomatic and asymptomatic patients in terms of familiarity for CD, which is apparently in contrast to the well-known lack of symptoms in familial cases of CD.[9] Further studies will be necessary to elucidate the high prevalence of symptomatic familial cases in PCD.

An open issue in the management of PCD pertains to the presence of symptoms that can be considered as indicators for prescribing GFD, regardless of the absence of severe small intestinal damage. Although no established guidelines are so far available, recent data suggest that a subset of symptomatic pediatric and adult PCD patients can benefit from GFD.[7,12] In recent studies, the percentage of children with symptomatic PCD showing significant clinical improvement after GFD was quite high, ranging from 55% (11/20 cases) to 91% (32/35 cases).[8,12] In adults with symptomatic PCD, a positive response to GFD has been reported in all cases,[7] although another study showed the spontaneous disappearance of symptoms on a GCD.[11] In the study by Kurppa et al,[7] clinical manifestations showed significant improvement in all PCD patients after 1 year of GFD. Notably, the group of PCD patients (n = 10) left on GCD experienced a dramatic worsening of the clinical manifestations. The results emerging from our study demonstrating that gluten withdrawal leads to a significant improvement of both intestinal and extraintestinal manifestations in all symptomatic patients clearly expand our previous understanding of this issue and support the concept that GFD should be prescribed to adult symptomatic PCD patients. Again, in line with Kurppa et al,[7] GFD normalized gynecologic disorders, because women with recurrent miscarriages were able to carry pregnancies to term.

A great dilemma facing the scientific community is whether and to what extent adult asymptomatic PCD may evolve to ACD. On the basis of pediatric literature data, the majority of asymptomatic PCD cases developed neither symptoms nor villous atrophy during long-term follow-up.[8,9,12] In 3-year, 6-year, and 9-year follow-up, the progression from PCD to ACD in children was observed in 14%, 27%, and 33% of 175 asymptomatic cases, respectively.[12] Male gender, slight mucosal inflammation at onset, and a particular genetic profile identified a subgroup of patients prone to develop severe intestinal damage over time. Compared with the previous study, the percentage of patients evolving from PCD to ACD in a family study was much lower (5%).[9] Using caution before commencing a GFD in asymptomatic children is supported by the spontaneous negativization or fluctuation of serologic markers on a GCD. In a 2-year follow-up of asymptomatic infants born to CD parents, EmA and tTGA disappeared spontaneously in 18 (86%) and fluctuated in 2 (9%) out of 21 PCD patients on a GCD.[9] Two other studies demonstrated the disappearance of antibodies in 15%–20% of cases and fluctuation in 33%–37% during a mean 3-year follow-up.[8,12] Moreover, the majority of pediatric patients with stable antibody positivity did not develop severe mucosal damage in a long-term (up to 9 years) follow-

up.[12] However, studies on adult PCD patients on a GCD are scant, limited by short follow-up periods, and indiscriminately include symptomatic and asymptomatic patients, making data difficult to interpret. In 1 study that was based on a small sample size (24 cases) and a very short follow-up (20 months) only one-fifth of PCD cases showed a progression to villous atrophy.[11] In a more recent study on 57 PCD cases followed up for 12 months, only 7% progressed to ACD despite the persistence of serologic tests in 80% of cases.[17] Our data, which are based on a prospective design and considerable follow-up (up to 10 years), showed that only 1 of 16 adults (6%) with asymptomatic PCD on a GCD developed villous atrophy. Clearly, a higher number of asymptomatic PCD patients will be required to confirm the low progression of PCD to ACD. Antibody markers disappeared or fluctuated in 5 of 16 (31.5%) asymptomatic PCD patients, a figure overlapping the results reported in children by Auricchio et al.[12] In the 4 cases with antibody negativization, both EmAs and tTGAs (positive at a very low titer at onset) disappeared in the first 6 months of follow-up. Finally, previous data raised the hypothesis that the positivity for IgA anti-TG2 deposits in the small intestinal biopsies may be a useful indicator predicting villous atrophy in children with PCD.[8] However, these findings were not confirmed in our study because none of our cases with positive IgA anti-TG2 intestinal deposits at onset progressed to ACD in the follow-up. However, our findings were based on a small sample size, and further research is expected to shed light on the relevance of IgA anti-TG2 deposits for ACD progression.

In conclusion, the present study provides novel knowledge on the very debated topic of PCD. First, we clearly demonstrated that GFD is highly recommendable for adult symptomatic PCD patients because gluten withdrawal is associated with a significant improvement of intestinal and extraintestinal symptoms/manifestations. Second, asymptomatic patients should continue a GCD although under strict surveillance, ie, clinical, serologic, and histologic follow-up. Third, our study highlights that only a small proportion of asymptomatic adult PCD patients progresses to ACD over time. Thus, our study expands our understanding of PCD to adult patients and paves the way to research for those cases that are prone to develop overt CD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.10.024.

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Conflicts of interest
The authors disclose no conflicts.

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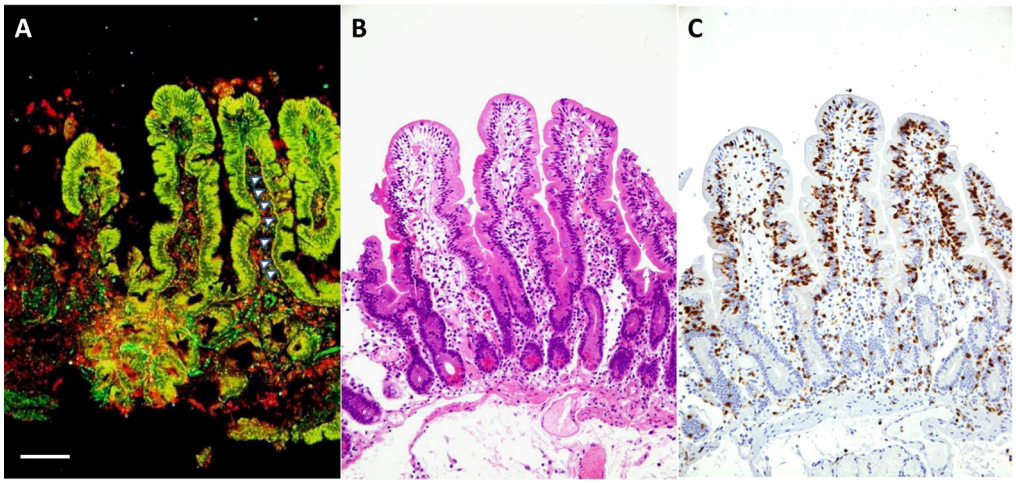

Supplementary Figure 1. Other representative photomicrographs illustrating IgA anti-TG2 intestinal deposits (*A*, *arrowheads*), side-by-side with histologic (*B*) and immunohistochemical (*C*) findings of a patient with PCD. Note the dense CD3 immunostaining indicating an abundant lymphocytic infiltrate and increased IELs. Calibration bar for *A*–*C* = 25 μm.