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Palmoplantar pustulosis and gluten sensitivity: a study of serum antibodies against gliadin and tissue transglutaminase, the duodenal mucosa and effects of gluten-free diet

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None declared.

Summary

Background Palmoplantar pustulosis (PPP) is a chronic inflammatory disease affecting mainly smoking women. Some patients also have psoriasis. A subgroup of patients with psoriasis has been shown to have silent gluten sensitivity with relevance for their psoriasis. Nothing is known about gluten sensitivity in PPP.
Objectives To find out whether any patients with PPP are gluten-sensitive and whether this might be relevant for the PPP activity.
Patients and methods One hundred and twenty-three patients (113 women) with PPP participated. Screening for IgA antibodies against gliadin and tissue transglutaminase (tTG) was performed, the duodenal mucosa in patients with and without these antibodies was studied and the effect of a gluten-free diet (GFD) was followed up.
Results Twenty-two patients (18%) had IgA antibodies against gliadin and nine of 94 (10%) against tTG. Twelve patients with antibodies and 11 without underwent gastro-duodenoscopy. Four displayed villous atrophy, whereas all other specimens were judged as essentially normal at routine staining. However, with immunohistochemistry, the numbers of CD3+ and CD8+ lymphocytes in the epithelium were found to be increased in patients with any type of antibody, although they were most numerous in those with both types of antibodies. Seven of 123 patients (6%) had coeliac disease (three previously diagnosed). Patients with antibodies who adhered to the GFD displayed total or nearly total clearance of the skin lesions and normalization of the antibody levels.
Conclusions Patients with PPP should be screened for antibodies against gliadin and tTG. Those with antibodies can be much improved on a GFD regardless of the degree of mucosal abnormalities.

Palmoplantar pustulosis (PPP) is a chronic and intensely inflammatory disease with pustules, erythema and scaling localized to the palms and soles. Ninety per cent of the patients are women and 95% are smokers at the onset of the disease.[1] Cessation of smoking can improve PPP,[2] although some patients do not seem to respond and total clearance is not achieved. PPP has been considered to be a variant of psoriasis and about 18% of the patients also have psoriasis lesions of the vulgaris type. However, PPP has genetic characteristics different from those of psoriasis vulgaris.[3]

PPP is often treatment-resistant and about 30% of patients have long periods of sick-leave or have a disability pension because of their PPP, which is often associated with one or several other disorders.[1] The lack of regimens with good clinical effects in PPP, as well as the diversity of evaluation models, were recently addressed in a review by Marsland *et al.*[4]

The target for the inflammation in PPP is the palmoplantar eccrine sweat duct, where neutrophil and also eosinophil granulocytes migrate outwards to form a pustule in the lowest part of the stratum corneum.[5,6] In the papillary dermis below the pustule there is a dense infiltration of CD4+ lymphocytes and mast cells.[5] There is also evidence that the papillary endothelium is involved, as 47% of PPP sera added to palmar skin sections from healthy women displayed a reactivity with the endothelium when screened with immunofluorescence.[7] If the normal palmar skin is taken from a smoker, PPP sera also react with the acrosyringium, where nicotine has been shown to be excreted,[8] which indicates that smoking can upregulate the reactivity.[7]

It has long been known that among patients with PPP there is an increased prevalence of autoimmune thyroid disease. Recently we have also found a high prevalence of abnormal calcium homeostasis[1] as well as of diabetes type 2 in patients with PPP. Thus, PPP is associated with autoimmune co-morbidity, but it is not yet known whether the skin disorder and the co-existing diseases have a pathogenetic background in common.

Coeliac disease is also an autoimmune disorder and involves production of IgA antibodies against gliadin, endomysium and tissue transglutaminase (ETG). In our first study of PPP[5] we observed a few patients with concomitant coeliac disease in whom the PPP improved when the patients adhered strictly to a gluten-free diet (GFD). The importance of this finding is not fully understood. We have therefore screened a large group of patients with PPP for the presence of serum antibodies against gliadin and tTG, performed gastro-duodenoscopy with duodenal biopsies in patients with and without such serology, and followed up the patients during a long period on a GFD.

Patients and methods

Patients

Consecutive patients with PPP (113 women and 10 men, mean age ± SD at the time of the examination 53 ± 11 years and mean age at the start of PPP 44 ± 13 years) referred to the outpatient Department of Dermatology at the University Hospital, Uppsala, Sweden, participated in the study. The project was approved by the local Ethics Committee and all patients gave their informed consent. All patients answered a questionnaire concerning their medical history and medication, smoking habits, sick-leave and disability pension.

All patients were examined by the same dermatologist (G.M.). The severity of the PPP varied. Both yellow and old brown pustules were counted, the degree of erythema and scaling was graded 0–3 and the involved area was marked on a template. Some patients had 50–100 yellow pustules and erythema and scaling involving the whole plantar surface as well as the palms, whereas others had only a few pustules and mild erythema and scaling. The PPP was also recorded as mild, moderate or severe. Mild PPP was defined as the presence of only 1–3 yellow pustules, grade 1 erythema and desquamation (on a scale of 1–3), and < 10% involvement of the palms/soles. The PPP was considered moderate if there were 3–20 pustules, the erythema and desquamation graded as 2, and < 30% of the palms and soles was involved. Severe PPP was defined as > 20 pustules, grade 3 erythema, desquamation, involvement of ≥ 30% of the area.

All patients were asked if they had any of a number of gastrointestinal symptoms such as nausea, vomiting, abdominal distension, pain, flatulence or diarrhoea. Body mass index (BMI) was calculated as weight (in kg)/[height (in m)].[2] Some anamnestic and clinical data are presented in Table 1.

Table 1 Some data on the medical history and clinical and laboratory variables of 123 patients with palmoplantar pustulosis (PPP)

Variables	n (%)
History of/or concomitant disease	
Psoriasis vulgaris	30 (24)
Arthritis (two with rheumatoid arthritis)	10 (8)
Hyperthyroidism	4 (3)
Hypothyroidism	10 (8)
Coeliac disease (diagnosed before first visit for PPP)	3 (2)
Crohn disease	0 (0)
Ulcerative proctitis	3 (2)
Diabetes type 1	3 (2)
Diabetes type 2	10 (8)
Pernicious anaemia	4 (3)
Dermatitis herpetiformis	1 (1)
Vitiligo	2 (2)
Chronic candidiasis	1 (1)
Sweet syndrome	1 (1)
Hypertension/cardiovascular disease	26 (21)
Psychiatric disease [manic-depressive disease (1), schizophrenia (1), depression (18)]	20 (16)
Sick-leave/disability pension	54 (44)
Smoking habits	
Never	8 (6)
Former	17 (14)
Current	98 (80)
Gastrointestinal symptoms	40 (33)
Body mass index, all patients, mean (range)	26·5 ± 4·3 (17·5–41)
Screening results	
IgG antibodies against thyroglobulin and/or thyroperoxidase (n = 110)	23 (21)
IgA antibodies against gliadin	22 (18)
IgG antibodies against gliadin	3 (2)
IgA antibodies against tissue transglutaminase (n = 94)	9 (9·6)
Medication	
Levothyroxine	11 (9)
Insulin	4 (3)
Beta-blockers (4), angiotensin II antagonists (4), calcium-channel blockers (5), hydrochlorothiazide (3)	16 (13)
Glibenclamide, metformin	8 (7)
Antidepressives	8 (7)

Blood samples

Blood samples were obtained from all 123 patients for screening for antibodies against IgA and IgG gliadin (IgA AGA and IgG AGA, respectively)[9] and from 94 patients for screening for IgA antibodies against tTG (normal, < 6 U L^{-1}). In addition to routine blood examination in all patients, we also measured antibodies against thyroglobulin and thyroperoxidase, IgG, IgA and IgM, thyroid-stimulating hormone, thyroxine, folic acid and cobalamine in serum.

Gastroscopy–duodenoscopy with biopsies of the duodenal mucosa

Patients who gave informed consent and had elevated levels of antibodies against gliadin and/or tTG were referred to a gastroenterologist (G.K.). Patients with PPP with no serological findings indicating gluten sensitivity, who were undergoing gastroscopy for other medical reasons, also consented to having an extra biopsy taken for immunohistochemistry. Five mucosal biopsy specimens were taken from the duodenum distal to the papilla of Vater in conjunction with upper gastrointestinal endoscopy. One of the specimens was snap-frozen in chilled isopentane and stored at −70 °C, and the others were fixed in 4% formaldehyde and paraffin-embedded separately.

Processing of the specimens

Sections from each of the paraffin-embedded specimens from the duodenal mucosa were stained with haematoxylin and eosin and Alcian Blue–periodic acid-Schiff and examined at the Department of Pathology with regard to the villous architecture and to inflammatory cells in the epithelium and lamina propria. Frozen sections were used for visualization of CD3+, CD8+ and CD4+ T lymphocytes in the duodenal mucosa as previously described.[10]

Microscopy

The results of the immunohistochemical examinations of the duodenal specimens were analysed on coded slides with a Leica Q Win computerized image system with a digital camera, DC 200 (Leica Microscopy and Scientific Instruments Group, CH-9435 Heerbrugg, Switzerland). The numbers of CD3+ and CD8+ T lymphocytes per millimetre epithelium were determined and the percentage of CD3+ and CD4+ areas in the lamina propria in the villi were analysed as previously reported.[10] The lamina propria in the villi was chosen for estimation of the CD4 lymphocyte infiltration because the area measured can be defined more easily there than in the lower parts of the lamina propria. Usually the CD4 staining was estimated in ten fields and only villi cut longitudinally were chosen for evaluation.

Expression of tTG in palmar skin from a healthy woman and from involved palmar skin in a patient with PPP was studied as previously described in nonhairy skin and in lesional psoriasis.[11]

Gluten-free diet

Patients with antibodies against gliadin and/or tTG were asked to adhere to a GFD for at least 6 months regardless of the results of the duodenal biopsies, and were followed up for at least 2 years. Three patients without such antibodies also consented to adhere to a GFD. Before starting the GFD all patients received detailed information from a dietician.

Statistics

The degree of significance was tested with the nonparametric Mann–Whitney U-test for unpaired two-group comparison.

Results

Anamnestic and clinical data

As is evident from Table 1 psoriasis (indistinguishable from the vulgaris type), arthritis, thyroid disease, diabetes type 2, hypertension/cardiovascular disease and depression were common disorders among the patients with PPP, as was long sick-leave and disability pension. Twenty-six patients had one or several autoimmune disorders. Never-smokers had mild PPP. Thirty patients had severe PPP.

Three patients had coeliac disease that had been diagnosed previously; in one it was combined with dermatitis herpetiformis. One of these patients adhered strictly to a GFD and had only barely visible and transient PPP during a period of severe mental stress. The other two did not adhere strictly to such a diet and the severity of their PPP did not change during a 10-year period.

In answer to questions about gastrointestinal symptoms, 40 patients stated that they had some symptom, but patients who had antibodies against gliadin or tTG did not report more symptoms than those without. The mean BMI was similar in those with and without these antibodies.

Three patients had a history of proctitis and one of them was found to have high levels of AGA and tTG antibodies and partial villous atrophy.

Screening results

Twenty-two patients (17·9%) had elevated levels of IgA AGA (≥ 51 U L^{-1}) (Table 1) and three with IgA AGA also had raised IgG AGA, but none had isolated IgG AGA. Usually the IgA AGA values were only slightly elevated (51–100 U L^{-1}).

Increased levels of tTG antibodies were found in nine of 94 sera (9·6%) (Table 1). Serum from our first patient with subtotal villous atrophy was AGA-positive, but no serum for analysis of tTG antibodies was available. Six of nine tTG-positive sera were AGA-positive. As found in our first study on PPP,[5] serum-IgA was elevated compared with that in blood donors. Women with PPP had a serum-IgA level (mean ± SD) of 2·8 ± 1·6 g L^{-1}, compared with 2·1 ± 0·7 g L^{-1} in controls ($P < 0{\cdot}0001$). The highest value was noted in those with AGA and/or tTG antibodies, namely 3·1 ± 1·9 g L^{-1} ($n = 19$), but the difference between those with and without these antibodies was not significant.

Duodenal biopsies

In addition to the three patients with previously known gluten intolerance and villous atrophy mentioned above, 12 patients with IgA AGA and/or tTG antibodies had undergone gastro-

duodenoscopy. (One patient with tTG = 7 U L^{-1} was not examined.) Another 11 patients, all without these antibodies, were included for comparison; five had arthritis in addition to PPP and six were investigated for other medical reasons. Frozen biopsy specimens for immunohistochemistry were available from 18 patients and routine biopsy results from all.

Routine staining of paraffin-embedded specimens from 12 patients with AGA and/or tTG antibodies revealed total villous atrophy in one, subtotal villous atrophy in two and partial atrophy in one patient. Three of these four patients were not aware of any gastrointestinal symptoms, whereas one had a history of proctitis. (Frozen specimens were available from two of these four patients.)

Specimens from five other patients with AGA and/or tTG antibodies displayed a focal increase in intraepithelial lymphocytes and an increased number of inflammatory cells in the lamina propria, but were considered as essentially normal; specimens from two AGA-positive patients and one tTG-positive but AGA-negative patient were judged by the pathologists to be normal.

The specimens from the 11 remaining patients with PPP who were all AGA- and tTG-negative were evaluated as normal at routine staining.

Immunohistochemistry

Table 2 shows the results of the CD3, CD8 and CD4 staining of the frozen duodenal biopsy specimens. Figure 1 shows the individual values for CD3+ and CD8+ lymphocytes in the epithelium in patients (without arthritis) with no antibodies and those with antibodies only against tTG or gliadin and those with both these antibodies. The largest mean number of intraepithelial CD3+ lymphocytes ($P = 0{\cdot}0527$ vs. those with only AGA or tTG antibodies) and the largest percentage area of CD4+ lymphocytes in the villi ($P = 0{\cdot}0527$) were found in patients who had both AGA and tTG antibodies and the lowest number of intraepithelial lymphocytes in those with no AGA or tTG antibodies and no arthritis. The number of CD3+ cells in the epithelium was significantly higher in specimens from AGA- and/or tTG-positive patients ($n = 10$) than in those from AGA/tTG-negative patients ($n = 3$) ($P < 0{\cdot}05$).

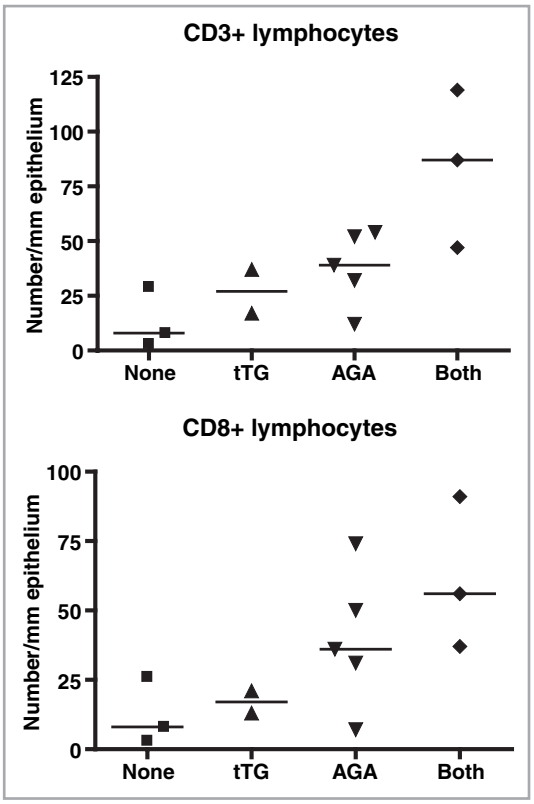

Fig 1. Individual numbers of CD3+ and CD8+ lymphocytes per millimetre epithelium in the duodenal mucosa in patients with palmoplantar pustulosis (PPP) with no antibodies against gliadin or tTG (none), antibodies only against tTG (tTG), only against gliadin (AGA) and against both tTG and gliadin (both). Data from patients with arthritis not included.

Table 2 PPP, CD3+ and CD8+ T lymphocytes in the duodenal epithelium (mean ± SD) and CD3+ and CD4+ T lymphocytes in the lamina propria of the villi (mean % stained area ± SD)

	n	CD3+ cells per mm epithelium	CD8+ cells per mm epithelium	CD3+ area in villi (%)	CD4+ area in villi (%)	Comments
PPP with tTG and AGA	3	84 ± 36	61 ± 27	15 ± 11	14 ± 2	Two with villous atrophy
PPP with tTG, no AGA	2	27 ± 14	17 ± 6	4 ± 0·8	7 ± 6	
PPP with AGA, no tTG	5	38 ± 18	39 ± 25	6 ± 4	6 ± 3	
PPP without AGA, no tTG, no arthritis	3	13 ± 14[a]	12 ± 12	9 ± 5	9 ± 8	
PPP + arthritis, no AGA, no tTG	5	26 ± 19	16 ± 12	11 ± 13	8 ± 7	
PPP all without AGA and tTG	8	21 ± 18[b]	15 ± 11[c]	10 ± 11	8 ± 7	

For comparison: corresponding results in psoriasis vulgaris without antibodies against gliadin ($n = 7$): CD3+ cells 9 ± 5, CD8+ cells 9 ± 7 per mm epithelium and CD4+ area in villi (%) 3 ± 1.[10] PPP, palmoplantar pustulosis; AGA, IgA antibodies against gliadin; tTG, IgA antibodies against tissue transglutaminase. [a]$P = 0{\cdot}0280$ compared with AGA- and/or tTG-positive; [b]$P = 0{\cdot}0263$ compared with all AGA- and/or tTG-positive; [c]$P = 0{\cdot}0129$ compared with all AGA- and/or tTG-positive.

Patients with concomitant arthritis but no AGA and/or tTG antibodies showed an increased number of epithelial CD3+ cells, but the difference from the three AGA-negative patients without arthritis was not significant.

Expression of tissue transglutaminase in palmar skin

Figure 2 shows the expression of tTG in normal palmar skin and in lesional PPP skin from a patient with no AGA or tTG antibodies. A double staining (not shown in Fig. 2) with anti-tTG antibody and CD31 showed that tTG was present mainly in the endothelium, which was highly increased in the inflamed skin.

Effects of a gluten-free diet on the severity of the palmoplantar pustulosis

Table 3 shows the severity of the PPP before and during a GFD and also some anamnestic and clinical data. In all patients with raised AGA and/or tTG antibodies who adhered to the GFD the PPP cleared or greatly improved. The elevated AGA and tTG values became normalized in those who adhered to the diet. On the other hand those who did not adhere to the diet did not improve and the AGA and tTG levels remained elevated. Improvement was not related to the degree of mucosal changes. Thus it occurred both in patients with villous atrophy and in those with a minor lymphocyte increase.

In two of the patients there was an isolated moderate increase in tTG antibodies. One of them with disabling PPP showed no evidence of increased lymphocytes in the duodenal mucosa and the other with PPP associated with long periods of sick-leave had a mild increase. Both have had a remarkable improvement on GFD and have had no sick-leave since the start of the GFD.

Improvement was usually slow. It occurred in a shorter time—within a few months—in patients with PPP of moderate severity than in those with long-standing severe PPP, in whom the improvement continued for several years.

As shown in Table 3, the clearance has persisted for years. Our first patient with disabling PPP and diagnosed with coeliac disease who showed total clearance during a period of 10 years on GFD had a recurrence with moderate PPP after the death of several family members. In contrast to the other patients, three patients with severe PPP without AGA or tTG antibodies adhered to GFD for more than 1 year without any improvement.

Discussion

In this study we have shown that a large subgroup of PPP patients have IgA antibodies against gliadin and/or tTG despite absence of gastrointestinal symptoms, that the duodenal mucosal specimens in these patients display a spectrum from total villous atrophy to normal mucosa, and that most of the antibody-positive patients who adhere to a GFD displayed almost total or total clearance of their PPP.

We have previously reported that among patients with psoriasis vulgaris (PsoV)[9] and psoriatic arthritis (PsoA)[12] there is an increased prevalence of IgA AGA. In this study IgA AGA was found in a slightly higher proportion of the patients with PPP than in the other two psoriasis groups and was present both in patients with and those without PsoV lesions.

In contrast to patients with PsoV and PsoA, the patients with PPP had a high prevalence of IgA antibodies against tTG, these being found in nine of 94 patients (9·6%), all women. Recently Metzger *et al.*[13] reported from a population-based survey that 0·83% of women had raised levels of tTG antibodies. It is noteworthy that three of 94 (3%) showed an isolated increase in tTG antibodies. The proportion of patients with tTG antibodies among those with AGA (six of 22, 27·2%) was much higher than among PsoV patients with AGA, where we found only 4·1% with tTG antibodies, and in

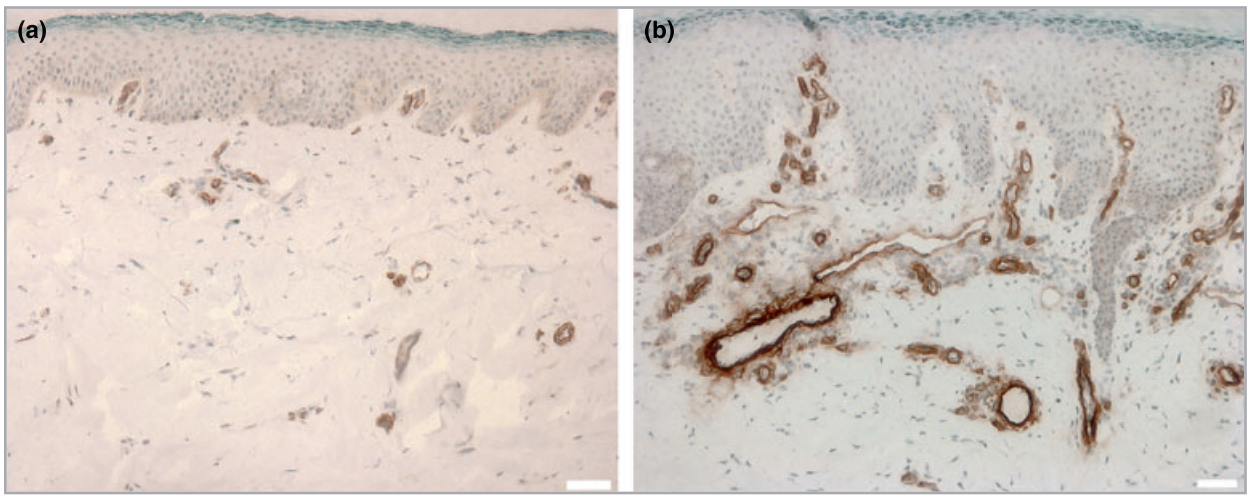

Fig 2. Expression of tissue transglutaminase (tTG) in (a) palmar skin from a healthy woman and (b) lesional skin from a patient with palmoplantar pustulosis with no AGA or tTG antibodies. Scale bars = 50 μm.

Table 3 Palmoplantar pustulosis (PPP) and effects of gluten-free diet (GFD)

Patient	AGA/tTG	Duodenal mucosa	PPP years	PPP severity before/on GFD	Adhered to GFD	AGA/tTG during GFD	Follow-up on GFD	Comments
1	AGA	Subtotal villous atrophy	9	Severe/cleared	Yes	Normal	16 years	Cleared in 10 years; smoker; recurrence moderate PPP after death of family members
2	AGA, tTG	Subtotal villous atrophy	30	Moderate/cleared	Yes	Normal	2 years	Also psoriasis, cleared, slight worsening after serious illness in family; smoker
3	AGA, tTG	Total villous atrophy	3	Moderate/cleared	Yes	Normal	4 years	Also rheumatoid arthritis; smoker
4	AGA, tTG	Partial villous atrophy	9	Moderate/cleared	Yes	Normal	5 years	Former smoker
5	No AGA, but tTG	Slight increase in IEL (CD3, CD8)	13	Moderate/cleared	Yes	Normal	4 years	Previously long sick-leaves, none on GFD; smoker
6	No AGA but tTG	Normal	4	Severe/mild	Yes	Normal	3 years	Elevated serum lipids; smoker
7	AGA, not tTG	Normal	35	Moderate/cleared	Yes	Normal	2 years	Resumed normal diet, mild recurrence after 3 months; smoker
8	AGA, not tTG	Increased IEL (CD3, CD8)	14	Moderate/cleared	Yes	Normal	6 years	Never-smoker
9	AGA, not tTG	Increased IEL (CD3, CD8)	4	Moderate/cleared	Yes	Normal	5 years	Mild psoriasis, cleared; heavy smoker
10	AGA, tTG	Subtotal villous atrophy	32	Severe/severe	Not strict	Elevated	10 years	Also diabetes type 1; former smoker
11	AGA not tTG	Partial villous atrophy	34	Moderate/moderate	Not strict	Elevated	10 years	Also diabetes type 1, dermatitis herpetiformis, dapsone; smoker
12	AGA, tTG	Increased IEL, some villi broadened	13	Severe/moderate	Not strict	Elevated	8 years	High levels of antibodies against thyroperoxidase; smoker
13	AGA no tTG	Slight increase in IEL, some villi broadened	16	Severe/moderate	Not strict	Elevated	8 years	Heavy smoker
14	No AGA, no tTG	Increased IEL (CD3, CD8)	6	Moderate/moderate	Yes	Normal	1 year	Also arthritis; former smoker
15	No AGA, no tTG	Increased IEL (CD3, CD8)	6	Severe/severe	Yes	Normal	1 year	Also arthritis; former smoker
16	No AGA, no tTG	Normal	12	Severe/severe	Yes	Normal	1 year	Former smoker

AGA, IgA antibodies against gliadin; tTG, IgA antibodies against tissue transglutaminase; IEL, intraepithelial lymphocytes; PPP years, duration of PPP before GFD

the PsoA group none of the AGA-positive patients had tTG antibodies.[13]

Seven patients with PPP had coeliac disease (four identified within the study) with total, subtotal or partial villous atrophy (5·7%), compared with 0·27% among Swedish blood donors.[14] Apart from the specimens from these patients, only nonspecific inflammation or no abnormalities at all were observed by the pathologists in routinely stained specimens from patients with antibodies. The moderate to mild increase in lymphocytes observed with immunohistochemistry was thus usually not obvious in the routinely stained specimens and is a nonspecific finding that will require further studies.

The largest number of lymphocytes both in the epithelium and in the lamina propria in the duodenal specimens was found in patients with both IgA AGA and tTG antibodies and villous atrophy, whereas patients with only one of these antibodies showed a modest increase in intraepithelial lymphocytes, and those without these antibodies had a normal number of lymphocytes. These findings indicate a link between the presence of antibodies and the lymphocyte increase.

However, as shown in Table 2, an increase in lymphocytes can be present in AGA/tTG-negative PPP patients who also have arthritis, as we recently reported in patients with PsoA without AGA.[10]

Patients with AGA or antibodies against tTG or both were asked to try to adhere strictly to a GFD regardless of the results of the duodenal examination. The outcome was very

good in those who adhered to the diet, with almost total or total clearance of the PPP during the years of follow-up, and normalization of the levels of antibodies against gliadin and tTG. In contrast, those who did not adhere to the diet neither improved nor showed normalization of their antibodies, which indicates that the reactivity against tTG and gliadin might be a pathogenetic factor in this group of patients with PPP. The role of these antibodies is also illustrated by the lack of effect of the diet in those without antibodies.

AGA has low specificity and sensitivity as a marker of villous atrophy (coeliac disease).[15] However, it was found in this study that AGA was associated with an increased number of lymphocytes in the duodenal epithelium and improvement of PPP during a GFD. These results indicate that AGA may be a useful marker for the presence of a discrete lymphocyte increase in the mucosa, which has relevance for the PPP activity. However, both the mucosa and the skin lesions need to be studied further, for example with regard to activated lymphocytes and transglutaminase reactivity *in situ* as reported from the studies of gluten-sensitive cerebellar ataxia.[16]

The mechanisms for the effect of GFD in patients with PPP with AGA and/or tTG antibodies are unknown. tTG is a multifunctional enzyme that has several roles in coeliac disease.[17] tTG has a widespread distribution. In the skin it is expressed in the endothelium, in particular in proliferating endothelium, and in the basal layer of the epidermis and in the jejunum there is subepithelial and endothelial expression. In our previous studies on the effects of GFD in patients with PsoV with AGA, both the endothelium and the expression of tTG were strongly reduced after 3 months on GFD. These changes were accompanied by a decrease in proliferation both in the endothelium and in dermal inflammatory cells.[11] However, it is not known if this effect is nonspecific or might be linked to tTG as an autoantigen as proliferaton of the endothelium is an early and characteristic event in PsoV irrespective of the presence or absence of AGA/tTG antibodies.

In lesional PPP skin there is a pronounced proliferation of the endothelium, which shows strong tTG expression, as seen in Figure 2 in a specimen from a patient *without* AGA or tTG antibodies. The palmoplantar endothelium may be involved in the pathogenesis of PPP, as we have found that 47% of PPP sera react with the papillary endothelium from a healthy person.[7] tTG might be one of the possible endothelial autoantigens or in some patients with tTG antibodies it might be a major autoantigen.

Why is the prevalence of tTG antibodies higher in PPP than in the other types of psoriasis despite a similar percentage of gliadin antibodies? A possible explanation might be that PPP may be a different disorder, as indicated by the results of recent genetic studies.[3] The female predominance, the high prevalence of autoimmune disease and the localization to the palms and soles also illustrate differences compared with PsoV and PsoA. The fact that 95% of patients with PPP are smokers at the onset of the disease, that smoking is associated with a 70 times higher risk of developing PPP[1] and that the few patients with PPP who are never-smokers have only mild PPP illustrate the role of smoking in PPP. Possibly smoking might also facilitate the development of antibodies, as has been shown in patients with rheumatoid arthritis who have citrulline antibodies.[18]

Several recent reports have discussed the need for more refined evaluation of seemingly normal mucosa in patients with serology indicating gluten sensitivity.[19,20] This is also illustrated by our results, with a discrete increase in lymphocytes in patients with AGA and/or tTG antibodies and clearance of long-standing PPP on a GFD, which strongly indicates that patients with minor mucosal changes may have gluten sensitivity.

PPP patients with antibodies did not have more gastrointestinal symptoms than those without, the BMI was not lower in the AGA/tTG-positive group and the severity of the PPP was similar. As there was no anamnestic or clinical evidence of gluten intolerance, none of the patients found to be gluten-sensitive would have been identified without screening for these antibodies.

As the results of our study show that there is a subgroup of patients with PPP who are gluten-sensitive and that a GFD can have a very good effect on their PPP, we suggest that patients with PPP should be screened routinely for antibodies against gliadin and tTG. Until more is known about gluten sensitivity in PPP, patients with antibodies should be investigated with gastro-duodenoscopy, although in the future the presence of these antibodies may be sufficient to recommend a GFD.

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