

Patients with Psoriatic Arthritis Have an Increased Number of Lymphocytes in the Duodenal Mucosa in Comparison with Patients with Psoriasis Vulgaris

ULLA LINDQVIST, GUDJON KRISTJÁNSSON, INGER PIHL-LUNDIN, EVA HAGFORSEN,
and GERD MICHAËLSSON

ABSTRACT. *Objective.* To determine if there is evidence of inflammation in the duodenal mucosa in patients with psoriatic arthritis (PsA) and to compare the results with those in patients with psoriasis vulgaris (PsV). *Methods.* Nineteen consecutive patients with PsA underwent gastroduodenoscopy, and biopsy specimens were taken from the duodenal and gastric mucosa. In addition to routine processing, the duodenal mucosal specimens were stained for CD3+, CD8+ and CD4+ T lymphocytes, tryptase-positive mast cells, and EG2-positive eosinophil granulocytes. The results were compared with those in duodenal mucosal specimens from patients with PsV and patients with irritable bowel syndrome. *Results.* Compared with PsV patients (without antibodies against gliadin), patients with PsA had a highly significant increase in intraepithelial CD3+ and CD8+ lymphocytes and also in CD4+ lymphocytes in the lamina propria in the villi. The lymphocyte increase was not related to presence of IgA antibodies against gliadin, endomysium, or transglutaminase, or to concomitant gastritis. Patients with PsA and PsV showed a pronounced increase in mast cells and eosinophil granulocytes. *Conclusion.* The increased lymphocyte infiltration in the duodenal mucosa in PsA, but not in PsV, might indicate different pathogenetic mechanisms in these psoriasis variants. (First Release Mar 15 2006; J Rheumatol 2006;33:924–7)

Key Indexing Terms:

INTESTINAL INFLAMMATION
GLIADIN ANTIBODIES

MAST CELLS
ENDOMYSIUM

EOSINOPHIL GRANULOCYTES
TRANSGLUTAMINASE

Patients with psoriatic arthritis (PsA) have skin lesions indistinguishable from psoriasis vulgaris (PsV), although the lesions are often less widespread, which may indicate pathogenetic and also genetic differences. Spondyloarthropathies can be associated with enteropathy, e.g., Crohn's disease and ulcerative colitis¹, but also with more nonspecific and subclinical inflammation²⁻⁵. It is not known if the upper part of the gastrointestinal tract might be involved in the pathogenesis of PsA. However, there is an increased prevalence of celiac disease and of anti-gliadin antibodies (AGA) in patients with PsA⁶. We examined the duodenal mucosa in a group of consecutive patients with PsA and compared the findings with those in patients with PsV and irritable bowel syndrome.

From the Section of Rheumatology, Section of Gastroenterology, and Section of Dermato-Venereology, Department of Medical Sciences, University Hospital, Uppsala, Sweden.

Supported by grants from the Swedish Psoriasis Association, the E. Welander and Finsen Foundations, the Swedish Medical Society, and the Medical Faculty of the University of Uppsala.

U. Lindqvist, MD, Section of Rheumatology; G. Kristjánsson, MD, Section of Gastroenterology; I. Pihl-Lundin, PhD; E. Hagforsen, PhD; G. Michaëlsson, MD, Section of Dermato-Venereology.

Address reprint requests to Dr. U. Lindqvist, Section of Rheumatology, Department of Medical Sciences, University Hospital, Uppsala, Sweden.
E-mail: ulla.lindqvist@medsci.uu.se

Accepted for publication November 23, 2005.

MATERIALS AND METHODS

Psoriatic arthritis. Nineteen consecutive patients with PsA underwent gastroscopy with biopsies of the gastric and duodenal mucosa. Anamnestic and clinical data are shown in Table 1.

Psoriasis vulgaris. For comparison, duodenal biopsy specimens from 35 patients with PsV with no arthritis were also analyzed (Table 1).

Irritable bowel syndrome (IBS). Duodenal biopsy specimens from 11 patients with symptoms compatible with IBS (no antibodies against gliadin), and no history of psoriasis or atopy, were obtained, with informed consent.

Gastroscopy with biopsies of the gastric and duodenal mucosa. Five mucosal biopsy specimens were taken distal to the papilla of Vater⁸. One was snap-frozen in chilled isopentane and stored at -70°C and the others were fixed in 4% formaldehyde and embedded in paraffin separately. In patients with PsA, 2 biopsy specimens were also taken from the antrum and corpus of the stomach.

Processing of specimens. Frozen sections were used for CD3+, CD8+, and CD4+ T lymphocytes in the duodenal mucosa and paraffin-embedded duodenal specimens for staining of mast cells⁹ and eosinophils¹⁰.

Microscopy. The routinely stained specimens from the duodenal mucosa were examined with regard to villous architecture, inflammatory cells in the lamina propria, and the degree of mononuclear cell infiltration (score 0–3) in the epithelium⁸.

The numbers of CD3+ and CD8+ T lymphocytes/mm epithelium were determined, and the percentage of CD3+ and CD4+ areas in the lamina propria in the villi were analyzed on coded slides using a Leica Q Win computerized image system with a DC 200 digital camera. Mast cells and eosinophil granulocytes in 4 sections were counted.

The study was approved by the local ethics committee.

Statistics. The Mann-Whitney U test for unpaired 2-group comparison was used for statistical analysis.

Table 1. Anamnestic and clinical data of 19 patients with psoriatic arthritis and of 35 patients with psoriasis vulgaris without a history of arthritis. Numbers are number of patients unless otherwise indicated.

	Psoriatic Arthritis	Psoriasis Vulgaris
No. of men/women	7/12	20/15
Mean age all patients, mean \pm SD yrs	53 \pm 11	45 \pm 13
Duration of arthritis, mean \pm SD yrs	6 \pm 7	
Duration of skin lesions, mean \pm SD yrs	18 \pm 10	19 \pm 13
Mono/oligoarticular arthritis	5	
Polyarticular arthritis	14	
Mean no. of swollen joints; tender joints \pm SD	3.7 \pm 2.7; 3.8 \pm 3.7	
Mean ESR, mm/h; mean pCRP, mg/l, \pm SD	13 \pm 10; 11 \pm 3	
Psoriasis vulgaris mean PASI score \pm SD (n = 15)	2.8 \pm 2.6	6.1 \pm 4.8
Palmoplantar pustulosis	4	0
Crohn's disease/ulcerative colitis	0/1	0/0
IgA antibodies against gliadin > 51 U/l	4	24
IgG antibodies against gliadin > 12 U/l	0	4
IgA antibodies against endomysium/ tissue transglutaminase	0	2
Serum IgA, g/l*		
Men	3.1 \pm 0.9 (n = 7)	2.9 \pm 1.1 (n = 19)
Women	2.5 \pm 1.0 (n = 11)	2.4 \pm 1.0 (n = 14)
NSAID until 2 weeks before gastroscopy	8	0
Methotrexate 5–7.5 mg/week	0	2

* Serum IgA in a reference group of blood donors⁶: men 2.4 \pm 1.1 g/l (n = 170), women 2.1 \pm 0.8 g/l (n = 128). PASI: Psoriasis Activity and Severity Index⁷. pCRP: plasma C-reactive protein.

RESULTS

Duodenal mucosa — routine histopathology

Psoriatic arthritis. An increased number of mononuclear cell infiltrates in the epithelium (score \geq 2–3) was observed in specimens from 6 patients (32%) and a slight increase (score 1–2) was observed in 8 patients (42%). Specimens from 6 patients displayed nonspecific mild to moderate inflammation. An increased number of eosinophils was observed in specimens from 10 patients (53%).

Psoriasis vulgaris. No increase in number of mononuclear cell infiltrates in the epithelium was seen in the specimens from AGA-negative patients. Twelve of 28 AGA-positive patients showed a slight increase in number of mononuclear cell infiltrates in the epithelium (score 1–2), and in 2 patients who also had antibodies against endomysium there was a pronounced increase in lymphocytes (score \geq 2–3), in one of them combined with partial villous atrophy.

Irritable bowel syndrome. Specimens from the patients with IBS displayed mild to moderate inflammation. Increased numbers of intraepithelial lymphocytes were not observed.

Immunohistochemistry

The results for CD3+ and CD8+ T cells in the duodenal epithelium and CD3+ and CD4+ T lymphocytes in the villi are summarized in Table 2 and illustrated in Figure 1.

CD3+ and CD8+ T lymphocytes in epithelium. The 15 patients with PsA without IgA AGA had significantly larger numbers of CD3+ and CD8+ T lymphocytes in the epithelium than patients with PsV with no AGA. Among patients with

PsV an increase was only observed in those with elevated AGA. However, 2 PsA patients with IgA AGA values of 835 and 102 U/l had 37 \pm 0 CD3+ and 38 \pm 1 CD8+ lymphocytes/mm epithelium, which were large numbers in the PsA group.

CD4+ lymphocytes in the villi. The percentage CD4+ area in the lamina propria in the villi was much higher in patients with PsA than in patients with PsV (p < 0.0001).

Mast cells and eosinophil granulocytes in the duodenal lamina propria. The number of tryptase-positive mast cells was increased in patients with PsA (55 \pm 32/mm² duodenal stroma; p = 0.0026) and PsV (131 \pm 57/mm², n = 33; p = 0.0001) compared with the number reported in patients with IBS (26 \pm 19/mm², n = 23)⁹. The number of eosinophil granulocytes in PsA (62 \pm 51/section) was also increased compared with IBS patients (23 \pm 31, n = 8; p = 0.0143)¹⁰.

Gastric mucosa. Three patients with PsA displayed chronic inflammation in the antrum and in 4 patients in the corpus (2 were positive for *Helicobacter pylori*). No correlation was found between the findings in the gastric and duodenal mucosa.

DISCUSSION

In this study patients with PsA had an increased number of lymphocytes in the duodenal epithelium and in the villi in comparison with PsV patients (without antibodies to gliadin). The increase in lymphocytes in PsA patients was not related to the presence of AGA or to more severe skin disease.

Table 2. Psoriatic arthritis, psoriasis vulgaris, and irritable bowel syndrome (IBS):CD3+ and CD8+ T lymphocytes in the duodenal epithelium (mean number \pm SD) and CD3+ and CD4+ T lymphocytes in the lamina propria of the villi (mean percentage stained area \pm SD).

	No. Patients	CD3+ Cells/mm Epithelium	CD8+ Cells/mm Epithelium	Percentage CD3+ Area in Villi	Percentage CD4+ Area in Villi
Psoriatic arthritis, no AGA	15	34.5 \pm 30.1 ^a	28.9 \pm 25.0 ^b	12.1 \pm 9.8	14.0 \pm 10.8 ^c
Psoriatic arthritis, with AGA	4	26.0 \pm 13.1	22.5 \pm 18.5	7.6 \pm 4.5	12.7 \pm 9.1
Psoriasis vulgaris, no arthritis, no AGA	7	9.2 \pm 4.5	8.6 \pm 6.7		2.5 \pm 1.0
Psoriasis vulgaris, no arthritis, with AGA	28	24.2 \pm 17.5	24.0 \pm 23.3		2.6 \pm 1.4 ^d
IBS, no AGA	11	21.9 \pm 13.9	21.6 \pm 11.9		7.0 \pm 3.6

Compared to psoriasis vulgaris, no anti-gliadin antibodies: ^ap = 0.0039; ^bp = 0.0072; ^cp = 0.0010. Compared to psoriatic arthritis, no anti-gliadin antibodies: ^dp < 0.0001.

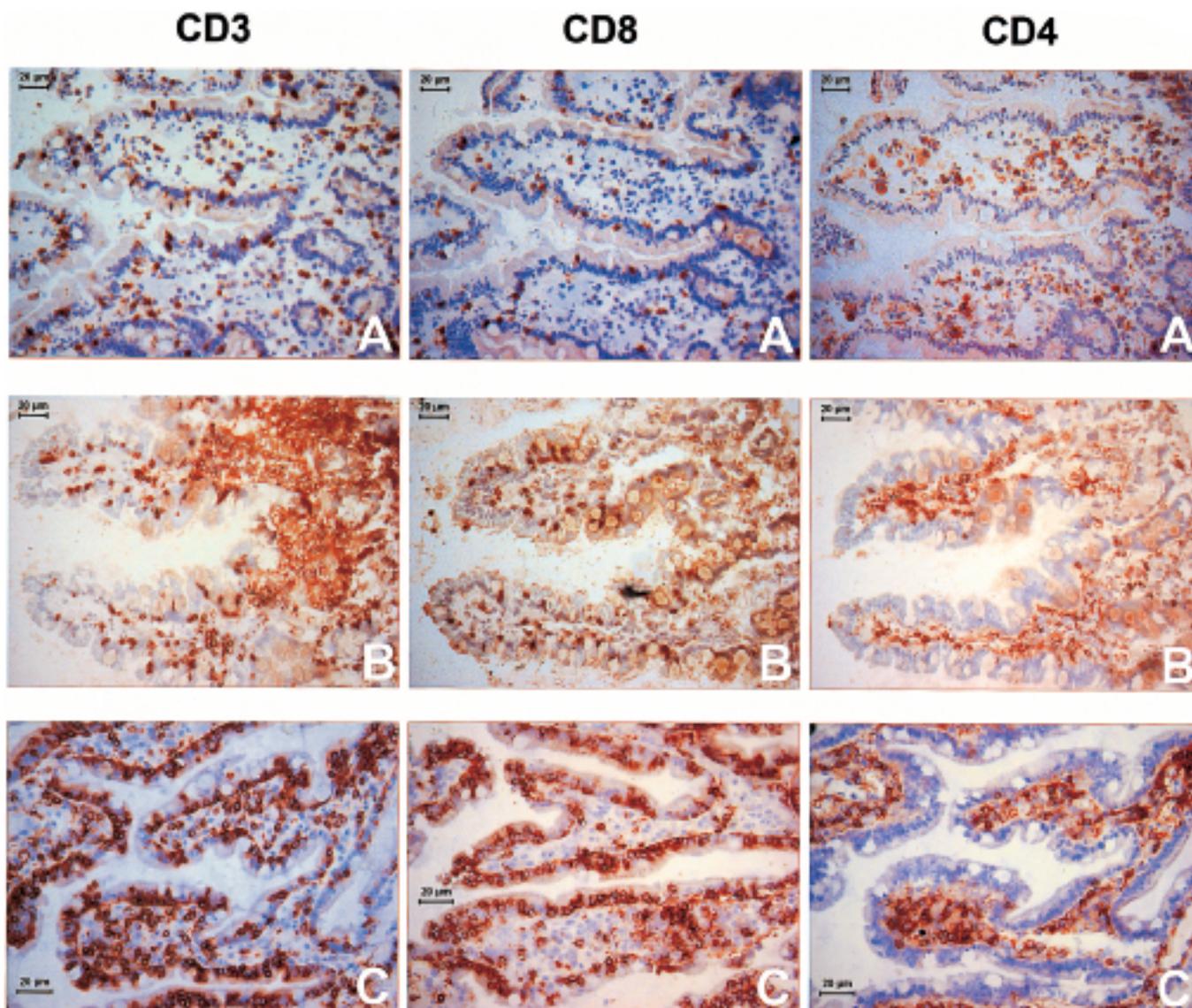


Figure 1. CD3+, CD8+, and CD4+ T lymphocytes in villi in the duodenal mucosa in (A) a patient with psoriasis vulgaris but no arthritis and no antibodies against gliadin; no increase in the number of lymphocytes in the epithelium or in lamina propria in the villi; (B) a patient with psoriatic arthritis (polyarticular arthritis): increased number of CD3+/CD8+ lymphocytes in the epithelium and CD3+/CD4+ lymphocytes in lamina propria in the villi; and (C) a patient with psoriatic arthritis (oligoarticular arthritis) and the largest number of intraepithelial lymphocytes in the arthritis group. Note dense infiltration of CD3+/CD8+ lymphocytes in the epithelium and CD3+/CD4+ lymphocytes in the lamina propria. All bars = 20 μ m.

The definition of “normal” numbers of mononuclear cell infiltrates in the epithelium is still uncertain. An attempt to clarify this issue was made by Hayat, *et al*¹¹, who examined paraffin-embedded duodenal biopsy specimens from 20 patients evaluated as normal. They found a mean number of lymphocytes \pm SD of $11 \pm 6.8/100$ epithelial cells (range 1.8–26). This is similar to the number found in our study in AGA-negative patients with PsV. We have found few reports on attempts to quantify lymphocyte infiltration in the lamina propria. Villi were chosen for estimation of lymphocyte infiltration as they are easier to define than selected areas in the lower lamina propria. The increased infiltration by CD4+ lymphocytes illustrates the differences in the duodenal mucosa between PsA and PsV.

Mild inflammation in IBS has been found in several recent studies¹². That the lymphocyte infiltration was somewhat more pronounced in PsA than in the IBS specimens also indicates that some type of inflammation is present in the PsA mucosa.

We previously reported that the number of mast cells⁹ and eosinophil granulocytes¹⁰ is greatly increased in the duodenal mucosa in PsV patients, but with no obvious relation to the clinical severity and no association with AGA. An increased number of these cells was also found in PsA. In this context it is of interest that mast cells have an important role in innate immunity¹³ and that they have a key role in several autoimmune conditions¹⁴.

It may be speculated that the increased lymphocyte infiltration in the duodenal mucosa in patients with psoriatic arthritis might indicate that psoriatic arthritis has an immune-mediated pathogenesis with a reaction to unknown dietary factors and/or to bacterial antigens and/or to autoantigens not present in psoriasis vulgaris.

REFERENCES

1. De Keyser F, Baeten D, van den Bosch F, et al. Gut inflammation and spondyloarthropathies. *Curr Rheumatol Rep* 2002;4:525-32.
2. Schatteeman L, Mielants H, Veys EM, et al. Gut inflammation in psoriatic arthritis: a prospective ileocolonoscopy study. *J Rheumatol* 1995;22:680-3.
3. Scarpa R, Manguso F, D'Arienzo A, et al. Microscopic inflammatory changes in colon of patients with both active psoriasis and psoriatic arthritis without bowel symptoms. *J Rheumatol* 2000;27:1241-6.
4. Porzio V, Biasi G, Corrado A, et al. Intestinal histological and ultrastructural inflammatory changes in spondyloarthropathy and rheumatoid arthritis. *Scand J Rheumatol* 1997;26:92-8.
5. Williamson L, Dockerty JL, Dalbeth N, Wordsworth BP. Gastrointestinal disease and psoriatic arthritis. *J Rheumatol* 2004;31:1469-70.
6. Lindqvist U, Rudsander A, Bostrom A, Nilsson B, Michaelsson G. IgA antibodies to gliadin and coeliac disease in psoriatic arthritis. *Rheumatology Oxford* 2002;41:31-7.
7. Fredriksson T, Pettersson U. Severe psoriasis — oral therapy with a new retinoid. *Dermatologica* 1978;157:238-44.
8. Michaelsson G, Kraaz W, Gerden B, et al. Increased lymphocyte infiltration in duodenal mucosa from patients with psoriasis and serum IgA antibodies to gliadin. *Br J Dermatol* 1995;133:896-904.
9. Michaelsson G, Kraaz W, Hagforsen E, Pihl-Lundin I, Loof L. Psoriasis patients have highly increased numbers of tryptase-positive mast cells in the duodenal stroma. *Br J Dermatol* 1997;136:866-70.
10. Michaelsson G, Kraaz W, Gerden B, et al. Patients with psoriasis have elevated levels of serum eosinophil cationic protein and increased numbers of EG2 positive eosinophils in the duodenal stroma. *Br J Dermatol* 1996;135:371-8.
11. Hayat M, Cairns A, Dixon MF, O'Mahony S. Quantitation of intraepithelial lymphocytes in human duodenum: what is normal? *J Clin Pathol* 2002;55:393-4.
12. Bradesi S, McRoberts JA, Anton PA, Mayer EA. Inflammatory bowel disease and irritable bowel syndrome: separate or unified? *Curr Opin Gastroenterol* 2003;19:336-42.
13. Marshall JS, Jawdat DM. Mast cells in innate immunity. *J Allergy Clin Immunol* 2004;114:21-7.
14. Rottem M, Mekori YA. Mast cells and autoimmunity. *Autoimmun Rev* 2005;4:21-7.