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Psoriasis Phenotype in Inflammatory Bowel Disease: A Case-Control Prospective Study

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Abstract

Background and aims: Whether inflammatory bowel disease [IBD] is associated with specific psoriasis phenotypes is undefined. In a case-control prospective study, we aimed to assess the severity and phenotype of psoriasis in IBD vs matched non-IBD controls with psoriasis [non-IBD].
Methods: From 2011 to 2013, dermatological assessment was performed in all IBD patients showing lesions requiring characterisation. In patients with psoriasis, assessment included: presence, characteristics, and severity. Each IBD patient with psoriasis was matched [gender, ethnicity, age ± 5 years] with one non-IBD patient with psoriasis. Statistical analysis: data were expressed as median [range], chi-square, Student's t test.
Results: Dermatological assessment was performed in 251 IBD patients [115 females, age 47 [16–85]; IBD duration 9 years [1–46]]: 158 Crohn's disease [CD] [63%], 93 ulcerative colitis [UC] [37%]. Psoriasis was detected in 62 [25%] IBD patients: 36 [58%] CD, 26 UC [42%; $p = 0.44$]. Clinical characteristics were comparable between IBD patients with or without psoriasis: age 50 [23–72] vs 47 [16–85]; IBD duration 9.5 [1–46] vs 9 [1–41]; p = non-significant]. The non-IBD group included 62 patients with psoriasis: 35 male; age 47 [18–75]. Mild psoriasis was more frequent in IBD vs non-IBD [87% vs 53%; $p < 0.0001$], whereas moderate and severe psoriasis were more frequent in non-IBD vs IBD [37% vs 13%, $p = 0.004$; 10% vs 0%; $p = 0.036$]. Plaque-type psoriasis was the most common phenotype in both IBD and non-IBD [$p < 0.0001$ vs others phenotypes].The frequency of plaque-type, nail psoriasis and psoriatic arthritis was lower in IBD vs non-IBD [$p = 0.008$; $p < 0.0001$; $p = 0.006$]. Psoriasis occurred after anti-tumour necrosis factor [TNF]α treatment in six CD patients [7%].
Conclusions: Severity and phenotypes of psoriasis may differ between patients with IBD and their matched non-IBD controls.

Keywords: Crohn's disease; ulcerative colitis; psoriasis; phenotype; severity

1. Introduction

Psoriasis is a common, chronic, idiopathic, inflammatory skin disease, with a typical relapsing and remitting course, affecting about 2–5% of the Caucasian population.[1,2] The diagnosis of psoriasis is made according to straightforward clinical findings, requiring histological analysis of the lesions in few cases. In 25% of cases,

psoriasis is associated with joint disease, known as psoriatic arthritis, although this condition has been reported to be a different entity with a distinct therapeutic spectrum.[2]

Since the 1960s, psoriasis has been associated with inflammatory bowel disease [IBD] in terms of epidemiology, pathogenesis, and genotype.[3,4] Common clinical and immunological features have indeed been described in IBD and psoriasis, probably due to shared susceptibility genes observed in genome-wide association studies.[5] The interleukin-23 [IL-23] pathway has indeed been similarly involved in the pathogenesis of IBD, psoriasis and psoriatic arthritis, even if multiple genes can regulate these pathways.[6]

The prevalence of psoriasis in patients with Crohn's disease [CD] has been shown to be higher than in non-IBD controls [9.6% vs 2.2%, $p < 0.02$], with a higher prevalence in CD than in ulcerative colitis [UC] patients [11.2% vs 5.7% with odds ratios [OR] at multivariate analysis of 2.49 and 1.64, respectively].[4,7,8]

Recently, several independent observations described the appearance of psoriatic eruptions in IBD patients treated with anti-tumour necrosis factor-α [anti-TNFα] treatments.[9,10] Psoriatic lesions indeed represent the most frequent dermatological adverse event in patients receiving anti-TNFα treatments, as reported by rheumatological studies.[11,12] A main mechanism able to determine the development of psoriatic lesions after anti-TNFα treatments has been suggested.[6] Interferon-α [IFN-α] production from dendritic cells, observed in psoriatic lesions, is inhibited by TNFα.[6] Therefore, blocking TNFα by using anti-TNFα treatments increases the production of IFN- α, thus inducing worsening or new appearance of psoriatic lesions.[6] Most patients showing psoriasis after anti-TNFα treatments appear to have no previous history of psoriatic lesions.

Several studies also investigated the possible relationship between the development of psoriasis and clinical characteristics of IBD in patients not treated with anti-TNFα [i.e. phenotype, IBD activity, family history of IBD, smoking, age].[13] No definite association has been described in this regard.

Whether IBD is associated with specific phenotypes of psoriasis[14] is currently undefined. On the basis of these observations, the aim of the present study was to assess, in a case-control prospective study, the severity and phenotype of psoriasis in patients with IBD, when compared with non-IBD controls with psoriasis [non-IBD] matched for clinical variables.

2. Materials and Methods

2.1. Study design

From January 2011 to November 2013, all IBD patients under regular follow-up at our tertiary IBD centre and requiring dermatological assessment were prospectively referred to a dedicated dermatologist from the same university/hospital. In particular, in a prospective case-control study, dermatological assessment was scheduled by the IBD-dedicated gastroenterologist after routine clinical assessment for IBD. Indication for a dermatological assessment included any skin lesion reputed by the IBD-dedicated gastroenterologist to deserve further characterisation, classification, and management.

For a proper evaluation of psoriasis phenotype in IBD, each IBD patient with psoriasis was prospectively matched for gender, ethnicity, and age [± 5 years] with one non-IBD patient with psoriasis, referring to the same dedicated dermatological unit.

2.2. Study population: IBD patients

The IBD group included patients with a diagnosis of CD or UC, defined according to current guidelines.[15] For each patient, clinical characteristics, including demographic data, gender, age, risk factors for IBD [family history of IBD, smoking habit, appendectomy] and characteristics of IBD [disease duration, site, extent, pattern, thiopurines and/or anti-TNFα use] were reported in a common database. Available data regarding family history of psoriasis were also reported.

Patients were enrolled according to the following inclusion criteria: 1] diagnosis of IBD made according to current clinical, histological or radiological criteria[15,16]; 2] regular follow up at our referral IBD centre; 3] compliance with dermatological assessment; 4] indication for dermatological assessment, given by the IBD-dedicated gastroenterologist in relation to the presence of any type of skin lesion, including psoriasis, deserving further evaluation; 5] available demographic and clinical characteristics reported in clinical records.

2.3. Study population: non-IBD patients

The non-IBD group included patients with a known diagnosis of psoriasis and no IBD. In order to ensure that the control group had no IBD, all control patients were selected after an accurate present and past medical history had excluded any sign or symptom compatible with either UC or CD [i.e. abdominal mass, perianal disease, other fistulae, erythema nodosum, pyoderma gangrenosum]. The absence of persisting haematochemical alterations compatible with chronic inflammation, as observed in subgroups of patients with IBD, was also a criterion. Due to the absence of clinical history, signs, symptoms, and blood chemistry alterations suggesting a previously unknown diagnosis of IBD, diagnostic procedures aiming to exclude IBD were considered not appropriate.

Non-IBD patients were enrolled according to the following inclusion criteria: 1] no present or past signs or symptoms compatible with IBD [above detailed]; 2] diagnosis of any type of psoriasis, as assessed by the same dermatologist evaluating patients with IBD; 3] compliance with dermatological assessment; 4] available clinical records, including demographic and dermatological characteristics. Characteristics considered for the analysis in non-IBD patients with psoriasis included: gender, ethnicity, age, psoriasis characteristics and family history of psoriasis.

Demographic and clinical characteristics of each IBD and non-IBD patient, including dermatological assessment, were prospectively collected.

2.4. Dermatological assessment

Dermatological evaluation in each IBD and non-IBD patient was performed by the same experienced dermatologist, and was focused on the detection and diagnosis of psoriasis. Psoriasis classification was according to a published consensus of the International Psoriasis Council [IPC].[14] In particular, the presence and characteristics of psoriasis were recorded and further classified as follows: sebopsoriasis, scalp psoriasis, plaque type psoriasis [trunk, arms], palmo-plantar psoriasis, nail psoriasis, inverse psoriasis, psoriatic arthritis, guttate psoriasis, and pustular psoriasis. Psoriasis that developed after anti-TNFα treatments was also reported. Severity of psoriasis was defined as mild, moderate, or severe [not applied to psoriatic arthritis].

In the IBD group, dermatological assessment was finalised to further characterise the skin lesions detected by the gastroenterologist and, in patients with psoriasis, to further characterise the type of the lesions [see above]. In patients with psoriasis, present or past use of any treatment for IBD was considered (immunosuppressants [IS]: azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX], tacrolimus [TAC], cyclosporine [CyS], infliximab [IFX],

adalimumab [ADA], and/or certolizumab [CTZ]; immunomodulators [IMM]: thiopurines and/or anti-TNFα). Specific treatments and outcome of psoriasis [resolution or worsening] were also recorded.

2.5. Statistical analysis

Data were expressed as median and range. The analysis of the data included the frequency of psoriasis in IBD patients and differences in terms of phenotype of psoriasis between IBD and non-IBD patients. Differences between cases and controls were assessed by the Student's t test [demographic characteristics] or by the χ^2 test [differences between frequency of psoriasis phenotypes], as appropriate. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. IBD population

From January 2011 to November 2013, 251 IBD patients were reported by the IBD-dedicated gastroenterologist to require dermatological assessment. Among these 251 IBD patients, there were 158 patients with CD [63%] and 93 with UC [37%]. The IBD group included 115 females [45.8%], and had a median age of 47 years [range 16–85] and a median IBD duration of 9 years [range 1–46]. Family history of psoriasis was reported by 17 of the 251 IBD patients [6.8%].

Tables 1 and 2 summarise demographic and clinical characteristics of the 158 CD and 93 UC patients enrolled, including the whole group and the subgroup of patients with or without psoriasis. When comparing clinical characteristics of UC vs CD patients, no significant differences were observed in terms of gender or family history of IBD [Tables 1 and 2]. On the other hand, the median age was significantly higher in patients with UC than with CD [p = 0.005] [Tables 1 and 2]. The median IBD duration was significantly higher in patients with CD than with UC [p = 0.038] [Tables 1 and 2]. As expected, when comparing CD vs UC patients, the CD group included a higher percentage of patients with previous appendectomy [p = 0.023], active smokers [p < 0.0001], current or past use of IS [thiopurine monotherapy or combined with anti-TNFα] [p = 0.003], or anti-TNFα monotherapy [p = 0.002] [Tables 1 and 2]. Present or past use of IS was reported by 101 [64%] of the 158 CD patients enrolled [Table 1], including past use in 71 [70%] patients [AZA 51, IFX 31, ADA 16, CTZ 3, CyS 4 and/or MTX 4]. Current use [including patients with past use] of IS was reported by 50 of the 101 [50%] patients including AZA [15], IFX [14], ADA [20], CTZ [n1], 6-MP [1] and/or TAC [1]. An established family history of psoriasis was reported by 9 of the 158 CD patients [6%].

As shown in Table 2, in the UC group present or past use of IS was reported by 41 [44%] patients, including past use in 22 patients [54%][AZA 16, IFX 9, ADA 5, and/or CyS 1]. Current use [including patients with a past use] of IS was reported by 27 of the 41 [66%] UC patients [AZA n17, IFX 7, 6-MP 1, and/or ADA 3]. An established family history of psoriasis was reported by 8 of the 93 UC patients [9%].

3.2. IBD patients and psoriasis

3.2.1. Clinical characteristics of IBD patients with and without psoriasis

The frequency and characteristics of psoriasis in patients with IBD patients and, separately, in patients with UC, CD, and non-IBD, are summarised in Table 3. Among the 251 IBD patients referred to the dermatologist, psoriasis was detected in 62 [25%], including 36 [58%] with CD and 26 [42%] with UC [Table 3]. In our IBD population, the frequency of psoriasis was comparable between patients with CD and UC [p = 0.44].

Among the 62 IBD patients with psoriasis, there were 26 females and 36 males [median age 50, range 23–72 years; IBD duration 9, 1–46 years]. In IBD patients with psoriasis, family history of IBD was reported by 4 [6%] and previous appendectomy by 9 patients [15%], and the population included 20 active smokers [32%]. Present or past use of IS was reported by 28 of the 62 IBD patients

Table 1. Clinical and demographic characteristics of Crohn's disease [CD] patients

	CD patients		
	Total [158]	Psoriasis [36]	No psoriasis [122]
Gender [males]	93 [59%]	24 [67%]	69 [57%]
Age [median years, range]	43 [16–80]	43 [23–70]	43 [16–80]
CD duration [median years, range]	10 [1- 46]	9 [1–46]	10 [1–41]
CD location			
L1 ileal	111 [70%]	24 [67%]	87 [71%]
L2 colonic	13 [8%]	3 [8%]	10 [8%]
L3 ileocolonic	33 [21%]	8 [22%]	25 [21%]
L4 upper isolated	1 [1%]	1 [3%]	0 [0%]
CD behaviour			
B1- Non stricturing, non penetrating	57 [36%]	15 [42%]	42 [34%]
B2- stricturing	60 [38%]	9 [25%]	51 [42%]
B3- penetrating	41 [26%]	12 [33%]	29 [24%]
Family history of IBD	22 [14%]	3 [8%]	20 [16%]
Smoking	57 [36%]	15 [42%]	42 [34%]
Appendectomy	20 [13%]	8 [22%]	12 [10%]
Immunosuppressants [IS][a]	101 [64%]	20 [56%]	79 [65%]
Thiopurines	65 [41%]	11 [31%]	52 [43%]
Anti-TNFα	68 [43%]	16 [44%]	52 [43%]

IBD, inflammatory bowel disease; TNF, tumour necrosis factor.

[a]Thiopurines, methotrexate, cyclosporine, tacrolimus, adalimumab, infliximab, and/or, certolizumab.

Table 2. Clinical and demographic characteristics of ulcerative colitis [UC] patients.

	UC patients		
	Total [93]	Psoriasis [26]	No psoriasis [67]
Gender [males]	43 [46%]	12 [46%]	31 [46%]
Age, median years [range]	55.5 [22–85]	54 [23–72]	47 [22–85]
UC duration, median years [range]	7.5 [1- 41]	10 [1–31]	7 [1–41]
UC extent			
Proctitis	33 [36%]	9 [35%]	24 [36%]
Left-sided	13 [14%]	5 [19%]	8 [12%]
Extensive	42 [45%]	10 [38%]	32 [48%]
Others[a]	5 [5%]	2 [8%]	3 [4%]
Family history of IBD	11 [12%]	1 [4%]	10 [15%]
Smoking	13 [14%]	5 [19%]	8 [12%]
Appendectomy	3 [3%]	1 [4%]	2 [3%]
Immunosuppressants[b]	41 [44%]	8 [31%]	31 [46%]
Thiopurines	34 [37%]	6 [23%]	27 [40%]
Anti-TNFα	21 [22%]	4 [15%]	17 [25%]

IBD, inflammatory bowel disease; TNF, tumour necrosis factor.
[a]Others: ileo-anal pouch [3: 1 psoriasis, 2 no psoriasis], ileo-rectal anastomosis [1, no psoriasis], or ileostomy [1, with psoriasis].
[b]Thiopurines, methotrexate, cyclosporine, tacrolimus, adalimumab, infliximab, and/or, certolizumab.

Table 3. Psoriasis severity and phenotype in inflammatory bowel disease [IBD] patients and in non-IBD controls.

Psoriasis characteristics	Patients with psoriasis			
	IBD [62]	UC [26]	CD [36]	Non-IBD [62]
Severity				
Mild	54 [87%][a]	24 [92%][c]	30 [83%][c]	33 [53%]
Moderate	8 [13%]	2 [8%]	6 [17%]	23 [37%][b,d]
Severe	0 [0%]	0 [0%]	0 [0%]	6 [10%][b]
Phenotype				
Scalp	18 [29%]	6 [23%]	12 [33%]	25 [40%]
Sebopsoriasis	8 [13%]	3 [12%]	5 [14%]	2 [3%]
Plaque type	35 [56%][e,f]	17 [65%]	18 [50%][g]	49 [79%][e]
Palmo-plantar	4 [6%]	2 [8%]	2 [6%]	6 [10%]
Nail	3 [5%]	1 [4%][i]	2 [6%][j]	22 [35%][h]
Inverse	8 [13%]	1 [4%]	7 [19%]	5 [8%]
Psoriatic arthritis	2 [3%]	2 [8%]	0 [0%]	13 [21%][k]
Guttate	1 [2%]	0 [0%]	1 [3%]	2 [3%]
Pustular	1 [2%]	0 [0%]	1 [3%]	1 [2%]
Anti-TNFα induced	6 [10%]	0 [0%]	6 [17%]	0 [0%]

UC, ulcerative colitis; CD, Crohn's disease; TNF, tumour necrosis factor.
[a]$p < 0.0001$ mild vs moderate and severe psoriasis in IBD; $p < 0.0001$ mild psoriasis in IBD vs non-IBD.
[b]$p < 0.0001$ mild and moderate vs severe psoriasis in non-IBD; $p = 0.004$ and $p = 0.036$ mild and moderate psoriasis in non-IBD *vs* IBD, respectively; $p = 0.001$ and $p = 0.011$ mild and moderate psoriasis in non-IBD vs UC, respectively.
[c]$p = 0.005$ and $p = 0.001$ mild psoriasis in UC and CD vs non-IBD, respectively.
[d]$p = 0.057$ and $p = 0.001$ moderate psoriasis in non-IBD vs UC and CD, respectively.
[e]$p < 0.0001$ plaque-type vs sebo, guttate, pustular, scalp, nail, and palmo-plantar within IBD and non-IBD.
[f]$p = 0.008$ plaque-type psoriasis in IBD vs non-IBD.
[g]$p = 0.013$ plaque-type psoriasis in CD vs non-IBD.
[h]$p < 0.0001$ nail psoriasis in IBD vs non-IBD.
[i]$p = 0.006$ UC vs non-IBD.
[j]$p = 0.002$ CD *vs* non-IBD.
[k]$p = 0.006$ and $p = 0.008$ psoriatic arthritis in non IBD vs IBD and CD, respectively.

with psoriasis [45%]. Among these 28 patients, past use of IS was reported by 16 patients [57%] [AZA 11, 6-MP 2, IFX 7, ADA 3, CTZ 2, or MTX 2]. Current and/or past use of IS was reported by 20 of the 28 patients [71%] [AZA 5, IFX 6, ADA 9]. A well-defined family history of psoriasis was reported by 15 [24%] patients with psoriasis.

In IBD, 189 of the 251 [75%] patients showed no psoriasis [medianage 44 years, range 16–85; IBD duration 9 years, range 1–41; 100 males]. Clinical characteristics were comparable between IBD patients with vs without psoriasis [median age 50 years, range 23–72 vs 47 years, 16–85; IBD duration, years: 9.5, range 1–46 vs 9, range 1–41, respectively; p = non-significant for both]. Among risk

factors, family history of IBD, the frequency of previous appendectomy, and active smoking were comparable between IBD patients with or without psoriasis [16% vs 6%; 7% vs 15%; 26% vs 32%, respectively; p = non-significant].

Current or past use of IS was reported by 110 [58%] IBD patients without psoriasis, including past use in 77 [70%] patients [AZA 56, IFX 33, ADA 18, CyS 3, CTZ 3, or MTX 2]. Current and/or past use of IS in IBD patients without psoriasis was reported by 57 of the 110 [52%] patients [AZA 27, 6-MP 1, IFX 15, ADA 27, TAC 1, or CTZ 1]. The frequency of a family history of psoriasis was higher in the 62 IBD patients with psoriasis vs the 189 IBD patients without psoriasis [24% vs 1%, respectively; $p < 0.0001$].

3.2.2. Clinical characteristics of CD patients with *vs* without psoriasis

CD patients with or without psoriasis were comparable in terms of gender, age, and CD duration [Table 1]. Present or past use of IS was also comparable between these 2 CD subpopulations. Among the 36 CD patients with psoriasis, present or past use of IS was reported by 20 patients [56%], past use by 13 [36%] patients [AZA 7, 6-MP 1, IFX 4, ADA 1, CTZ 2] and/or current use in 12 of 36 patients [33%] [AZA 3, IFX 4, ADA 6]. As observed in the whole IBD group, in CD subgroup also a definite family history of psoriasis was more frequent in patients with vs without psoriasis [19% vs 2%; $p < 0.0001$].

3.2.3. Clinical characteristics of UC patients with vs without psoriasis

UC patients with or without psoriasis were comparable in terms of gender, age, UC duration [Table 2], and previous or past use of IS. In particular, among 26 UC patients with psoriasis, current or past use of IS was reported by 8 patients [31%], including past use in 5 [19%][AZA 3, 6-MP 1, IFX 3, ADA 1] and/or current use in 3 [11%] [AZA 2, ADA 1]. A definite family history of psoriasis was more frequent in UC patients with vs without psoriasis [8 out of 26 [31%] vs 0 out of 67 [0%]; $p < 0.0001$].

3.2.4. Non-IBD patients with psoriasis

The non IBD-control group included 62 patients with psoriasis [35 males; median age 47 years, range 18–75], matched [1:1] with each of the 62 IBD patients with psoriasis. Characteristics of IBD patients and non-IBD controls with psoriasis were comparable in terms of median age, gender, and ethnicity [p = non-significant]. Family history of psoriasis was reported by 39 of the 62 non-IBD controls [63%].

3.2.5. Psoriasis phenotype in IBD and non-IBD controls

Table 3 summarises the psoriasis severity and phenotype in the 62 IBD patients and in the 62 matched non-IBD controls with psoriasis. Among the 62 IBD patients, the frequency of mild psoriasis was higher than the frequencies of both moderate and severe psoriasis [$p < 0.0001$ for both]. The frequency of moderate psoriasis was higher than the frequency of severe psoriasis [$p < 0.0001$]. Among the 62 non-IBD patients with psoriasis, the frequency of severe psoriasis was lower than the frequency of both mild and moderate psoriasis [$p < 0.0001$ for both]. When comparing the severity of psoriasis in IBD vs non-IBD groups, mild psoriasis [Figure 1] was detected in a higher proportion of IBD patients [$p < 0.0001$] [Table 3]. On the other hand, moderate psoriasis and severe psoriasis were more frequent in non-IBD than in IBD patients [$p = 0.004$ and $p = 0.036$, respectively] [Table 3]. The frequencies of mild and moderate psoriasis were also significantly higher in non-IBD vs UC patients [$p = 0.001$ and $p = 0.011$, respectively] [Table 3]. As for UC, when comparing the severity of psoriasis between CD and non-IBD patients, the frequencies of moderate and severe psoriasis were higher in non-IBD [$p = 0.057$], whereas the frequency of mild psoriasis was higher in CD patients [$p = 0.005$]. On the other hand, the frequencies of mild, moderate, and severe psoriasis were comparable between CD and UC patients [p = non-significant]. Figure 2 shows a case of severe diffuse plaque type psoriasis in a non-IBD patient.

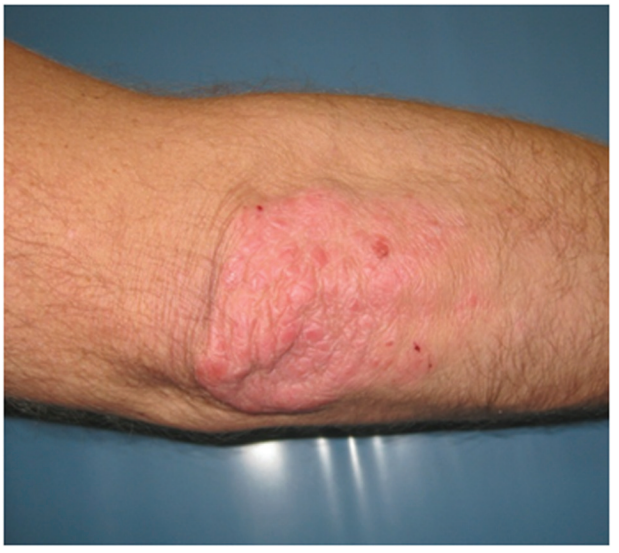

Figure 1. The figure shows skin lesions related to mild plaque-type psoriasis in one patient with UC not treated with anti-TNFα monoclonal antibodies. UC, ulcerative colitis; TNF, tumour necrosis factor.

When considering psoriasis phenotype, plaque type psoriasis [Figure 1] was the most common phenotype in both IBD and non-IBD patients [$p < 0.0001$ vs sebopsoriasis, guttate, pustular, scalp, nail, and palmo-plantar for both groups][Table 3]. Figures 3 and 4 show the presence of skin lesions related to sebopsoriasis in three patients with CD, and Figure 5 shows nail psoriasis in one patient with CD.

However, when comparing the frequency of psoriasis phenotypes in IBD vs non-IBD, a significantly lower frequency of plaque-type psoriasis was observed in our tested IBD vs non-IBD population [$p = 0.008$] [Figure 6, panel a]. Accordingly, the frequency of plaque type psoriasis was lower in our CD population than in non-IBD controls [$p = 0.013$], whereas the observed higher frequency of plaque type psoriasis in UC vs non-IBD did not reach statistical significance [Figure 6, panel a]. IBD patients showed a significantly lower frequency of nail psoriasis when compared with non-IBD controls [$p < 0.0001$] [Figure 6, panel b]. The frequency of nail psoriasis was also lower in our UC and CD populations vs non-IBD [$p = 0.006$; $p = 0.002$] [Figure 6, panel b]. Psoriatic arthritis was also significantly more frequent in our tested non-IBD than IBD populations [$p = 0.006$], as also in CD vs non-IBD patients [$p = 0.008$], but the difference with UC did not reach statistical significance [Figure 6, panel c].

3.2.6. Psoriasis and anti-TNFα use

When considering the whole group of 251 IBD patients, current or past use of anti-TNFα was recorded in 89 patients [35%], including 21 UC [23%] and 68 CD [43%].

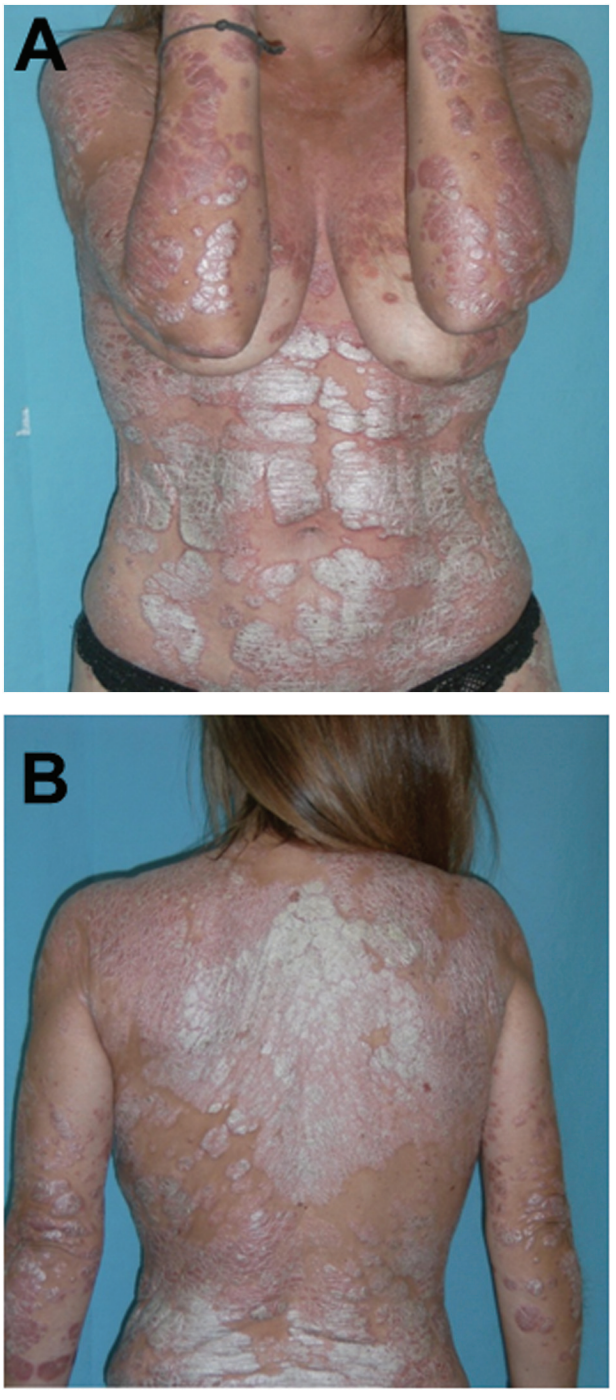

Figure 2. Severe diffuse plaque-type psoriasis in one non-IBD control patient: anterior view [panel a], posterior view [panel b]. IBD, inflammatory bowel disease.

During the study period, psoriasis occurred after anti-TNFα in 6 of the 89 IBD patients [7%], all with CD. Psoriasis after anti-TNFα treatment therefore occurred in 6 of the 68 CD [9%] and in none of the 21 UC patients [0%] [*p* non-significant]. Psoriasis in these 6 CD patients included palmo-plantar psoriasis [4][Figure 7], sebopsoriasis [1] and inverse psoriasis [1]. Among these 6 CD patients, 4 developed psoriasis after IFX and 2 after ADA. When considering the 4 patients with psoriasis after IFX, complete resolution was observed

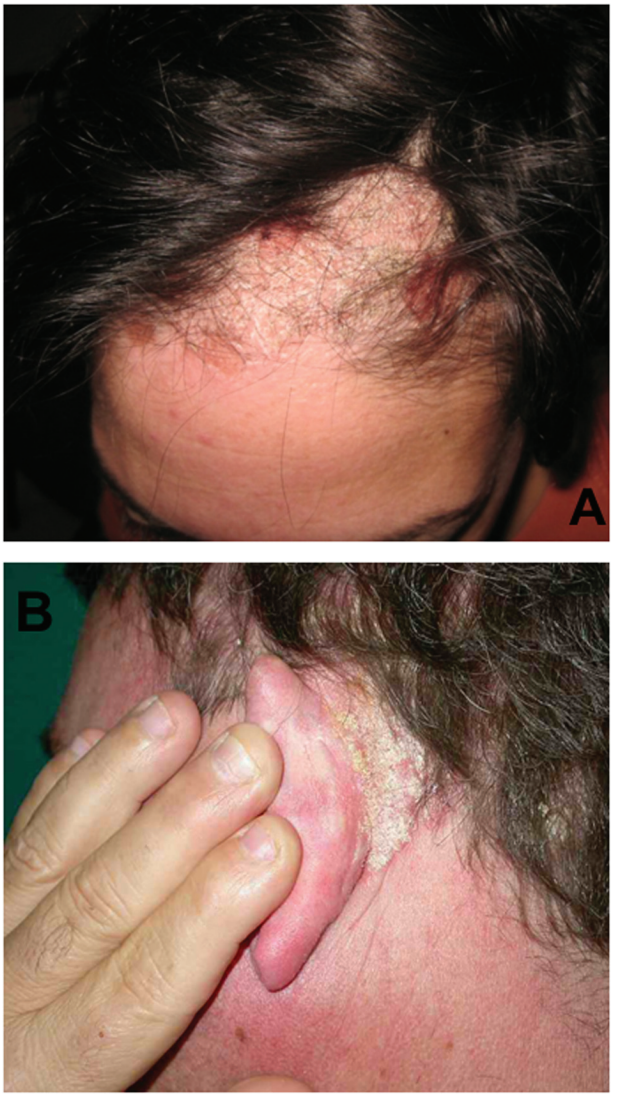

Figure 3. Scalp sebopsoriasis in two CD patients, with or without concomitant alopecia [panels a and b, respectively]. CD, Crohn's disease.

in 2, by using topical steroids in 1 patient, and after discontinuation of IFX, followed by CyS and MTX, in the second patient. The remaining 2 patients showed no resolution after IFX discontinuation and topical steroids. Among the 2 patients with psoriasis occurring after ADA, no resolution has currently been observed after ADA discontinuation, followed by CyS treatment in 1 patient.

3.2.7. Non-psoriatic skin manifestations in IBD patients

Among the 251 IBD patients referred to the dermatologist, 62 [25%] showed psoriasis. In the remaining 159 IBD patients showing lesions different from psoriasis, lesions were classified as: inflammatory and allergic skin conditions [i.e. seborrhoeic dermatitis, allergic dermatitis, drug reactions, mucositis, erythema nodosum, or acne-rosacea] in 79 patients [50%], infective skin lesions [i.e. fungal, viral, or Gram-positive bacterial infections] in 51 [32%], pigmented lesions [i.e. atypical naevi, seborrhoeic keratosis, haemangioma, including 1 malignant melanoma] in 27 patients [17%]; non-melanoma skin cancer [NMSC] [i.e. basal cell carcinoma, actinic keratosis, erythroplasia of Queyrat] in 16

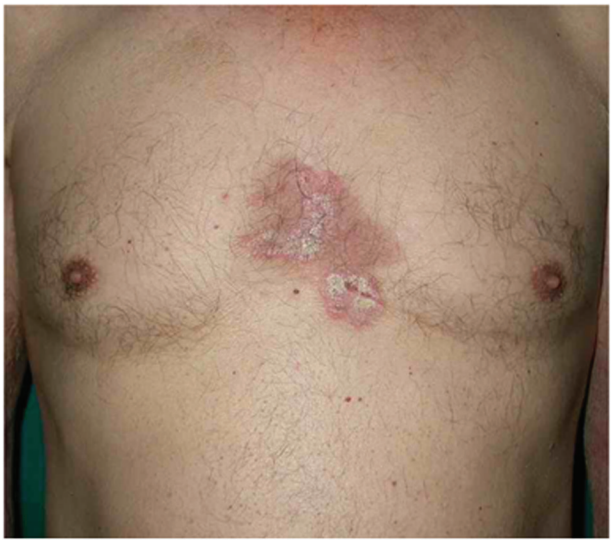

Figure 4. Trunk sebopsoriasis in one CD patient not treated with anti-TNFα monoclonal antibodies. CD, Crohn's disease.

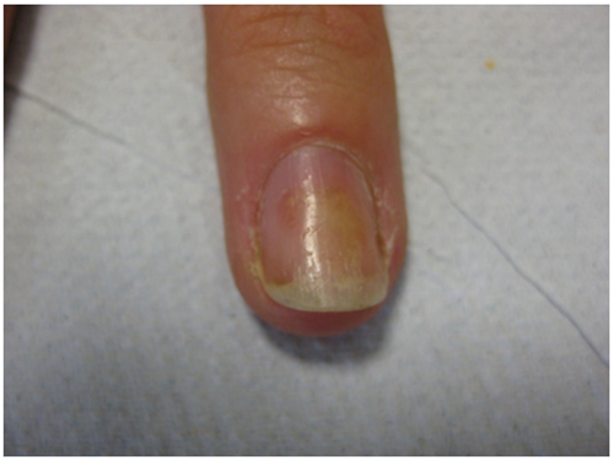

Figure 5. Nail psoriasis in one CD patient. CD, Crohn's disease.

[10%], hypopigmented lesions [i.e. vitiligo, guttate hypopigmentation] in 4 [3%] or alopecia [i.e. androgenic, telogen effluvium, universalis, cicatricial, areata] in 9 patients [6%]. Other skin lesions were observed in 11 patients [7%] [lamellar ichthyosis, hypertricosis, lichen sclerosus et atrophicus, neurodermatitis, hidradenitis suppurativa, annular granuloma, oral lichen planus, localised scleroderma].

4. Discussion

The association between psoriasis and IBD has been described since the 1960s.[3,4] Recently, the growing use of anti-TNFα treatments hasled to the unexpected observation that, although targeting TNFα shows efficacy for treating psoriasis, anti-TNFα may also induce the development or relapse of psoriasis in patients with IBD. The possible development of psoriasis in IBD patients treated with anti-TNFα[10] raised new interest regarding the possible relationship between psoriasis and IBD. Several studies investigated this issue,[17] including possible pathogenic mechanisms leading to psoriasis after anti-TNFα treatments in IBD. A role for IFNα[6,18] and IL-21 has been suggested.[19] Despite these evidences, to our knowledge no studies

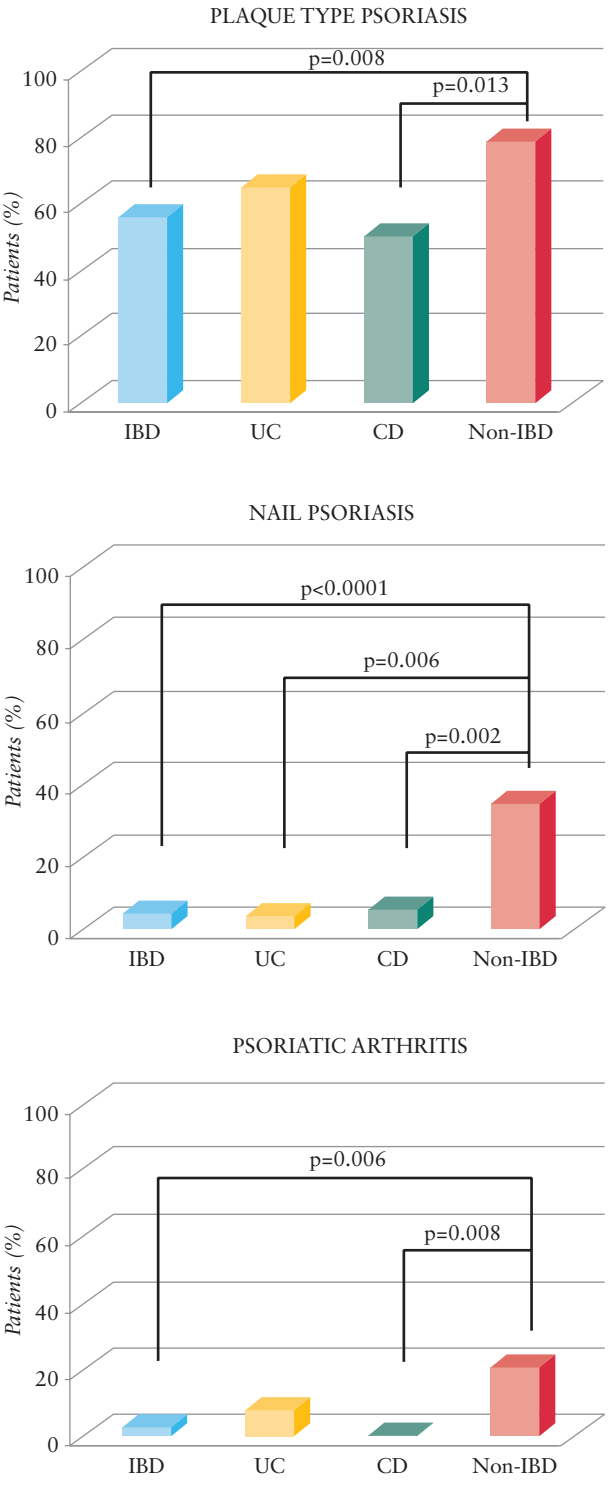

Figure 6. Histograms showing the frequency of plaque-type psoriasis [panel a], nail psoriasis [panel b], and psoriatic arthritis [panel c] in IBD, UC, CD and non-IBD patients. Panel a.: the frequency of plaque-type psoriasis was lower in IBD vs non-IBD [$p = 0.008$] and in CD vs non-IBD [$p = 0.013$]. Panel b: the frequency of nail psoriasis was lower in IBD vs non-IBD [$p < 0.0001$] and in UC and CD vs non-IBD [$p = 0.006$; $p = 0.002$, respectively]. Panel c: psoriatic arthritis was lower in IBD and in CD vs non-IBD [$p = 0.006$ and $p = 0.008$, respectively]. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

specifically investigated whether IBD is associated with specific characteristics of psoriasis [i.e. phenotype and severity], irrespective of anti-TNFα treatments. On the basis of these observations, in a

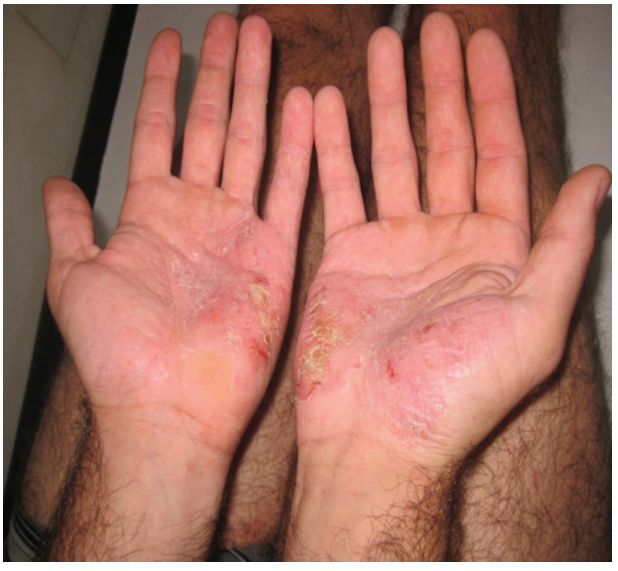

Figure 7. Pustular palmo-plantar psoriasis after anti-TNFα treatment in one CD patient. TNF, tumour necrosis factor; CD, Crohn's disease.

prospective study we aimed to address this issue by comparing the phenotype and severity of psoriasis in a consecutive series of IBD patients and non-IBD controls matched for clinical and demographic characteristics.

In our IBD population, almost one-fourth [25%] of patients had a diagnosis of psoriasis, with a comparable frequency in CD and UC. The observed high frequency of psoriasis in our study is explained by the tested IBD population, including only the subgroup of IBD patients referred to the dermatologist, due to skin lesions requiring further characterisation or for screening before IMM treatments. This observation accounts for the high proportion of IBD patients with a diagnosis of psoriasis in our study population. The aim of the present study was indeed to characterise the clinical characteristics of psoriasis in IBD vs non-IBD controls and not to assess the frequency of psoriasis in IBD.

According to current literature,[20,21] in our study population, clinical characteristics of IBD [site, extent, duration] appeared not to influence the frequency of psoriasis in either CD or UC. Clinical and demographic characteristics of tested UC and CD populations were comparable, with the exclusion of patients' age being higher in the UC vs the CD group. Nevertheless, the observed comparable frequency of psoriasis between UC and CD patients with or without psoriasis supports the observation that age did not significantly affect our findings. In our study, IBD patients and non-IBD controls were matched for demographic characteristics, thus allowing a proper comparison in terms of frequency, severity, and phenotype of psoriasis.

The main finding of the present study is that, when comparing the severity of psoriasis in IBD vs matched non-IBD controls, IBD patients showed a significantly higher frequency of mild psoriasis. Accordingly, IBD patients also showed a significantly lower frequency of both moderate and severe psoriasis compared with non-IBD controls. It is conceivable that corticosteroids, thiopurines, and/or anti-TNFα used for treating patients with IBD, may play a role in this finding, as these treatments may reduce the severity of the psoriatic lesions.[22,23,24] This is also supported by the observation that the frequency of mild, moderate, or severe psoriasis was comparable between patients with CD and UC. Whether the observed lower frequency of moderate/severe psoriasis in our IBD population is also observed in the general IBD population needs to be confirmed by larger studies, also in relation to the possible role played by different treatments used for IBD when considering different study populations. Although IBD, especially CD, can be asymptomatic and sometimes psoriasis can precede the diagnosis of CD, control patients were selected on the basis of a complete absence of present or past medical history, signs/symptoms, or blood chemistry alterations suggesting IBD. Due to the absence of any clinical indication, no additional diagnostic tests were performed in order to exclude IBD.

The second main message arising from our study is that, when comparing psoriasis phenotypes, IBD patients showed a significantly lower frequency of plaque-type, nail, and psoriatic arthritis when compared with non-IBD patients. Explanations for these findings, as also the possible pathogenic mechanisms leading to this observation in our IBD population, are currently not defined. Whether some of the immunological mechanisms involved in the pathogenesis of psoriasis [i.e. IL-23] may play a role in the observed different psoriasis phenotypes in our IBD and non-IBD populations, cannot be addressed in the present study. The aim of the study was indeed to initially assess the severity and phenotype of psoriasis in IBD vs matched non-IBD controls and not to address possible pathogenic mechanisms leading to these findings. Data on invasive skin biopsies and/or cytokine levels assessment were therefore considered not useful as a first step. However, the observed differences between IBD and non IBD patients developing psoriasis support the need for future epidemiological and *in vitro* studies to confirm and to further investigate this topic.

To our knowledge, no comparisons can ibe made with previous observations, as data in this regard are lacking.

When considering psoriasis phenotype, plaque-type psoriasis represented the most frequent phenotype in both IBD and non-IBD study populations. This finding is in agreement with current literature, supporting the conclusion that plaque-type psoriasis is the more frequent phenotype in the general non-IBD population,[25] thus supporting the reliability of dermatological assessment in our study.

In our study, the tested IBD population represented only a proportion of IBD patients evaluated by IBD-dedicated gastroenterologists during the study period [only IBD patients with skin lesions]. This subgroup analysis could represent a limit of the present study. However, two main observations support the contention that the tested IBD population is representative of the general IBD population. In particular, according to current literature,[26] the frequency of psoriasis was significantly higher in UC patients with a family history of psoriasis, although in CD patients this difference did not reach statistical significance. Moreover, characteristics of IBD patients appeared not to influence the frequency of psoriasis in our IBD population. This observation also is supported by current knowledge at this regard,[26] further suggesting the reliability of both the tested IBD population and the modality of dermatological assessment. Regarding the frequency, phenotype and severity of psoriasis in IBD patients treated with anti-TNFα, no conclusions can be drawn from the present study. In our series, psoriasis after anti-TNFα was indeed observed in only 6 of the 68 [9%] patients in CD and in none of the 21 [0%] patients with UC treated with anti-TNFα. Nevertheless, present findings indicate a quite high frequency of psoriasis developing after anti-TNFα treatments in patients with CD, in agreement with previous studies.[26] Present findings also suggests the need to further address this issue, due to the observed arduous clinical management when treating psoriasis developing after anti-TNFα treatment.

Present observations also further support a multidisciplinary approach to increase the quality of care of patients with IBD, as a dermatological evaluation may lead to a new diagnosis or to a detailed characterisation of skin lesions not properly assessed by IBD-dedicated gastroenterologists.

In conclusion, the present prospective case-control study showed a lower frequency of severe psoriasis in tested the IBD population. A lower frequency of plaque-type psoriasis, nail psoriasis, and psoriatic arthritis was also observed in tested IBD vs non-IBD populations. The reported observations may provide new evidences regarding the characteristics of psoriasis in IBD, including severity and phenotype, at least in our IBD population. Present findings may also add new clues useful for further studies focusing on the pathogenic mechanisms leading to psoriasis in patients with IBD, regardless of current or past use of anti-TNFα treatments. The growing evidences supporting the possible development of psoriasis in IBD patients treated with anti-TNFα indicate that psoriasis represents a currently relevant issue, in terms of pathogenic mechanisms and clinical management of patients with IBD.

Conflict of Interest

The authors declare no conflict of interests: http://ecco-jcc.oxfordjournals.org/lookup/suppl/doi:10.1093/ecco-jcc/jjv068/-/DC1

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