Brief Report

Association of Psoriasis with Autoimmune Disorders: Results of a Pilot Study

Abstract

Background: Association of psoriasis with other autoimmune diseases remains an ongoing research subject. **Objectives:** To investigate the association of psoriasis with other autoimmune disorders. **Materials and Methods:** We studied 80 (M: F 57:23) psoriasis patients aged 13–75 years for concurrent autoimmune disorders. After clinical examination, hemogram, fasting blood sugar, HbA1c, thyroid function tests, anti-TPO antibody, rheumatoid factor, anti-tTG antibody, anti-CCP antibody, ANA, anti-dsDNA antibody, anti-Ro antibody, and fecal calprotectin were estimated. **Results:** Mild-to-moderate and severe psoriasis was present in 86.3% and 13.8% patients, respectively. Psoriatic arthritis was present in 3.8% patients, all of whom also had severe psoriasis. Only 37 (46.3%) patients had clinical and/or sero-abnormality suggestive of autoimmune disorders; vitiligo in 3.8%, type-1 diabetes mellitus (DM) in 1.3%, and type-2 DM in 6.3% patients. Sero-positivity reflecting subclinical autoimmunity was noted for anti-CCP antibodies (in 2.5%), rheumatoid factor (in 2.5%), hypo- or hyper-thyroidism (in 8.8%), anti-TPO antibodies (in 5.0%), anti-tTG antibody (in 1.3%), ANA (in 5.0%), anti-dsDNA antibody (in 2.5%), and anti-Ro antibody in 11.3% patients. Elevated fecal calprotectin levels suggestive of inflammatory bowel disease (IBD) occurred in 11.2% of 27 patients. Multiple abnormalities happened in 2.5% patients. **Conclusion:** Apparently psoriasis patients seem to have a predilection for other autoimmune disorders particularly for vitiligo, diabetes mellitus, autoimmune thyroiditis, rheumatoid arthritis, and IBD. However, association between psoriasis and other autoimmune disorders at best remains tenuous for want of strong evidence. Nevertheless, screening for them will improve overall management of these patients. Cross-sectional study design and small number of study subjects remain important limitations.

Keywords: *Arthritis, autoimmune thyroiditis, celiac disease, diabetes mellitus, inflammatory bowel disease, rheumatoid arthritis, vitiligo*

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Introduction

Psoriasis, a common chronic inflammatory dermatosis, affects almost 0.5% to 11.4% persons of any age and gender worldwide and 0.44% to 2.8% in India.[1,2] Its etiology remains elusive but genetic, metabolic, and immunologic mechanisms have been implicated. A Th1 type of immune response and inflammatory cells, elevated TNF-α and other cytokines, chemokines, and growth factors are central to the inflammation in the dermal microenvironment and epidermal hyper proliferation occurs secondarily.[3] This chronic Th1 inflammatory milieu has been implicated for enhanced risk of cardiovascular mortality/morbidity (myocardial infarction, stroke), hypertension, chronic renal disease, metabolic syndrome or relevant components (obesity, dyslipidemia, atherosclerosis, type-2 diabetes mellitus), cancer, depression, and Crohn's disease significantly impairing quality of life in psoriasis patients.[4-7] This has led to current thinking that psoriasis is a systemic disease with numerous multiorgan complications because of chronic inflammation. Besides, smoking, alcoholism, obesity, low physical activity, medications (acitretin, cyclosporine, methotrexate), dyslipidemia, hyper homocysteinemia, and psychological stress are other identified risk factors for these co-morbidities.[8,9]

Psoriasis, an immune-mediated inflammatory dermatosis, in recent years has been widely viewed as an autoimmune disease in view of flare-ups in psoriasis being triggered by bacterial microbiota by molecular mimicry, for instance, between streptococcal and

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keratin proteins, the existence of homologous peptides between these proteins and CD8 + T cells' response to these homologous peptides.[10,11] The efficacy of various targeted therapies both in psoriasis and other autoimmune disorders further upholds this view. For instance, efficacy of TNF-α inhibitors (etanercept, infliximab, adalimumab, certolizumab pegol), IL-12/23 inhibitor (ustekinumab) in psoriasis and inflammatory bowel disease, and Janus Kinase inhibitor (tofacitinib) in psoriasis, rheumatoid arthritis, atopic dermatitis, and vitiligo suggests common immune pathways for these disorders and psoriasis.[12-14] Furthermore, pathways that are associated with autoimmunity such as T-cell development in thymus or periphery, T-cell proliferation, or activation that may include immune synapse formation regulators have been demonstrated in psoriasis.[15] A meta-analysis of a single mutation of CD226, Gly307Ser (rs763361) has suggested that this modification is associated with an increased risk of developing various autoimmune disorders including psoriasis.[16]

Apart from genetic predisposition, the evidence for considering psoriasis as an autoimmune disease also includes overlap of several biochemical pathways with those altered in other autoimmune diseases such as Crohn's disease, type-I diabetes, and rheumatoid arthritis. In addition, psoriasis is found frequently associated with some major autoimmune disorders including systemic lupus erythematosus, autoimmune thyroid disease, celiac disease, inflammatory bowel disease (IBD), especially Crohn's disease, multiple sclerosis, Sjögren's syndrome, vitiligo, and alopecia areata.[17,18] However, the issue whether psoriasis should be considered a *bona fide* autoimmune disease remains contested given that no autoantigen(s) or self-reactive T cells that trigger the disease have been authenticated. Thus, the association of psoriasis with other autoimmune diseases remains a subject of ongoing research. We carried out this study to find out the profile of autoimmune disorders among Indian patients with psoriasis for paucity of such data.

Materials and Methods

For reasons of feasibility, 80 consecutive patients with chronic plaque psoriasis from the dermatology outpatient clinic of a tertiary care institute were enrolled for this pilot study between April 2017 and March 2018. This cross-sectional study was approved by Institutional Ethics Committee. Patients with common confounding factors such as those on systemic retinoids, corticosteroids, or other immunomodulator drugs in last 3 months or with preexisting diabetes mellitus (DM), hypertension, hepato-renal disease, obesity (BMI >30 kg/m^2), collagen vascular disorders, or malignancy, were not included. Children aged <12 years and pregnant and lactating women were also excluded. Demographic profile, family/personal medical history, and clinical details of psoriasis or other autoimmune disorders were recorded after informed (personal/parental/guardian's) consent. The severity of psoriasis was graded as mild (PASI <6), moderate (PASI = 6–12), and severe (PASI >12). Psoriatic arthritis was classified by criteria of Moll and Wright as asymmetrical mono/oligoarthritis, symmetrical polyarthritis, distal interphalangeal joint arthritis, axial arthritis, and arthritis mutilans.[19]

Blood sample (5 ml) was collected after overnight fasting by antecubital venous puncture for relevant tests performed in institutional central research laboratory. Complete hemogram and biochemical analysis were carried out by standard protocols. HbA1C was measured by Boronate affinity principle, thyroid function tests and anti-thyroid peroxidase (anti-TPO) antibodies were measured using chemiluminescent immunoassay (CLIA). Rheumatoid factor was detected by latex particle slide agglutination test and anti-CCP antibodies were assayed by chemiluminescent microparticle immunoassay (CMIA). Enzyme-linked immunosorbent assay (ELISA) was performed for quantitative estimation of serum ANA and anti-tTG antibodies. Quantitative estimation of serum anti-dsDNA and anti-Ro antibody in study subjects and equal number of age and gender matched healthy volunteers (M: F = 57:23, 2.47:1) was performed by ELISA to obtain baseline values as the test kit cut-off values were not provided in the package insert. Fecal calprotectin levels were measured from day's first stool sample by fluoroenzyme immunoassay in 47 volunteering patients. Manufacturers' protocols were followed for all laboratory tests.

Statistical analysis

The data obtained was tabulated and analyzed by using MS Word Excel software. The continuous data are presented as means and standard deviation, and categorical variables are calculated as frequencies and percentages.

Results

Table 1 depicts baseline clinicoepidemiologic features of 80 (M: F = 57:23, 2.47:1) patients aged between 13 and 75 years (mean ± SD = 42.04 ± 13.47 years). The disease duration was 2 months to 30 years (mean ± SD = 58.8 ± 60.6 months). Mild-to-moderate and severe psoriasis was present in 69 (86.25%) and 11 (13.75%) patients, respectively. Three (3.75%) patients with severe psoriasis had symmetric polyarthritis (in one) and asymmetric oligoarthritis in 2 patients.

One or more clinical and/or deranged laboratory parameters indicative of a subclinical autoimmune disorder were detected in 37 (46.25%) patients [Table 2]. Clinically, 3 (3.8%) patients had vitiligo comprising vitiligo universalis in one and focal vitiligo in 2 patients. One (1.3%) patient had type-1 DM and

Table 1: Baseline characteristics of psoriasis patients and controls

Baseline characteristics		Number of Patients (%) *n*=80	Number of Control (%) *n*=80
Gender	Males (M)	57 (71.25)	57 (71.25)
	Females (F)	23 (28.75)	23 (28.75)
	M:F	2.47:1	2.47:1
Age in years	Range	13-75	15-70
	Mean±SD	42.04±13.47	42.53±13.26
	≤20	5	5
	21-30	14	15
	31-40	14	9
	41-50	29	32
	51-60	10	13
	>60	8	6
Duration of psoriasis	Range	2 months-30 years	-
	Mean±SD (months)	58.82±60.62	-
	<5 years	46 (57.5%)	-
	5-10 years	26 (32.5%)	-
	>10 years	08 (10%)	-
PASI score (severity)	<6 (Mild)	41 (51.25%)	-
	6-12 (moderate)	28 (35%)	-
	>12 (Severe)	11 (13.75%)	-
Psoriatic arthritis	Asymmetric mono or oligoarthritis	2 (2.5%)	-
	Symmetric polyarthritis	1 (1.25%)	-

5 (6.3%) patients were detected with type-2 DM. Two (2.5%) patients with polyarthritis had positive anti-CCP antibody and 2 (2.5%) patients without arthritis showed isolated positivity for rheumatoid factor. Deranged thyroid status was present in 7 (8.8%) patients and comprised hyperthyroidism in one (1.3%) and hypothyroidism in 2 (2.5%) patients. One of the patients with hypothyroidism also had psoriatic arthritis. Four (5.0%) patients with euthyroid status demonstrated elevated levels of anti-TPO antibodies.

Anti-tTG antibody was detected in one (1.3%) patient who was otherwise asymptomatic for celiac disease or gluten enteropathy/sensitivity. Four (5.0%) patients showed positive ANA, 2 (2.5%) patients had anti-dsDNA antibody positivity, and 9 (11.3%) patients had positive anti-Ro antibody reflecting the possibility of subclinical autoimmunity.

The reports for fecal calprotectin levels were available in 27 of these 37 patients and 6 (16.2%) of them showed elevated levels (>120 mg/kg); one of them also had psoriatic arthritis. The values were equivocal in 7 (18.9%) patients. All these patients were asymptomatic for IBD.

Associations with multiple autoimmune disorders noted in 2 (2.5%) patients included type-1 DM with hypothyroidism in one, and vitiligo with highly elevated fecal calprotectin in another.

Discussion

The overall clinicoepidemiologic features and presence of psoriatic arthritis in our study subjects corroborate as described previously.[8,9,20]

Clustering of psoriasis with various autoimmune disorders such as Crohn's disease, celiac disease, multiple sclerosis, systemic lupus erythematosus, autoimmune thyroid disease, and rarely with Sjögren's syndrome, vitiligo, and alopecia areata favors the hypothesis of psoriasis being an autoimmune disease.[17,18,21] Presence of one or more clinical and serological abnormality suggestive of autoimmune disorders in our 37 (46.3%) patients also corroborates. Sharquie *et al.*[22] measured frequencies of vitiligo in psoriatic patients and psoriasis in vitiligo patients and found that frequency of psoriasis among vitiligo patients was 6% while it was 2% for vitiligo among psoriasis patients. However, it remains difficult to comment on which disease was initiated first in a scenario when psoriasis appears only in vitiliginous area sometimes. Vitiligo was observed in 0.8% patients in a retrospective study of 4700 Indian patients with psoriasis.[23] Coexistent focal or universal vitiligo noted in our 3 (3.8%) patients more or less corroborates foregoing observations. The phenomena of such co-existence and co-localization remain poorly understood and Koebner's phenomenon, a feature observed in both the diseases, structural similarities between antistratum corneum antibodies and anti-melanocyte antibodies, and a common neuropeptide remain commonly implicated causative factors.[21] Varying with severity psoriasis also has been identified as an independent risk factor for developing type-2 DM.[24,25] The pooled odds ratio was 1.53 for mild psoriasis and 1.97 for severe psoriasis in a meta-analysis.[26] Similarly, the observed hazard ratio for incident DM in another cohort of 108132 psoriasis patients was 1.4%, 1.11%, and 1.46% in mild, moderate,

Table 2: Association of psoriasis with autoimmune disorders in 37 patients with positive results

Suspected autoimmune disease	Laboratory investigations	Methods/ equipment (manufacturer)	Baseline normal values	Number of patients (%) *n*=80	Remarks
Vitiligo	Clinical	Clinical	NA	3 (3.8)	Focal vitiligo=2, Universal vitiligo=1
Diabetes mellitus	Fasting Blood Sugar	ERBA Mannheim automated analyser XL-300 (ERBA Diagnostics Mannheim, GmbH, Germany)	<126 mg/dl	1 (1.3)	Type-1 DM=1, Type-2 DM=5 (Psoriasis was moderate to severe in 4 of these patients)
	HbA1C	Boronate affinity test principle (Nycomed Pharma, Oslo, Norway)	<6.5 mg%	5 (6.3)	
Rheumatoid Arthritis	Rheumatoid factor	Latex particle slide agglutination test	<8 IU/ml	2 (2.5)	Two patients had no arthritis
	Anti-CCP antibody	CMIA/ARCHITECT i2000SR (Abbott Core Laboratory, USA)	<5 U/ml	2 (2.5)	Both had symmetric poly arthritis
Autoimmune thyroid disorders	Thyroid function tests	CLIA/Immulite 1000, (Seimens Healthcare Diagnostics Products Ltd., UK)	T3 69-202 ng/dl T4 4.4-11.6 µg/dl TSH 0.53-5.4 µIU/ml	7 (8.8)	Hypothyroidism=2 (one patient had psoriatic arthritis), Hyperthyroidism -1, Equivocal values=4
	Anti-TPO antibodies		<35 IU/ml	4 (5.0)	All these had euthyroid status
Celiac disease	Anti-*t*TG IgA antibody	ELISA (DRG Instruments, Germany)	Positive ≥10 U/ml	1 (1.3)	Patient was clinically asymptomatic
Inflammatory bowel disease	Fecal calprotectin*	Fluoroenzyme Immunoassay (Thermo Fischer Scientific, USA)	Highly suggestive >120 mg/kg Equivocal 51-120 mg/kg Normal 0-50 mg/kg	6 (16.2)[$] 7 (18.9) 0	Values are for 27 of 37 patients who volunteered for this test
Other autoimmune disease markers	ANA	ELISA (Calbiotech Inc. USA)	Detectable >1.1 Nondetectable <0.9 Borderline positive 0.9-1.1	4 (5.0) - -	Titers were not measured
	Anti-dsDNA antibody	ELISA Research kits, (Shanghai Qayee Biotechnology Co. Ltd., China)	155.96-574.7 pg/ml	2 (2.5)	Baseline values were obtained from 80 healthy human volunteer controls [Table 1]
	Anti-Ro antibody		17.67-217.51 ng/ml	9 (11.3)	

CLIA, Chemiluminescent immunoassay; CMIA, Chemiluminescent Microparticle Immunoassay; ELISA, Enzyme-linked immunosorbent assay; Anti- tTG, anti-tissue-transglutaminase; *Only 47 of 80 patients had consented for Fecal calprotectin estimation, [$]One patient had psoriatic arthritis

and severe psoriasis, respectively.[24] Association of type-1 DM and psoriasis too has been postulated on the basis of genetic studies. Genome wide scan locus on chromosome 4 has linked psoriatic arthritis and type-1 DM and other autoimmune diseases.[27] Wu *et al.*[12] observed an odds ratio of 1.0 (0.96–1.1) for type-1 DM in a retrospective analysis of 25341 patients with psoriasis. Our 5 (6.3%) patients had incident type-2 DM and psoriasis was moderate to severe in four of them. Similarly, type-1 DM was present in another patient who had mild psoriasis as well as hypothyroidism corroborating these observations. However, clinical association of DM and psoriasis in general needs further elucidation.

Infiltration of immune cells into the synovium in rheumatoid arthritis and in psoriatic skin is considered one of the principal characteristics of both the diseases.[28] Thus, these individuals are more likely to develop concurrent autoimmune diseases compared to those without arthritis. Wu *et al.*[12] observed a higher odds ratio for developing an autoimmune disease in patients with psoriatic arthritis than with psoriasis alone. We also made similar observations as 2 (2.5%) patients with polyarthritis were sero-positive for anti-CCP antibodies, while other 2 (2.5%) patients without arthritis demonstrated sero-positivity for rheumatoid factor reflecting possibility of concurrent rheumatoid arthritis. One patient with psoriatic arthritis also had concurrent hypothyroidism and elevated fecal calprotectin levels suggestive of IBD reflecting overall propensity of these patients for developing other autoimmune disorders.

Thyroid abnormalities are not uncommon in psoriasis patients and occurred as increased levels of at least one thyroid hormone in 22% patients, especially with high PASI score in a case control study.[29] Hypothyroidism in 5.4%, hyperthyroidism in 2.7%, and anti-TPO antibodies in 13.5% patients were reported in a retrospective study recently.[20] However, the difference was not statistically

significant for gender, age, duration, and severity of psoriasis when compared with patients with normal thyroid function tests. Deranged thyroid status in 7 (8.8%) patients in this study was consistent with hyperthyroidism in one and hypothyroidism in 2 patients. Other 4 (5.0%) patients with euthyroid status had elevated anti-TPO antibodies indicating possible subclinical autoimmune thyroiditis. However, for small number of patients, the significance of our observations currently will be conjectural and further studies will perhaps delineate the role of these hormones in etiopathogenesis of psoriasis as an autoimmune disorder.

A significant elevation of serum anti-transglutaminase and anti-gliadin antibodies levels compared to controls reported in psoriasis patients as well as increased incidence of severe psoriasis in patients with celiac disease reflect their possible link.[30-33] Woo *et al.*[30] had 7.7% of 130 psoriatic patients with sero-positivity for anti-tTG antibody, whereas anti-gliadin antibodies were observed in 16% psoriasis patients in another study which also demonstrated severe and difficult to control disease in 14% compared to 7% cases with normal levels.[31] Psoriasis patients with celiac disease-associated anti-gliadin IgA antibody said to have severe psoriatic arthritis with pronounced inflammation and morning stiffness.[32] However, the prevalence of celiac disease in patients with psoriasis is variable with contrasting reports across ethnicities and regions.[34-37] Only one (1.3%) patient showed anti-tTG antibody who was otherwise asymptomatic clinically and its significance in him remains unknown for want of endoscopic confirmation of diagnosis.

Psoriasis patients may also demonstrate asymptomatic bowel inflammation. Whereas 10% patients with Crohn's disease had relatives affected with psoriasis, the prevalence was only 2.9% among controls.[38] The gut-skin axis theory and similarity of microbiological environment of the gut of patients suggests a common link between psoriasis and IBD despite contrasting observations.[39-41] However, Tsai *et al.*[40] did not observe higher risk of Crohn's disease among Taiwanese patients with psoriasis in contrast to IBD and psoriasis as being risk factors for each other in a Danish study.[41] The fecal calprotectin levels in our 6 (16.2%) of 37 patients were suggestive of possible concurrent but asymptomatic IBD, while equivocal levels in other 18.9% patients indicates its possible underlying association in a few cases. However, fecal calprotectin estimation is not highly specific of IBD compared to clinicopathological correlation.

It has been demonstrated that psoriasis can be significantly associated with Sjögren's syndrome, ankylosing spondylitis, Bechet's disease, systemic lupus erythematosus, systemic sclerosis, and dermatomyositis/polymyositis.[12,42] Although we did not observe any of these disorders clinically in our patients, positive serology for anti-Ro antibody in 11.3%, ANA in 5.0%, and anti-dsDNA antibody in 2.5% patients, respectively, reflects possible underlying autoimmune activity warranting a long-term follow-up.

Limitations

Long-term follow-up or post treatment/remission assessment of study parameters was not a part of the study. ELISA does not measure ANA titers. Fecal calprotectin has low diagnostic specificity for IBD compared to colonoscopy and histopathology and could not be estimated in all subjects. Cross-sectional study design, small number of patients, and lack of controls were other limitations.

Conclusion

The presence of clinical and laboratory abnormalities in patients with psoriasis reflects subtle autoimmunity or a predilection for isolated or multiple diseases within the psoriasis-associated autoimmunity spectrum which may remain asymptomatic. However, the association between psoriasis and other autoimmune disorders at best remains tenuous for want of quality evidence and long-term studies. Better-designed future studies will perhaps further our understanding of entire spectrum of psoriasis as an autoimmune disorder. Nevertheless, screening for concurrent autoimmune disorders seems prudent for a holistic management of patients with psoriasis.

Statement of ethics

The study was approved by Institutional Ethics Committee (Rgn no: ECR/490/Inst/HP/2013/RR-16). Informed consent was obtained from all study subjects for enrollment and publication of material with the understanding that their names and initials will not be published and due efforts will be made to conceal their identity but anonymity cannot be guaranteed. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 as revised in 2013.

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Conflicts of interest

There are no conflicts of interest.

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