A Case of Recalcitrant Prurigo Nodularis with Heightened Expression of STAT 3 and STAT 6 and its Dramatic Response to Tofacitinib

Dear Editor,

Prurigo nodularis (PN) is a chronic, intensely pruritic disease of unknown etiology, which is usually recalcitrant to therapy, and manifests clinically as multiple, firm, hyperkeratotic, eroded papulonodular lesions distributed symmetrically on the extensors and trunk. While numerous factors seem to play a role, the predominant mechanism involves neural hyperplasia and a T helper cell (Th) 2 predominant cytokine response.[1] The break work by suppressing inflammation, and the various agents used include pregabalin, gabapentin, cyclosporine, methotrexate, and thalidomide.[2] Tofacitinib is a Janus kinase (JAK) inhibitor that has been used with variable results, but there is no case of the translative use of JAK inhibitor concomitant with JAK-STAT expression data with this class of drugs.[3]

A 38-year-old woman presented to the dermatology outpatient department with generalized excoriated papulonodular lesions over both upper and lower limbs (extensors > flexors), trunk including buttocks, with sparing of the middle one-third of back and chest, for the past 12 years [Figure 1a]. Pruritus grading severity score (PGSS) was 15 out of 19 at presentation, thereby implying a severe and generalized form of the disease.[4] An investigation panel was carried out to rule out any secondary cause of PN, including a complete blood count, fasting sugar levels, liver and kidney function tests, thyroid function tests, viral markers (HIV-ELISA, hepatitis B and C serology), erythrocyte sedimentation rate, stool for occult blood, serum IgE, chest X-ray and ultrasound abdomen, all of which were within normal limits.

The treatment history included superpotent topical corticosteroids, emollients, camphor-containing lotions, oral antihistamines, and nortriptyline.[2] Based on a previous study,[5] she was administered low-dose thalidomide [50 mg bid], which effected partial improvement, but the condition recurred within three months of stopping the drug.

As part of an ongoing study,[1] a histopathological assessment with immunohistochemistry (IHC) expression was done for STAT 1, 3, and 6. This is relevant as STAT is the counterpart signal pathway that mediates the action of cytokines. STAT 1, 3, and 6 were used to demonstrate the activity of Th1, Th17/Th2, and Th2 cells, respectively.[1] A lesional and a non-lesional skin biopsy was obtained to compare the IHC results. STAT 3 and 6 in lesional skin showed positive nuclear staining in basal cells [Figure 2]. However, STAT 1 in lesional skin and STAT 1, 3, and 6 in non-lesional skin were negative for nuclear staining.

Inhibition of the JAK receptors can suppress the effect of the signaling pathway and the T helper subtypes. As depicted in Table 1, the relevant expression of STAT 3 and 6 can be adequately suppressed by tofacitinib, (JAK1, 3, and 2 inhibitor), and thus its administration would prevent the effect of dominant Th2 cytokines mediated by STAT 6 and Th2 cells.[6] Based on this evidence, tofacitinib was started in the dose of 5 mg bid for the first four weeks along with clobetasol propionate 0.025% cream twice a day, with antihistamine and emollient, with the patient showing prompt resolution in pruritus and sleep disturbances in 10 days. The dose was then tapered to 5 mg once a day for the next two months and then stopped. The PGSS at four weeks became 9 (moderate grade), and at 12 weeks was

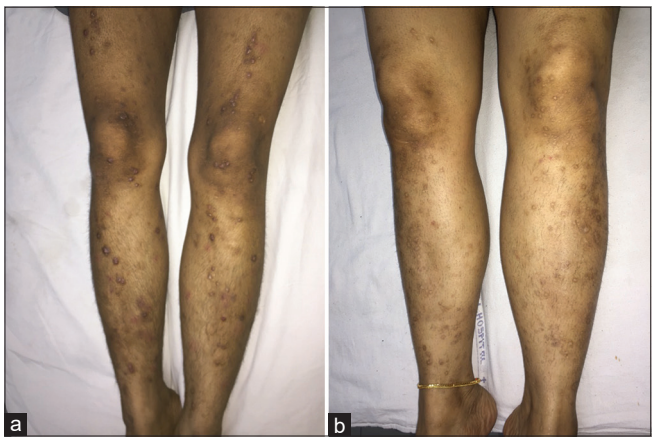

Figure 1: (a) Hyperkeratotic and eroded papulonodules are present bilaterally symmetrically over both lower limbs. (b) Presence of post-inflammatory hypopigmentation and hyperpigmentation present over both lower limbs after the subsidence of the disease

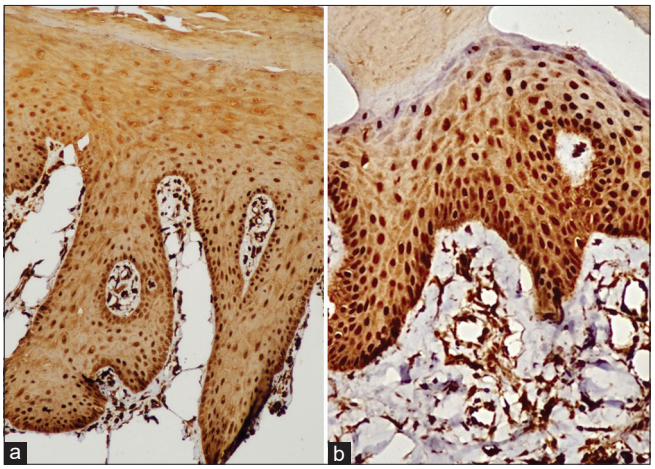

Figure 2: The immunohistochemistry staining is identified by nuclear staining predominantly in the basal layer with STAT 3 positivity (a) and STAT 6 positivity (b), respectively (IHC, 20x)

Table 1: Overview of the signaling pathway mediated by the major cytokines that activate the various subsets of T helper cells via the JAK-STAT pathway[6]

	Cytokines acting as ligands for JAKs	JAKs activated	STATs activated	T helper cells activated	Cytokines released
Naive CD4+T cells	IL-12	JAK 1 and JAK 2	STAT 1	Th1 cells	Interferon-γ, TNF α
	IL-4	JAK 1 and JAK 3	STAT 6	Th 2 cells	IL-4, IL-5, IL-13
		JAK 1 and JAK 2	STAT 3	Th 2	IL-31
	IL-4, IL-21, TGF β1	JAK 1 and JAK 3	STAT 6	Th 9 cells	IL-9, IL-10
	IL-6, IL-23, TGF β1, IL-1, IL-21	JAK 1, JAK2, and TYK 2	STAT 3	Th 17 cells	IL-17A, IL-17F
	IL-6, TNF α	JAK 1, JAK2, and TYK 2	STAT 3	Th 22	IL-13, IL-21, IL-22

IL=interleukin, JAK=Janus kinase, STAT=Signal transducers and activators of transcription, CD=Cluster of differentiation, TGF=Transforming growth factor, TNF=Tumor necrosis factor, TYK2=tyrosine kinase 2, Th=T helper cells

4 (mild grade). [Figure 1b]. Apart from PGSS, a numerical rating scale (NRS) was also used. The initial NRS score was 9; four weeks later, it was 5, and eight weeks later, it was 2. The drug was well tolerated by the patient, with no side effects noted.

It is established that PN is characterized by an increased expression of interleukin IL-4, IL-13, IL-31, IL-17, all of which mediate their effect via the JAK-STAT pathway. A recent study has established the role of STAT 3 and STAT 6,[1] and while no oral STAT inhibitor is commercially available, JAK inhibitors are approved for varied indications and would effectively curtail the STAT expression and the predominant cytokine expression. Although there are reports of variable efficacy of JAK inhibitors in PN, we attempted to translate its clinical effects based on heightened STAT expression, which makes its use justifiable, unlike previous cases where no concomitant STAT expression was studied. The dramatic response in our case is possible because the drug inhibits the pathogenic Th cells' cytokines, such as IL-4, IL-13, and IL-31, which initiate and perpetuate PN. It seems that based on existing data,[1,2] the drug is ideally suited for PN.[2]

Notably, our case had failed numerous systemic agents, including low-dose thalidomide[5] and possibly therapy tailored to the tissue cytokine, and JAK/STAT expression would be the ideal mode of drug selection.[2] While the present data on JAK inhibitors in PN is restricted to case reports, a prospective study with a correlation with IHC or mRNA expression of JAK/STAT and cytokines can validate the use of JAK inhibitors in PN.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Agrawal D, Sardana K, Mathachan SR, Bhardwaj M, Ahuja A, Jain S. A prospective study examining the expression of STAT 1, 3, 6 in prurigo nodularis lesions with its immunopathogenic and

therapeutic implications. J Cosmet Dermatol. 2022;21:4009-15.
2. Agrawal D, Sardana K, Mathachan SR, Bhardwaj M, Ahuja A, Jain S. A prospective study examining the effect of selected topical and systemic drugs on pruritus grading system score and STAT 6 expression in patients of prurigo nodularis. Indian J Dermatol 2021;66:638-44.
3. Molloy OE, Kearney N, Byrne N, Kirby B. Successful treatment of recalcitrant nodular prurigo with tofacitinib. Clin Exp Dermatol 2020;45:918-20.
4. Al-Qarqaz FA, Aboosi MA, Shiyab DA, Batainch A. Using pruritus grading system for measurement of pruritus in patients with diseases associated with itch. J Med J 2012; 46:39-44.
5. Sardana K, Gupta A, Sinha S. An observational analysis of low-dose thalidomide in recalcitrant prurigo nodularis. Clin Exp Dermatol 2020; 45:92-6.
6. O'Shea J, Gadina M, Siegel RM. Cytokine and cytokine receptors. In:Rich RR, Fleisher TA, Shearer WT, Schroeder HWJr, Frew AJ, Weyand CM, editors. Clinical Immunology: Principles and Practice. 5th ed. Elsevier, 2019. p. 127-55.

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