Immune stimulus exposure as a trigger for the development of chronic pruritus and circulating blood type 2 inflammation

Jaya Manjunath, BS,[a,b,c] Viviane Liao, BS,[a,b,c] Anusha Kambala, BS,[a,b] Aaron Bao, BA,[a,b,c] Alexander L. Kollhoff, MD,[a,b,c] Emily Z. Ma, BS,[a,b,c] Brenda Umenita Imo, MS,[a,b] Hannah Cornman, BS,[a,b] Sriya V. Reddy, BS,[d] Kevin K. Lee, BS,[a,b,c] Weiying Lu, BS,[d] Selina M. Yossef, BA,[d] Madan M. Kwatra, PhD,[d] and Shawn G. Kwatra, MD[a,b]

Background: Chronic pruritus (CP) is a poorly characterized condition associated with intense pruritus without a primary skin eruption. This condition tends to emerge more commonly in older adults, and there is limited research on triggering factors.

Objective: To explore the clinical characteristics and pathophysiology of CP following exposure to an immune stimulus.

Methods: Clinical characteristics and plasma samples were collected from 15 patients who developed CP following an immune stimulus such as checkpoint inhibitors or vaccination. A multiplex panel was used to analyze plasma cytokine concentrations within these patients.

Results: Most immunotherapy-treated patients experienced CP during treatment or after 21 to 60 days of receiving treatment, while vaccine-stimulated patients developed pruritus within a week of vaccination. Plasma cytokine analysis revealed elevated levels of 12 cytokines in patients with immune-stimulated CP compared to healthy controls. Notably, T helper 2 (Th2) related cytokines interleukin (IL)-5 (fold change 2.65; $q < 0.25$) and thymic stromal lymphopoietin (fold change 1.61 $q < 0.25$) were upregulated.

Limitations: Limitations of this study include limited sample size, particularly in the plasma cytokine assay.

From the Department of Dermatology, University of Maryland School of Medicine, Baltimore, Maryland[a]; Department of Dermatology, Maryland Itch Center, University of Maryland School of Medicine, Baltimore, Maryland[b]; Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland[c]; and Department of Anesthesiology, Duke University School of Medicine, Durham, North Carolina.[d]

Authors Manjunath and Liao are co-first authors with equal contributions.

Drs M.M. Kwatra and S.G. Kwatra contributed equally as senior authors.

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Correspondence to: Shawn G. Kwatra, MD, Joseph W. Burnett Professor and Chair, Department of Dermatology, University of Maryland School of Medicine, Office: 419 West Redwood Street, Baltimore, MD 21201. E-mail: kwatra.shawn@gmail.com.

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Conclusions and Relevance: This study reveals triggers of CP development and describes alterations in blood Th2 markers in patients with CP, including IgE, increased blood eosinophils, and cytokines IL-5 and thymic stromal lymphopoietin. (JAAD Int 2024;16:97-102.)

Key words: cytokines; dermatology; pruritus; type 2 inflammation.

INTRODUCTION

Chronic pruritus (CP) is a burdensome condition diagnosed in patients with CP, in which the etiology remains unknown and idiopathic itch lasts at least 6 weeks. It is a common condition that can be linked to dermatologic, renal, hepatobiliary, neurologic, and psychogenic etiologies.[1] More prevalent among older adults, CP is a heterogeneous disease with underlying neuroimmune dysregulation.[2]

Prior studies have identified subsets of patients with CP with evidence of type 2 inflammation, suggested by elevated levels of eosinophils, IgE, and interleukin (IL)-31.[3-5] However, the potential role of external immune stimuli such as immunotherapy, vaccinations, and viral infections in triggering CP remains understudied. This study examines the clinical characteristics, blood biomarkers, and triggering factors among patients with CP.

CAPSULE SUMMARY

- Fifteen patients developed chronic pruritus without a primary skin eruption following immune stimulus exposure, including immunotherapy. There was upregulation of IgE, blood eosinophils, and Th2-related cytokines IL-5 and thymic stromal lymphopoietin.
- These results highlight the underlying Th2-biased immune polarization of chronic pruritus triggered by immune stimulation.

METHODS

Patients were enrolled between 2019 and 2022. Circulating plasma biomarkers from adult patients with immune-stimulated CP were compared against those from 14 age-, sex-, and race-matched healthy controls. Inclusion criteria included a diagnosis of CP by a board-certified dermatologist and a Worst Itch Numeric Rating Scale score of at least 6. Healthy controls included patients with clinically healthy skin and no pruritus. Demographic, clinical characteristics, and laboratory values were collected at the time of blood draw. The normal range of IgE was defined as <100 kU/L and increased blood eosinophils was defined as an absolute eosinophil count greater than 0.3 K/mm^3, or eosinophil percentage greater than 4%.[2,6] History of atopy was defined as the presence of at least 2 of 3 prior diagnoses with asthma, allergic rhinitis, or atopic dermatitis, as performed previously.[7] Written, informed consent was obtained from each study participant.

Plasma biomarker measurement and statistical analysis

To evaluate plasma biomarkers of inflammation/immune response in 6 patients (3 stimulated by nivolumab, 1 stimulated by R(rituximab)-C(cyclophosphamide) H(doxorubicin hydrochloride) O(vincristine sulfate), P(prednisone) (R-CHOP), and 2 stimulated by COVID-19 vaccination) we employed V-PLEX Human Biomarker 54-Plex Multiplex Plates (Cat#K15248D, MesoScale Diagnostics). All samples were tested in duplicate.

All statistical analyses were performed in R version 4.0.3. Biomarkers with >33% of samples below the detection limit (DL) were dichotomized into binomial variables with values below the DL as negative and values above the DL as positive. For all other biomarkers, values below the DL were imputed with half the DL. We only generated fold change (FC) from continuous biomarkers that had samples with <33% of the samples below the DL. Cytokine concentrations were log transformed and normalized for plate variations using ComBat from Bioconductor package sva based on a plasma reference sample run alongside samples in all the plates. Cytokine concentrations of continuous biomarkers were compared using the Mann-Whitney U test, with the Benjamini-Hochberg procedure to correct for multiple comparisons.

RESULTS

Clinical characteristics

Fifteen patients, 11 male and 4 female, were included in this cohort (Table I). The median age was 70 years old, and 14 patients were Caucasian. Five patients had a history of atopy with the presence of at least 2 of 3 prior diagnoses with asthma, allergic rhinitis, or atopic dermatitis prior to developing CP.

Patients developed CP after treatment with programmed cell death protein 1 inhibitors pembrolizumab, nivolumab, and cemiplimab (Fig 1). One

Abbreviations used:

CP:	chronic pruritus
IL:	interleukin
R-CHOP:	R(rituximab)-C(cyclophosphamide)H (doxorubicin hydrochloride) O(vincristine sulfate), P(prednisone)
Th2:	T helper 2
WI-NRS:	worst itch-numerical score rating

patient developed CP after R-CHOP, within 1 year. CP also occurred after messenger RNA COVID-19 vaccination and Tdap vaccination. Additionally, 1 patient presented with CP after a shingles flare, suggesting a varicella zoster viral stimulus.

Most immunotherapy-treated patients experienced pruritus during treatment or after 21 to 60 days of receiving treatment, while vaccine-stimulated patients developed pruritus within a week of vaccination. Pruritus lasted between 6 months to 7 years.

Treatments

Response to treatment was defined as Worst Itch - Numerical Score Rating (WI-NRS) reduction of 4 points. The most successful treatment was intramuscular triamcinolone, causing a 4-point reduction in WI-NRS in 3 out of 6 patients, although relapse occurred within 4 to 7 weeks. Notably, all 3 patients experiencing symptom relief with intramuscular triamcinolone had a COVID-19 immune stimulus. Triamcinolone 0.1% cream caused a 4-point reduction in WI-NRS in 2 out of 10 patients with immunotherapy-induced CP (Table I). Gabapentin was effective in 2 patients with nivolumab/ipilimumab and R-CHOP-induced CP, causing a greater than 4-point reduction in WI-NRS. Dupilumab, a monoclonal antibody targeting interleukin 4 receptor, alpha (IL4Ra), led to improvement in 2 patients, causing a greater than 4-point reduction in WI-NRS. Abrocitinib, a Janus kinase 1 inhibitor blocking Janus kinase-signal transducer and activator of transcription-signaling, was effective in 1 patient who experienced CP after COVID vaccination, leading to a 10-point drop in WI-NRS.

IgE and eosinophils

IgE was increased in 3 patients following exposure to immune stimulus. One patient successfully treated with intramuscular triamcinolone had elevated absolute eosinophils to 9.9 and 12.4 that decreased to near 0 after treatment that resulted in 0/10 WI-NRS after 21 months.

Plasma cytokines

CP patients and healthy control patients had similar mean age (72.2 ± 13.2 versus 65.1 ± 9.3), sex (66.7% versus 40% male), and race (100% Caucasian vs 75% Caucasian). Twelve plasma cytokines were elevated in immune-stimulated patients with CP as compared to healthy controls ($q < 0.25$). Th2-related cytokines that were upregulated included IL-5 (FC 2.65) and thymic stromal lymphopoietin (FC 1.61) (Fig 2). Other elevated pro-inflammatory cytokines included IL-6 (FC 2.66), IL-8 (FC 1.77), IL-17A (FC 3.80), tumour necrosis factor alpha (FC 1.75), interferon-gamma (FC 2.10), Macrophage inflammatory protein 1 alpha (FC 1.53), MCP4 (FC 2.16), Fms Related Receptor Tyrosine Kinase 1 (FC 1.25), IFN-gamma-inducible protein 10 (FC 1.74), and Soluble Vascular Cell Adhesion Molecule-1 (FC 1.39).

DISCUSSION

In this study, mainly older adult patients developed CP following immune stimulation, with increased IgE levels and blood eosinophils poststimulation. Additionally, plasma analysis revealed upregulated Th2-related cytokines IL-5 and thymic stromal lymphopoietin in patients with immune-stimulated CP compared to healthy controls. The patients' high median age aligns with the increased incidence of CP in older adults, potentially linked to immunosenescence, skin barrier deterioration, and neurotrophic dysfunction, which could represent predisposing factors for CP triggered by immune stimuli.[8]

Among the elevated Th2-related cytokines in CP were IL-5 and thymic stromal lymphopoietin, which induce mast cell degranulation and eosinophil activation through the Janus kinase-signal transducer and activator of transcription pathway and promote Th2 cell differentiation.[9,10] Elevation of these cytokines, along with atopic disposition and increased blood eosinophils present across several cases highlight the critical role of the Th2 axis in CP triggered by an immune stimulus. Th1 cytokines IFNγ, tumour necrosis factor alpha, and IFN-gamma-inducible protein 10, and Th17-associated cytokines IL-6 and IL-17A were also elevated, indicating broader inflammatory involvement.

Limitations of this study include limited sample size, particularly in the plasma cytokine assay. In this study we present 15 patients with CP that developed CP following an initial immune stimulus of immunotherapy, vaccination, or viral flare. Findings across history, lab values, and plasma cytokines, were consistent in demonstrating an immune-stimulated form of CP involving primarily Th2 polarization.

Table I. Patient demographics of 15 patients with chronic pruritus

Patient No./age/sex	Immune stimulus	Duration of itch, months	IgE	Abs Eos	% Eos	Attempted treatments*	Successful treatments and length before response	WI-NRS change with successful treatment
1/70/M	Nivolumab	9	NA	Normal	Elevated before and after immune stimulus	Triamcinolone 0.1% cream, gabapentin	Triamcinolone 0.1% cream	8 → 1
2/79/M	Nivolumab	12	Normal	Progressive increase throughout and after immune stimulus	Progressive increase throughout and after immune stimulus	NBUVB, gabapentin, triamcinolone 0.1% cream	None	7 → no follow-up
3/80/M	Nivolumab/ ipilimumab	36	NA	Elevated before and after immune stimulus and treatment	Progressive increase throughout and after immune stimulus	NBUVB, gabapentin, triamcinolone 0.1% cream	Gabapentin, triamcinolone 0.1% cream (3 mo)	7 → 1
4/62/M	Pembrolizumab	17	Elevated after immune stimulus	Elevated before and after immune stimulus	Elevated before and after immune stimulus	Dupilumab, triamcinolone 0.1% cream	Triamcinolone 0.1% cream	6 → 0
5/63/M	Pembrolizumab	5	Elevated after immune stimulus	Normal	Normal	IMK, NBUVB, gabapentin, dupilumab	Dupilumab,1 mo	10 → 0
6/74/F	Pembrolizumab	36	NA	Elevated before and after immune stimulus	Elevated before and after immune stimulus	Gabapentin, triamcinolone 0.1% cream	None	8 → no follow-up
7/73/M	Cemiplimab	18	Normal	Progressive increase throughout and after immune stimulus	Progressive increase throughout and after immune stimulus	Triamcinolone 0.1% cream	None	9 → no follow-up
8/54/M	R-CHOP	84	Normal	Normal	Elevated after immune stimulus and decreased to normal after treatment	Gabapentin	Gabapentin, 12 mo	10 → 3
9/68/M	Initial COVID-19 vaccination (Pfizer)	12	NA	Normal	Elevated after immune stimulus and decreased to normal after treatment	IMK, antihistamines, permethrin, dupilumab, triamcinolone 0.1% ointment	IMK, 6 mo	7 → 2

10/86/M	Initial COVID-19 vaccination (Pfizer)	24	NA	Normal	Elevated after immune stimulus and treatment	IMK, gabapentin	IMK	8 → 0
11/62/F	Second COVID-19 vaccination (Moderna)	8	Elevated after immune stimulus and decreased after treatment	Elevated after immune stimulus and treatment	Normal	Abrocitinib	Abrocitinib,12 wk	10 → 0
12/75/F	Second COVID-19 vaccination (Pfizer)	15	Normal	Elevated after immune stimulus and decreased to normal after treatment	Elevated after immune stimulus and decreased to normal after treatment	IMK	IMK, immediately	9 → 0
13/90/F	Second COVID-19 vaccination (Moderna)	24	Normal	Normal	Normal	ILK, NBUVB, antihistamine, dupilumab, gabapentin, triamcinolone 0.1% cream	Dupilumab with antihistamine, and 1 dose ILK	10 → 0
14/23/M	Tdap vaccination	9	Normal	Elevated after immune stimulus	Elevated after immune stimulus	IMK, gabapentin	None	7 → no follow-up
15/67/M	Shingles flare	84	NA	Elevated after immune stimulus and decreased to normal after treatment	Elevated after immune stimulus and decreased to normal after treatment	IMK, gabapentin, dupilumab	IMK (immediately after)	7 → 4

Abs Eos, Absolute eosinophil count; *ILK*, intralesional kenalog; *IMK*, Intramuscular triamcinolone; *NA*, not available; *NBUVB*, Narrowband UVB.
*All patients also attempted antihistamines and topical steroids.

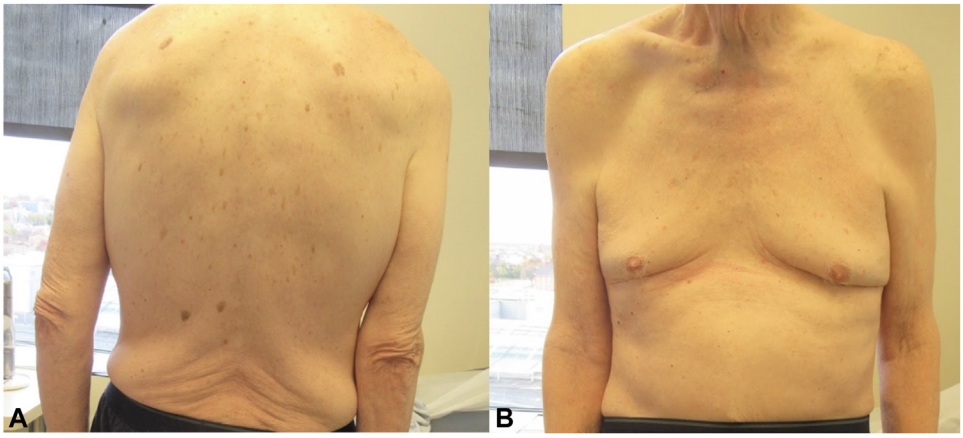

Fig 1. A and **B,** Chronic pruritus developed in a 79-year-old male shortly after starting treatment with nivolumab for metastatic melanoma. The patient experienced intense pruritus without a primary skin eruption.

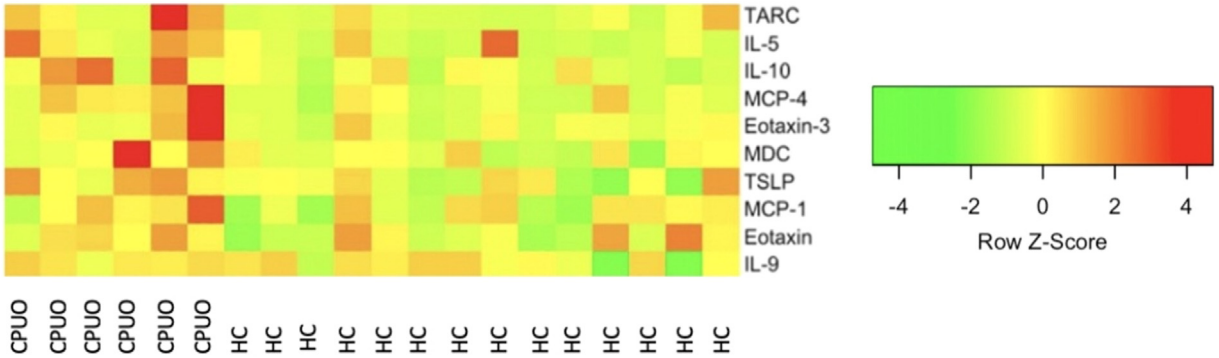

Fig 2. Heatmap of Th2 cytokines in chronic pruritus (CPUO) and matched healthy control (HC) patients. The color intensity scale represents the log-transformed cytokine concentrations, with red corresponding to the greatest concentration. *TSLP*, Thymic stromal lymphopoietin. *IL*, Interleukin; *MCP*, monocyte chemoattractant protein; *MDC*, macrophage-derived chemokine; *TARC*, thymus and activation regulated chemokine.

Conflicts of interest

Dr Shawn Kwatra is an advisory board member or consultant for AbbVie, Celldex Therapeutics, Incyte Corporation, Galderma, Pfizer Inc, Regeneron Pharmaceuticals, and Menlo Therapeutics; and is a recipient of a Dermatology Foundation Medical Dermatology Career Development Award.

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