

in the patient in this article. In making the diagnosis of TCWS, it is important to note other clinical entities in the differential diagnosis including flaring atopic dermatitis, allergic contact dermatitis, drug hypersensitivity reactions, infectious causes, and cutaneous T-cell lymphoma, all of which are possibilities in the referenced patient. Patch testing may be warranted given the possibility of an allergy to the steroid molecule itself or a cream excipient versus other potential triggers. Histopathology may also be helpful and is essential for excluding some entities in the clinical differential diagnosis. Although it is possible that the case presented by Nguyen et al is an atypical presentation of a rare disorder, we have concerns that in this particular case the correct diagnosis was not established given the lack of diagnostic evaluation such as biopsy or patch testing.

Clinical guidelines support that TCSs, when used appropriately, remain key to the management of inflammatory skin conditions. Given the rarity of this condition and lack of high-quality evidence, the diagnosis of TCWS should remain a diagnosis of exclusion handled with caution to avoid unnecessary deviation from the standard of care.

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Reply to "Severe topical corticosteroid withdrawal syndrome or enigmatic drug eruption?"



To the Editor:

We thank Tracy et al¹ for their comments regarding our report on topical corticosteroid withdrawal syndrome (TCWS) as it provides an opportunity to further elaborate on TCWS as a diagnosis.

As allergists and immunologists, we are no strangers to the use of corticosteroids via all routes of administration. We certainly continue to use corticosteroids on a day-to-day basis for our patients for a myriad of conditions. This relative comfort with our mainstay of therapy, however, should not leave us complacent. The many risks of systemic corticosteroids including withdrawal are well known. As much as we would like to believe that topical use of steroids negates many of these risks, our trust in this ostensible safety profile simply due to an alternate route of administration may ultimately prove misplaced.²

In their correspondence, the authors suggested that the diagnosis of TCWS might be inaccurate due to lack of diagnostic biopsy or patch testing. To answer the commentor: patch testing at the time of our subject's presentation would not have been feasible given the severity and extent of body surface involved. Furthermore, subsequent positive patch test result to other agents now will not exclude our clinical diagnosis then because they can be concomitant anyway. In addition, the utility of patch testing against crisaborole when our subject is currently using it regularly, would have little academic nor clinical utility now. Not having been updated in recent years, neither the current American Academy of Dermatology nor American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma, and Immunology atopic dermatitis guidelines mention topical steroid withdrawal as a potential concern with topical steroid use.^{3,4} There is currently no consensus on specific diagnostic criteria nor have pathognomonic histologic findings been defined.^{5,6} Therefore, even if a biopsy was performed, this would still have been a clinical diagnosis in the end.

The purpose of the case presentation was to bring forth a clinical observation and raise awareness. We agree that TCWS should remain a diagnosis of exclusion and should be handled with caution. Because clear diagnostic criteria are lacking for TCWS, although many providers question its prevalence or even its existence, more awareness and research is warranted, or it will continue to be missed.

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Need to define a subgroup of patients with idiopathic mast cell activation syndrome



To the Editor:

We applaud Gülen et al¹ for their recent publication on selecting the right criteria and proper classification to diagnose mast cell activation syndromes (MCAS). Confusion among health professionals and patients rests primarily with the definition of idiopathic MCAS.

It remains unexplained why two important aspects of the original description of MCAS by Akin et al² have been dropped: (1) inclusion of neurologic symptoms, and (2) elevated 24-hour urine mast cell mediator metabolites. The latter exclusion is particularly puzzling because Ravi and colleagues³ reported that of 25 patients with MCAS, urinary 11beta-prostaglandin-F2alpha was more frequently elevated than N-methyl histamine (two of 25 patients) and serum tryptase (10 of 25 patients). Because the diagnosis of those MCAS patients was stringent, one wonders whether the requirement for tryptase measurements may be justified or practical, because few emergency rooms or clinical sites are able to measure tryptase associated with an acute episode, even in the setting of anaphylaxis. In fact, elevated levels of another mast cell-derived mediator, platelet activating factor (PAF), were reported to be more strongly associated with the severity of anaphylaxis than either histamine or tryptase.⁴

Increasing evidence suggests that many patients thought to have MCAS along with neurologic and cognitive symptoms have extreme sensitivity to odors and stress, are resistant to treatment with antihistamines, omalizumab, or both, and do not have elevated serum levels of tryptase (Table I). This should not be surprising because mast cells can be stimulated by many neuroimmunomodulatory triggers, leading to the release of mediators other than histamine or tryptase.⁵

The review by Gülen et al¹ provides a useful breakdown of MCAS, but it does not discuss triggers that may contribute to idiopathic MCAS. Instead, any known trigger (eg, stress) is combined into the category of secondary MCA with no explanation. Does this mean that as more mast cell triggers are identified, they, too, will be relegated to secondary MCA? That would imply that idiopathic MCAS will never be associated with triggers of its own unless it is limited by default to innate and not external triggers.

Many idiopathic MCAS patients describe sudden mast cell reactivity to multiple triggers (old and new) after a catastrophic event such as a death in the family, major surgery, or extensive trauma: in other words, physical or emotional stress. Hence, a possible innate trigger of mast cells could be the key stress mediator, corticotropin-releasing hormone, the main receptor for which (CRHR-1) was shown to be expressed and functional on

TABLE I. Proposed subgroup of neurosensitive mast cell activation syndrome patients

Presence of neurologic and cognitive symptoms
Extreme sensitivity to odors and stress
Resistance to treatment with antihistamines, omalizumab, or both
Absence of serum tryptase elevation
Potential serum elevation of corticotropin-releasing hormone, platelet activating factor, and vascular endothelial growth factor

human mast cells, leading to selective release without tryptase or vascular endothelial growth factor.⁶

Maybe we should consider a distinct subgroup of neurosensitive MCAS patients in whom the criteria of a positive response to antihistamines and elevated serum tryptase levels do not necessarily apply (Table I). An analogous case would be that of chronic spontaneous urticaria patients, because as many as 40% are resistant to treatment with antihistamines and are characterized by elevated levels of PAF.⁷ Potentially useful new serum biomarkers that would need to be validated could include corticotropin-releasing hormone, PAF, and vascular endothelial growth factor (Table I).

There should be renewed efforts to identify useful biomarkers for MCAS that also may lead to different treatment approaches. For instance, rupatadine (which is available in Canada and is mentioned in Table I in Gülen et al¹) is a potent histamine-1 receptor antagonist, but it also has anti-PAF and mast cell blocking actions. Diagnostic criteria should characterize patients more accurately, but they should also reflect the realities of patients, who have often guided the health profession toward new or more refined diagnostic entities.

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