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Generalized Pruritus Relieved by NSAIDs in the Setting of Mast Cell Activation Syndrome

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To the Editor:

Mast cell activation syndrome (MCAS) is a newly recognized collection of disorders that typically involves multiple organ systems and symptoms can include flushing, pruritus, angioedema, and dermatographism.[1] These symptoms are unified by the fact that they can be explained by the effects of mast cell-derived factors such as histamine, leukotrienes, and prostaglandins on various tissues. The proposed criteria for MCAS include episodic signs and symptoms consistent with mast cell activation involving multiple organ systems, increased markers of mast cell activation, and an appropriate response the medications that target mast cell activation or their effector molecules.[2,3,4] Markers of mast cell activation can include serum tryptase and/or urinary metabolites of mast cell-derived mediators such as histamine, prostaglandin D_2 (PGD_2), 11β-PGF_2, and leukotriene E_4.[2,3,4] Recent criteria indicate that certain markers of mast cell activation such as serum tryptase may be more specific than others and thus the role of various factors are still emerging in the MCAS literature.[3,4] However, tests such as the prostaglandin metabolite 11β-PGF_2 may be useful when serum tryptase is inconclusive, and the results of prostaglandin metabolite tests can be used to guide therapy.[2] We present a case of generalized pruritus presenting in the setting of MCAS that was responsive to the non-steroidal anti-inflammatory drug (NSAID) ibuprofen.

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A 72-year-old female presented with an 18-month history of generalized pruritus associated with a rash. The past medical history was notable for adult-onset asthma and allergic rhinitis. She was treated with the anti-IgE agent omalizumab, which predominantly blocks activity on mast cells and basophils. Although her asthma symptoms improved, her chronic itch persisted despite treatment with both omalizumab and antihistamines. Her initial numerical rating scale (NRS) itch score was 6/10. The physical exam was notable for eczematous pink patches on the chest, back, upper and lower extremities. A skin biopsy showed subacute spongiotic dermatitis with eosinophils and, thus, she was treated presumptively for atopic dermatitis. However, her itch was unresponsive to topical steroids, calcineurin inhibitors, and narrow band UVB therapy.

Laboratory work-up was notable for elevated eosinophils of 1.54 K/mL (reference range 0–0.05 K/mL) but otherwise a normal complete blood cell count. Additionally, electrolytes and renal, hepatic, biliary, and thyroid function tests were all within normal limits. CRP, ESR, IgE, and serum tryptase were also within the normal range. Although serum tryptase is the most specific marker of mast cell activation, when inconclusive other urinary metabolites can be explored.[2] In light of high suspicion for MCAS, we obtained a 24-hour urine for 11β-PGF_2 and found that the patient's urinary concentration was 15,976 pg/mg Cr (reference range <5,205 pg/mg Cr). Given her history of episodic allergic processes in the upper airways, lungs, and skin as well as her refractory pruritus and elevated urine 11β-PGF_2, a preliminary diagnosis of MCAS was made. The patient was started on ibuprofen 400 mg daily as needed given a prior history of exposure with no adverse reactions. Strikingly, she noted marked and rapid improvement of her itch (NRS itch score of 0/10) upon increasing her dose to 800–1600 mg divided twice daily, which correlated with a reduction of urinary 11β-PGF_2 to a normal level of 4,713 pg/mg Cr (reference range <5,205 pg/mg Cr). It was also noted that whenever she stopped taking ibuprofen her itch would rapidly resume back to baseline levels of 6/10.

PGD_2 and its metabolite 11β-PGF_2 can be useful diagnostic and therapeutic markers in MCAS.[2,3,4] PGD_2 is synthesized via the cyclooxygenase pathway in mast cells and can cause vasodilation. In the liver and lungs, PGD_2 is converted to 11β-PGF_2 which also retains biologic activity.[5] PGD_2 may be selectively released by mast cells even in the absence of histamine, possibly explaining why antihistamines can be ineffective as in this patient.[6] However, the precise mechanism of action of PGD_2 in generalized pruritus is unknown. Notwithstanding this, we hypothesized that inhibiting the cyclooxygenase pathway with an NSAID and blocking the synthesis of PGD_2 may alleviate symptoms of generalized pruritus in the setting of MCAS. Similarly, aspirin has previously been shown to abate generalized pruritus and flushing in this disease along with a reduction of urinary 11β-PGF_2.[7]

This case highlights the importance of considering MCAS in a patient presenting with generalized pruritus in addition to other symptoms of mast cell activation. Although this patient failed multiple mast cell modulators (e.g, antihistamines and omalizumab) with regard to her chronic pruritus, her symptoms did improve once she was treated with an NSAID. The identification of elevated urinary 11β-PGF_2 played a critical role in her diagnosis and therapeutic outcome. Thus, this case underscores the potential benefits of

considering MCAS in patients with generalized pruritus and other features of allergic disorders.

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Clinical Implications:

This case suggests that mast cell activation syndrome (MCAS) may underlie generalized pruritus and therefore offer a novel therapeutic approach upon proper diagnosis of MCAS.