operating notes, and also consideration of isosulfan blue as a potential culprit.

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REFERENCES


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Reply to “Isosulfan blue-induced perioperative systemic allergic reactions”

To the Editor:

We thank Dr Kelso for his correspondence1 to our article “Perioperative allergic reactions: allergy assessment and subsequent anesthesia” in the Journal of Allergy and Clinical Immunology: In Practice.2

Blue dyes including methylene blue, patent blue, and isosulfan blue are used clinically to identify sentinel lymph nodes in patients undergoing oncologic evaluations. A recent meta-analysis describes a 0.06% anaphylaxis rate to blue dyes, whereas another single-center study describes hypotension on 0.5% of cases using isosulfan blue dye. Overall, blue dyes are indeed being increasingly identified as “hidden” causative agents of perioperative allergic reactions,3,4 and allergists should include them in the list of possible causative agents when evaluating patients with perioperative allergic reactions. Allergists can also perform dye skin testing using the published nonirritating skin testing concentrations as part of the comprehensive evaluation in cases where dyes were used.5,6

We agree that a thorough review of the electronic medical records including the anesthesia record and operative report is needed as part of the allergy consultation and assessment. At our academic medical center, we also review the operating room nursing record, which may document irrigations such as heparin and saline mixture, bacitracin and saline mixture, and Visipaque dye given intra-arterially. Lastly, a comprehensive approach to perioperative allergic reactions should include review of the medication administration report where all agents given during a procedure should be thoroughly documented.

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REFERENCES


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The allergic effector unit: From basic science to drug-targetable mast cell–eosinophil interactions in patients

To the Editor:

We read with great interest Guillet et al’s Clinical Communication1 presenting the effect of mepolizumab administration in an eosinophilic bronchial asthma patient with concomitant idiopathic mast cell (MC) activation syndrome. The authors found that mepolizumab administration resulted in a reduction of blood eosinophilia, eosinophil cationic protein (ECP), and serum tryptase levels, with amelioration of asthma, gut, and skin symptoms. Interestingly, although both omalizumab and mepolizumab reduced serum tryptase, only the latter decreased asthma symptoms. This is possibly due to omalizumab binding to circulating free IgE, thus not affecting already bound IgE.2

The reduction in tryptase and ECP serum levels might be due to a direct effect of mepolizumab on MCs. It was published that administration of mepolizumab in pediatric eosinophilic esophagitis significantly reduced MC numbers and occurrence of MC-eosinophils (Eos) couples due to inhibition of IL-9 production from Eos, thus influencing MC survival in the gut.3 Mepolizumab can affect the Eos, which, when not inhibited, engage MCs in a physical and soluble crosstalk we named allergic effector unit (AEU). Indeed, in previous works, we showed that the activating receptor CD48 on human cord blood-derived MCs engages CD244/2B4 on peripheral blood Eos, resulting in activation of both cells.4 Importantly, MCs and Eos produce several mediators

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such as SCF, IL-3, IL-5, TNFα, PGD₂, and tryptase, which enhance the activation status of both cells.⁴,⁵

This interaction has therefore short- and long-term proinflammatory effects on both cells. On MCs, the crosstalk induces tryptase and β-hexosaminidase release and Lyn and Syk phosphorylation within 1 to 2 hours after MC-Eos engagement.⁶ On Eos, it causes eosinophil peroxidase release, LAMP-1 expression, and chemotaxis from 1 to 3 hours after the interaction begins.⁵ Remarkably, both cells present with increased TNFα and GM-CSF release and prolonged survival 1 to 7 days after initiation of the crosstalk, highlighting the role of the AEU in perpetuating allergic inflammation.⁴,⁶ The AEU might account for the persistence of lung symptoms after omalizumab administration, possibly by its prominent role in the lungs rather than IgE-dependent MC activation.

The authors propose that the MC-Eos interactions might involve receptors such as Siglec-7 and Siglec-8, which were described, together with CD300a, as inhibitory receptors (IRs) on both cells.⁷,⁸

Although it is reasonable to think that IRs might also participate in modulating the AEU, because the involved cells do express the respective ligands, for example, sialoglycans for Siglecs⁶,⁹ and phosphatidylethanolamine/phosphatidylserine for CD300a,¹⁰ in the time frame we analyzed we did not detect any inhibition of functionality of MCs or Eos ascribable to IR activation.

The novelty of the communication, together with the important clinical result, is that the AEU, mostly studied in vitro, appears to be a central component in allergic and nonallergic human diseases. In light of our reports and the evidence provided by the authors, mepolizumab might influence the course of MC-related diseases due to the formation of the AEU in the inflammation sites. However, more studies are required to unravel the effectiveness of anti-Eos compounds in diseases involving MC activation due to a concomitant tissue eosinophilia.

To the Editor:

We thank Puzzovio and Levi-Schaffer for their interest in our article, “Eosinophil-mast cell interaction: mepolizumab leads to a reduction of clinical symptoms and serum tryptase in a patient with eosinophilic asthma and idiopathic mast cell activation,” and their commentary on potential pathogenetic mechanisms leading to the reduction of symptoms and serum tryptase levels.⁷ They highlight multiple interesting potential interaction mechanisms between mast cells and eosinophils, leading to the immediate and long-lasting response to treatment with mepolizumab in our patient with idiopathic mast cell activation syndrome.

The authors themselves have extensive experience in studying eosinophil–mast cell interactions. They point out the importance of the allergic effector unit (AEU) and potential mechanisms of interaction between eosinophils and mast cells, namely the reduced secretion of IL-9 by eosinophils after mepolizumab treatment,¹¹ direct physical crosstalk,⁵ and bidirectional activation via release of soluble mediators.⁷ Potential mechanisms of interaction are summarized in Figure 1.⁴-⁶

Recent observations suggest that eosinophils might contribute to the perpetuation of chronic mast cell–driven diseases. For example, in chronic spontaneous urticaria (CSU), elevated numbers of infiltrating eosinophils have been observed in the lesional patient skin but not in the uninvolved skin.² In addition, low counts of peripheral blood eosinophils or even the complete absence of eosinophils in patients with CSU (ie, eosinopenia) is associated with higher disease activity, type IIb autoimmunity, and a poorer response to treatment.¹ Successful treatment of CSU with mepolizumab or another IL-5 receptor targeting monoclonal antibodies has been reported in case reports and case series, and clinical trials are currently performed and evaluated.