

CORRESPONDENCE

Extensive blistering is a predictor for severe complications in children with mastocytosis

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To the Editor,

With interest, we have read the article by Alvarez-Twose et al. studying 111 children with mastocytosis in the skin (MIS) to identify predictors for severe mast cell activation episodes (1). The results showed that 12 children (11%) suffered symptoms which required hospitalization and that those children showed extensive cutaneous disease involving >90% of body surface area (BSA) as well as higher total basal serum tryptase levels. There are several comments about the results and conclusions.

First, this study confirms and extends previous findings on predictors of anaphylaxis in children and adults with mastocytosis, where 4/46 (9%) of children had a history of anaphylaxis. All of these children were reported to show an extent of skin lesions of >45%, and tryptase levels were significantly elevated (2). The somewhat higher cumulative incidence for mast cell activation episodes in the study of Alvarez-Twose (11% vs 9%) can be explained by the fact that some severe mast cell activation episodes do not fall within the definition of anaphylaxis.

Secondly, a study on the association between extent of skin involvement and basal tryptase levels has been cited to have failed to show a significant correlation (3). However, it may have been pointed out that this association has been quoted to be $P < 0.06\%$ in 19 patients and that larger, more randomly distributed lesions may have interfered with the scoring. Inclusion of a higher number of children with more severe disease would have been likely to show a significant association supporting the notion that skin involvement and basal serum tryptase levels are correlated in children with mastocytosis.

Finally, it should be highlighted that blistering episodes in children are predictors for severe mast cell activation

episodes. Flushing and pruritus alone may look worrisome for parents and doctors, but mast cell mediator release appears to be minimal as reflected by levels of mature tryptase (1). On the contrary, extensive blistering disease should be regarded as a predictor for severe complications in children with mastocytosis. In the study of Alvarez-Twose, all children with severe episodes requiring hospitalization had blisters (1). Mean mature tryptase levels and range were 1.0 ng/ml (<1–1.1 ng/ml) for patients without and 34.4 ng/ml (<1–193.0 ng/ml) for those with blistering during such an episode ($P < 0.004$; Mann–Whitney test) indicating substantial mediator release of from activated mast cells in association with blistering (1). In case reports, rare fatal complications in children with mastocytosis were also mostly reported in association with severe blistering episodes (4, 5). Thus, the conclusion that extensive blistering should be identified as an indicator of massive mast cell activation potentially leading to severe complications in mastocytosis is in agreement with data presented in the study by Alvarez-Twose as well as with reports in the literature.

Conflict of interest

Both authors indicate no conflict of interest.

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REPLY

We have read with great interest the Letter to the Editor by Brockow and Ring and really do appreciate their wise comments. We would like to take this opportunity to clarify some of the questions raised and also to discuss in more detail some aspects regarding highly symptomatic pediatric mastocytosis with extensive cutaneous involvement.

It should be emphasized that the aim of our study was to identify predictors for the severity of mast cell (MC)-mediator related symptoms in children at the onset of disease (within the first 18 months) which were graded following consensus recommendations (1); in turn, in the study conducted by Brockow, anaphylaxis was defined following well-established criteria and data were apparently recorded at any time during disease course. Therefore, the different inclusion criteria used in the two studies may contribute to the slight differences observed in the frequency of anaphylaxis; nevertheless, it should be noted that the overall prevalence of anaphylaxis among our pediatric mastocytosis patients has been previously reported (2). We fully agree with Brockow and Ring in that not all patients with severe MC activation symptoms included in our study fulfilled currently accepted criteria for anaphylaxis (3); more precisely, there were two children with diffuse cutaneous mastocytosis (DCM) who suffered from pruritus, extended blistering and flushing. Strictly, this combination of symptoms fails to meet such criteria for anaphylaxis since flushing is widely considered also as a cutaneous manifestation. However, it is largely known that flushing results from increased cutaneous blood flow caused by vasodilation due to MC mediators such as histamine, and that in a variable proportion of patients it precedes the development of potentially life-threatening vasodilation-related events such as hypotensive collapse. These observations raise the question about whether flushing might more likely be considered as a systemic vascular event rather than a skin restricted symptom.

Another relevant issue to be highlighted relies in a relatively common misinterpretation of the term 'diffuse' in

the definition of DCM, by physicians unacquainted with the disease. Inappropriate evaluation of skin involvement can lead to misdiagnose extensive nodular or maculopapular variants involving most of the body surface area as DCM. Although in some cases extensive maculopapular and nodular forms can be difficult to distinguish from each other during acute MC-mediator release episodes, due to urtication and swelling of maculopapular lesions mimicking nodules, both variants differ from DCM in the existence of healthy skin areas which are free from lesions. Conversely, DCM is characterized by a diffuse thickening of the entire skin which typically shows a *peau d'orange* (orange peel) appearance without individual lesions (4).

Independently from the clinical variant, virtually all children with any of these three subtypes of extended cutaneous disease suffer from recurrent diffuse blistering episodes, especially at disease onset. Noteworthy, apart from the increase of serum mature tryptase levels in these cases highlighted by Brockow and Ring, strikingly high total tryptase levels in the blisters' fluid were also detected in our study (1), further reflecting the high degree of MC-activation during severe blistering episodes. Given the association of diffuse blistering with the extension of cutaneous involvement, strict avoidance of triggering factors together with early continuous intensive antimedator therapy and careful daily skin care, are mandatory in all pediatric cases with extended cutaneous mastocytosis in order to avoid potentially fatal outcomes.

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