

Editorial

The Role of Eosinophils

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Originally, the Eosinophils were considered only as a protective cell, e. g. in host defence against parasites. At present, the Eosinophils is regarded also as pro-inflammatory cell that can mediate allergic disease. Recent studies indicate a role for Eosinophils disruption and degranulation in inducing tissue destruction [1].

Eosinophilia is frequently associated to AD and generally its degree correlates with the severity of the disease. Although the pathophysiology of AD is not fully understood, there is evidence that Eosinophils may play an important role in this process (Table 1).

Several potent, toxic and cationic proteins have been described in the Eosinophils granules. These include Major Basic Protein (MBP), Eosinophil-derived Neurotoxin (EDN), Eosinophil Cationic Protein (ECP), and Eosinophil Peroxidase (EPO) (for details on these products and on Eosinophils see the paper by Per Venge in this issue). These granule matrix cationic proteins have been implicated in tissue damage associated with cutaneous inflammation [2,3] and their role in the pathophysiology of AD is in the process of explanation.

It has been shown that some of these cationic proteins are elevated in the peripheral blood of patients with AD. There is also evidence for Eosinophils disruption and degranulation in the affected skin [1]. Finally, an active participation of Eosinophils in patch-test reactions to inhalant allergens has been shown in patients with AD [4]. Eosinophils are not only active in mediating allergic inflammation, but interact in cellular networks with antigen presenting cells, mast-cells, and T lymphocytes. These other cells influence Eosinophils maturation, mobilization, tissue localization and activation.

Eosinophil cationic proteins in serum of patients with AD usually, serum levels of MBP are elevated in patients affected by various disorders associated to Eosinophilia and correlate significantly with the number of peripheral blood Eosinophils [3,4]. An exception to this rule is patients with AD and urticaria in whom the elevated serum level of MBP does not necessarily correlate with blood Eosinophilia. However, several studies have shown both increased levels of MBP in the peripheral blood and peripheral activation of Eosinophils. Although Eosinophils degranulation into the bloodstream cannot be excluded, this strongly suggests that Eosinophils degranulate locally in the skin with subsequent escape of MBP in the circulation.

Elevated serum and tissue levels of EDN were found in patients with AD and the results of this study provide further evidence that

Eosinophils degranulation occur in AD [1]; like MBP, it's probable that EDN is mainly produced locally in the skin. In addition, this study seems to indicate that peripheral blood EDN may be a more sensitive marker of Eosinophils degranulation than peripheral blood MBP [1].

According with other authors, we found elevated serum levels of ECP in children with AD [5]. Serum levels of ECP were 12.2 ug/l \pm 9.6 in children with AD, and 6.6 ug/l \pm 3.7 in normal children ($p < 0.001$). We were not able to show any correlation between ECP serum levels and total IgE as well as between the absolute number of peripheral blood Eosinophils and ECP serum levels. Therefore, it seems likely that elevated ECP serum levels in patients with AD may reflect the activation of Eosinophils in the skin. It has been reported that in vitro ECP can induce an increased histamine release [6] and can suppress T-lymphocytes function via a non-toxic mechanisms [7]. Therefore it is tempting to speculate that Eosinophils cationic proteins, besides noxious effects for the skin, may contribute to the profound immunologic abnormalities described in patients with AD. The detection of raised ECP levels in serum of AD patients represents only an indirect measure of the pathological process taking place in the skin. In our experience measure of ECP might represent a non invasive tool to assess the activity of AD in relation to Eosinophils involvement in this disease.

Eosinophil disruption in tissue of patients with AD although peripheral blood Eosinophilia is a common feature of AD, accumulation of tissue Eosinophils is not prominent. Several studies have shown Eosinophils disruption and loss of morphological identity in the skin of patients with AD [8-10]. More recently, it has been studied the Eosinophils degranulation in tissue. Immunofluorescent staining of the affected skin, demonstrated extensive deposition of MBP in the absence of many tissue Eosinophils suggesting that Eosinophils degranulate in the skin. The dominant pattern of MBP deposition consisted of febrile fluorescence in the upper dermis. The other pattern consisted of scattered granules in the dermis. On the contrary, the specimen from unaffected skin showed minimal fine febrile MBP deposition in the upper dermis [1]. Interestingly, extensive MBP deposition in the skin was demonstrated in two children who experienced eczematous lesions after DBPCFC, thus indicating again the role of FA and Eosinophils in AD [1].

EDN deposition was also studied by Leiferman in patients with AD [1]. AD skin specimens showed extensive granular extracellular EDN deposition in the upper dermis, thus producing further evidence for EDN role in AD. Electron microscopy examination showed Eosinophils degeneration and disruption with many free granules in the dermis, thus corroborating the evidence of Eosinophils degranulation in AD [1].

The role of Eosinophils in patch-test reactions to inhalant allergens in patients with AD Bruynzeel-Koomen et al. [2] performed intracutaneous testing and patch-test with house dust mite and grass pollen allergens in patients with AD. Positive patch-test reactions

Table 1: Data in favor of the relationship between Food allergy and AD.

* Children with AD show positive skin tests to foods and food specific IgE
* Children with AD may experience immediate cutaneous food allergic reactions such contact urticaria or generalized urticaria or Non cutaneous such as Vomiting, Diarrhea, Rhinitis, etc.
* Children with AD may show improvement of AD after appropriate elimination diet.

were not found in normal controls or atopic patients without atopic dermatitis. These patch-tests caused eczematous lesions. Analysis of the cellular infiltrate demonstrated an influx of Eosinophils into the dermis, starting from 2-6 hours after patch-testing. Immunostaining with antibodies against granular constituents of the Eosinophils revealed that infiltrating Eosinophils were in an activated state and had lost part of their granular contents. At 24 hours Eosinophils also appeared in the epidermis. Histologically a predominance of T cells of the helper/inducer phenotype has been observed; activated Eosinophils which have lost their granular contents are also seen in these lesions. Electron microscopy showed that in the epidermis some Eosinophils were in close contact with Langerhans cells suggesting a cell-cell interaction. It has been suggested that immediately after patch-testing some of the allergen penetrates the epidermis, binds to the IgE molecules on mast-cells in the dermis and induces an immediate type reaction; the mast-cell releases an Eosinophils chemotactic factor and some of the infiltrating Eosinophils become activated [2]. The cellular contact between Eosinophils and Langerhans cells suggests the release of an Eosinophils chemotactic factor from Langerhans cells. These results strongly suggest an active role for Eosinophils in patch-test reactions to inhalant allergens in patients with AD.

Conclusion

Scientific evidence accumulated in the last years indicates that food and inhalant allergens can trigger AD. As a consequence a state of "skin hyperreactivity", similar to bronchial hyperreactivity described in allergic patients with asthma, frequently occurs. Therefore no specific stimuli can trigger and worsen the skin lesions. Eosinophils, like in asthma, seem to play an important role in inducing and maintaining the skin lesions.

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