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Occurrence of Sezary syndrome following the initiation of anti-IL-5 drug

Bio-P-12

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INTRODUCTION

Anti-IL-5 drugs, which inhibit the Th2 pathway, have been developed for the treatment of severe asthma and are currently under investigation in chronic spontaneous urticaria and atopic dermatitis. **We report the first case of Sezary syndrome (SS) occurring under benralizumab.**

OBSERVATION

A 74-year-old patient received benralizumab for severe asthma. One month after, he developed **erythroderma associated with palmoplantar keratoderma**. Skin biopsy revealed **perivascular and atypical lymphocytic infiltrate with irregular nuclear contours and mild epidermotropism** (Figure 1). Peripheral blood immunophenotyping revealed an expanded $CD4^+$ T-cell population **containing 20% $CD7^+CD26^-CD158k^+$ atypical T cells, *i.e.* 0.6 G/L of Sezary cells**. The CD4:CD8 ratio was 6:1 and T-cell clonality was similar in skin and blood. **Therefore, we concluded that the patient had stage IVB1b SS.**

We measured the patient's cytokine signature using a **27-multiplex bead-based Luminex® assay** (ThermoFischer Scientific, Massachusetts, USA). The patient's sample was compared to the plasma of two untreated IVB1b stage SS patients, and that of two healthy donors.

Plasma levels of eotaxin, IL-4, IL-17 and CCL3 were increased in the benralizumab-treated patient compared to both healthy donors and both SS patients, whereas **levels of CXCL10 were lower** (Figure 2). IL-5 levels were undetectable in all specimens. **As expected in SS, other Th2 pathway cytokines (IL-9 and IL-13) were slightly increased** compared to healthy donors, **while Th1 pathway cytokines (IL-1, IL-7, IL-8) were slightly decreased** ; our benralizumab-treated patient showed the same profile as the two SS patients concerning these cytokines (data not shown). IL-2, IL-6, IL-10, INFγ, and TNFα levels were low in all specimens.

The patient was treated with extracorporeal photopheresis and methotrexate, while maintaining benralizumab, which allowed a good control of both asthma and SS.

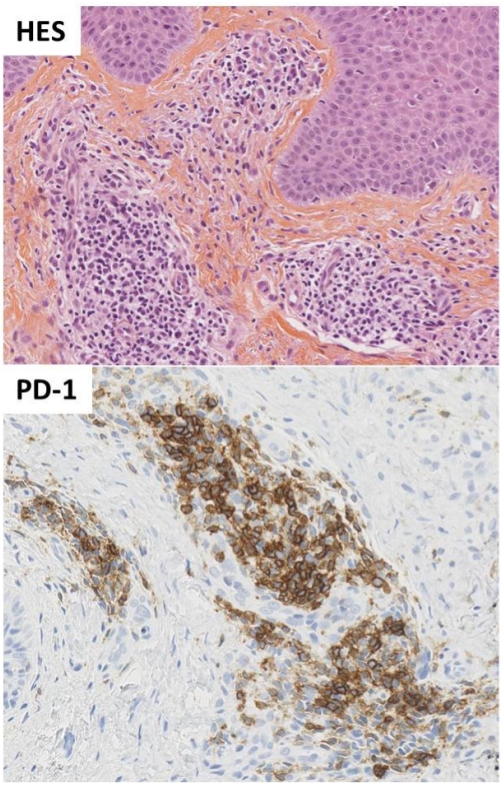

Figure 1. Histological section of a skin biopsy (HES staining and PD1 immunostaining), showing a perivascular dermal lymphoid infiltrate made of small to medium-sized atypical cells with irregular and cerebriform nuclei, associated with mild epidermotropism.

DISCUSSION

In SS, both malignant and tumor microenvironment cells are characterized by a Th2 bias that results in a skewed antitumor response. Since a Th1 environment enhances immune responses against cancer development, **the inhibition of Th2 pathway could be beneficial in patients with SS**. There have been recent reports of patients whose symptoms, including severe pruritus, have significantly improved with dupilumab (anti-IL-4/13). However, our observation, as well as reported cases of worsening or development of cutaneous T-cell lymphoma under dupilumab suggest the existence of **paradoxical phenomena**. Indeed, our patient presented a marked elevation of eotaxin and a mild increase of IL-4, both actors of Th2-mediated inflammation in asthma and in SS. In addition, recent studies suggest a role for IL-17, the levels of which were markedly increased in our patient, in the tumor escape mechanism in SS.

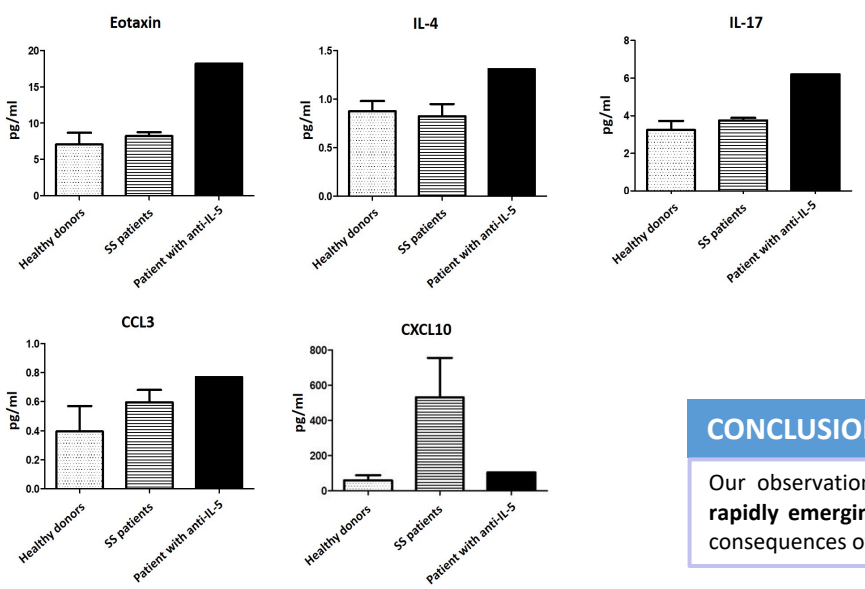

Figure 2. Patient's cytokine signature compared to two healthy donors and two IVB1b stage SS patients, using Luminex® assay.

Furthermore, the receptor for CCL3, CCR4, is found on tumor cells and regulatory T cells and is particularly involved in the development of SS. Finally, the observed decrease of CXCL10 could be responsible for the loss of Sezary cell epidermotropism and their consequential presence in the blood.

Inhibition of one immune pathway may result in an imbalance in cytokine production and cause, in susceptible patients, paradoxical activation of other immune pathways responsible for inflammatory or neoplastic processes. Dedicated studies are needed to establish a causal link between IL-5 inhibition and the immunological alterations that may have contributed to the development of SS in our patient.

CONCLUSION

Our observation is proof of the need for **caution in the use of rapidly emerging cytokine pathway inhibitors**, the immunological consequences of which remain poorly understood.

The authors have no conflict of interest to declare.