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Letter to Editor

Differential Expression of Toll-like Receptors and Antimicrobial Peptides in the Patients with Sézary Syndrome and Idiopathic Erythroderma

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Letter to Editor

Erythroderma, characterized by the presence of erythematous patches and plaques affecting more than 80% of the body surface, is a manifestation of different cutaneous and systemic diseases [1]. Up to 20% of patients may remain undiagnosed thus characterizing Idiopathic Erythroderma (IE) [2]. Sézary Syndrome (SS) is an erythrodermic and leukemic variant of cutaneous T-cell lymphoma [3]. Moreover, sepsis from bacterial infections have been identified as a significant cause of mortality among these patients [4]. Toll-Like Receptors (TLRs) responsible for recognizing bacterial components (TLR2, TLR4, TLR5 and TLR9), along with the Antimicrobial Peptides (AMP), including Human Beta-Defensin (HBD) and Cathelicidins (CATH) play a significant role in the innate cutaneous immunity.

Therefore, this study investigates the expression of these TLRs, HBD and CATH, by immunohistochemistry in skin of SS patients compared to health donors and IE. We included skin biopsies of SS patients (n = 7; 6 M/1 F), with a median age of 61 years (range: 25 to 80 years), patients with IE (n = 8; 7M/1F) with a median age of 60 (range: 39 to 90 years) and a control Healthy Donors group (HD, n = 18; all F) with a median age of 48.9 (range: 21 to 77 years). The healthy donor skin samples were archival, collected from plastic surgery. The patients were followed up in the Cutaneous Lymphomas Clinic of Hospital das Clínicas, Division of Dermatology, University of São Paulo Medical School, Brazil. We performed immunohistochemistry assays of skin samples, to verify TLR2, TLR4, TLR5, TLR9, HBD and CTH expression. The tissue sections were incubated with the primary antibodies, followed by the amplification system and revealed with 3,3' diamibenzidine. Negative reaction controls were obtained by omitting the primary antibody. The images were analyzed with Image-Pro Plus software. We verified an upregulation of TLR4 and TLR9 in the epidermal sections of IE and SS compared to HD (Fig. 1). In the dermis, TLR4 was increased only in IE compared to HD samples. TLR4 recognizes LPS from most Gram-negative species and TLR9 recognizes self and non-self-nucleic acids. In contrast, TLR2 and TLR5 expression was increased in both the epidermis and dermis only in IE compared to HD. TLR2 and TLR5 expression in SS was similar to that in HD samples. TLR2 is the primary receptor that recognizes *S. aureus* and other gram-positive bacteria [5]. Since bacterial colonization is commonly found in both SS and IE skin, we expected increased expression of TLR2 in both groups. However, TLR2 was upregulated only in IE, suggesting an unresponsiveness in SS patients, which may contribute to bacterial colonization and increase the risk of severe outcomes. In the dermis, TLR2 expression was reduced in both SS and IE. Similarly, TLR5 expression was increased only in IE patients, both in the epidermis and dermis, compared to HD (Fig. 1). TLR5 has an affinity for flagellin, a protein found in Gram-negative pathogens such as *Pseudomonas aeruginosa*, which is a major cause of nosocomial infections. This finding suggests a possible impairment in TLR response in SS patients, which requires further investigation. More sampling needs to be done to confirm the analyses. The small sample size is one limitation of this study, but the rarity of the disease must be taken into account.

AMP expression revealed enhanced expression of HBD, but not CATH, in SS and IE compared to HD (Fig. 2), suggesting an association between AMP expression and erythroderma. Both peptides contribute to the body's antimicrobial defense, CATH also plays a role in modulating the immune response and promoting wound healing. This suggests that understimulation of CATH could favor the erythoderma condition.

Our results indicate that despite *S. aureus* colonization, erythrodermic SS skin did not exhibit increased TLR2 and TLR5 expression, which may contribute to increased susceptibility to bacteria. This unresponsiveness seems to be due to chronic stimulation caused by the persistence of bacterial colonisation, which leads to immune evasion by pathogens in order to avoid overstimulation of the immune response. These observations highlight the importance of improving the host's ability to mount effective innate immune responses against bacterial agents for therapeutic purposes.

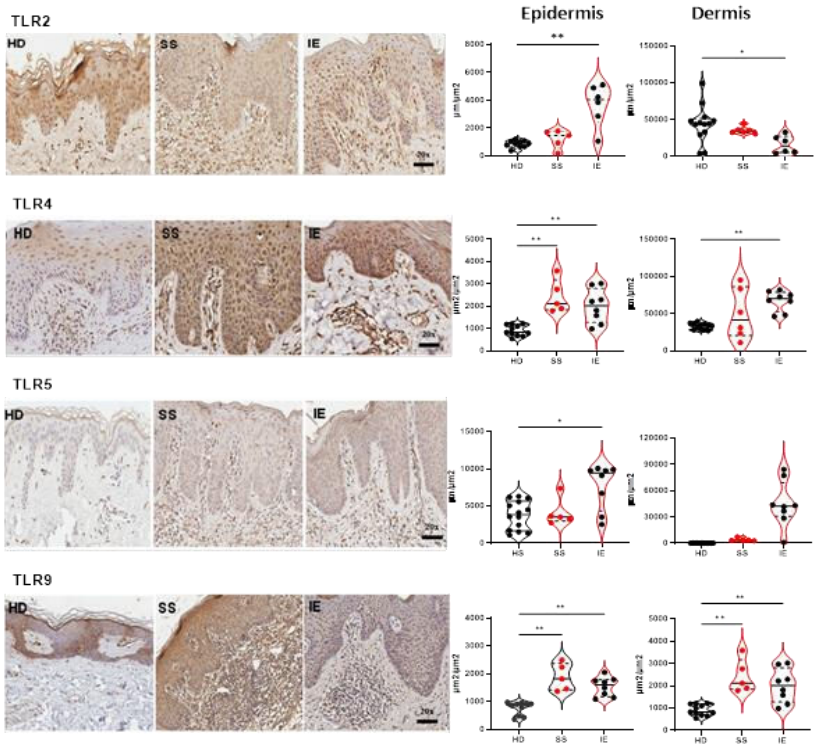

Figure 1: Cutaneous TLRs expression in idiopathic erythroderma and Sezary syndrome. Expression of TLR2, TLR4, TLR5 and TLR9 in epidermis and dermis of skin from health donor (HD, n=12-14), Sezary syndrome (SS, n=7) and idiopathic erythroderma (IE, n=8) analyzed by immunohistochemistry. Values are expressed as median and interquartile. Kruskall-Wallis test. *p ≤ 0.05, **p ≤ 0.01, **** p ≤ 0.0001.

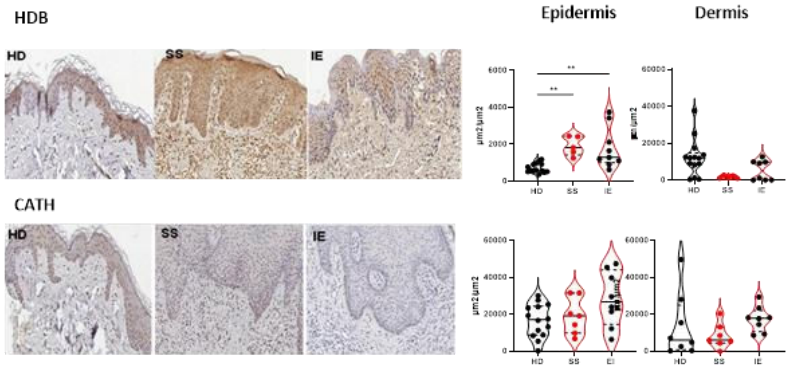

Figure 2: AMPs cutaneous expression in Sezary syndrome and idiopathic erythroderma. Beta-defensin (HBD) and Cathelicidin (CATH) expression in epidermis and dermis of skin from health donor (HD, n=12-14), Sezary syndrome (SS, n=6) and idiopathic erythroderma (IE, n= 6-8) analyzed by immunohistochemistry. Values are expressed as median and interquartile. Kruskall-Wallis test **p ≤ 0.01.

Keywords: Sézary Syndrome; Erythroderma Skin; Innate Immunity; Toll-Like Receptors, Defensins

Conflicts of Interest

The authors declare no conflict of interest in this paper.

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Ethics Statement

The patients in this manuscript have given written informed consent to publication of their case details. The present study was evaluated and approved by the Research Ethics Committee of the University of São Paulo School of Medicine under number 10127118.1.0000.0068.

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