Case Report **OPEN ACCESS**

Overexpression of linker for activated T cells, cyclooxygenase-2, CD1a, CD68 and myeloid/histiocyte antigen in an inflamed seborrheic keratosis

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Abstract

Context: Inflamed seborrheic keratoses are generally associated with the accumulation of variable numbers of lymphocytes and histiocytes in the superficial dermis. The precise immunologic mechanism of this histologic phenomenon is not known **Case Report:** A 62-year-old male presented with a patch on the right neck with additional features of inflammation. Skin biopsies for hematoxylin and eosin examination, as well as for immunohistochemistry analysis were performed. **Results:** H&E staining demonstrated classic features of an inflamed seborrheic keratosis. Overexpression of LAT, COX-2, CD1a, and CD68 was noticed in the inflammatory infiltrate. A strong presence of CD1a was also seen in the epidermis suprajacent to the inflammation. Myeloid/histiocyte antigen was strongly expressed by the keratinocytes**. Conclusion**: A complex immune response seems to be involved in the pathophysiology of an inflamed seborrheic keratosis.

Keywords: Inflamed seborrheic keratosis, linker for activation of T cells (LAT), cyclooxygenase-2 (COX-2), CD1a, CD68, myeloid/histiocyte antigen.

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Introduction

Seborrheic keratoses represent benign, localized proliferations of basaloid keratinocytes, often associated with clinical hyperkeratosis and hyperpigmentation. Few studies have specifically addressed the development of the immune response in an inflamed seborrheic keratosis.

Case Report

A 62-year-old male presented with and inflammatory plaque on his right neck. Clinical examination demonstrated a large, hyperkeratotic, verrucous plaque with evidene of surrounding inflammation. A lesional skin biopsy was taken for hematoxylin and eosin (H & E) analysis, and immunohistochemistry (IHC) studies were also performed.

Skin biopsies for hematoxylin and eosin examination, as well as for immunohistochemistry (IHC) analysis were performed as previously described [4, 5].

Examination of the H & E tissue sections demonstrated epidermal hyperplasia with minimal cytologic atypia; pseudo-horn cyst formation was present. The base of the lesion displayed a relatively flat morphology. An infiltrate of lymphocytes and histiocytes was also present within the papillary dermis, immediately subjacent to the lesion. Next, IHC stains were reviewed against linker for activated T cells (LAT), cyclooxygenase-2 (COX-2), CD1a and CD68. These special stains displayed strong expression of these molecules within the previously described dermal inflammatory infiltrate. In addition, myeloid/histiocyte antigen was strongly, focally expressed by lesional keratinocytes (Figure 1).

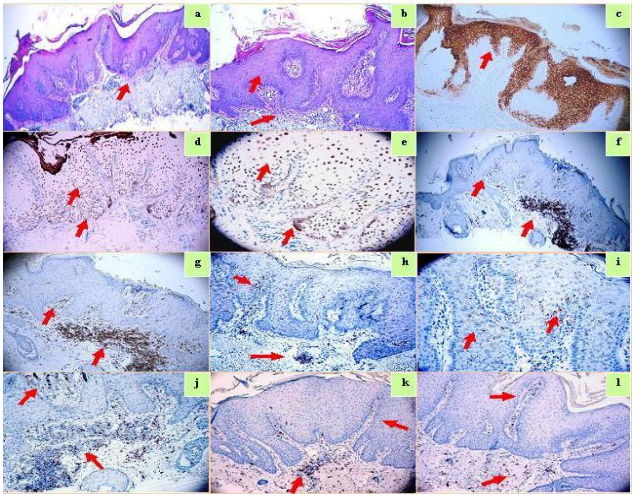

Fig. 1 1a, b H & E sections demonstrating at low and high magnification epidermal hyperplasia with pseudo-horn cyst formation and a moderately dense, superficial dermal perivascular infiltrate(red arrows). **1c,** IHC staining for cytokeratin AE1/AE3 revealing strong epidermal staining in the epidermis, sparing basaloid keratinocytes (brown staining; red arrows). **1d** and **1e,** IHC demonstrating strong, punctate expression of myeloid/histoid antigen throughout the entire epidermis, with some marking of basaloid keratinocytes(brown staining; red arrows). **1f** and **1g,** reveal strong staining with LAT in the superficial dermal perivascular infiltrate, and in the dermal papillae (dark brown staining; red arrows). **1h** and **1i,** strong staining with CD1a around upper dermal blood vessels, in the basement membrane zone (BMZ), in epidermal keratinocytes, and in the dermal papillae (dark brown staining; red arrows). **1j** Strong staining with COX-2 around upper dermal blood vessels, below the BMZ, and in the dermal papillae (dark brown staining; red arrows). **1k** and **1l**, strong staining with CD68 around the upper dermal blood vessels, below the BMZ, and in the dermal papillae (dark brown staining; red arrows).

Discussion

Inflamed seborrheic keratoses are associated with the accumulation of variable numbers of lymphocytes and histiocytes in the superficial dermis [1-3]. The inflammatory component of inflamed seborrheic keratoses is often clinically spontaneous, composed mainly of lymphocytes, and may represent a phenomenon analogous to those occurring in halo nevi or regressing melanomas [1-3]. Consistent with our findings, the response seems to be distinctly different from the histopathologic and immunophenotypical inflammation in experimentally rubbed seborrheic keratoses. Specifically, previous authors described seborrheic keratoses that were experimentally in rubbed in five patients, and biopsied at varying intervals after rubbing. Microscopic examination revealed both acute and chronic patterns of histologic change.[2] Hemorrhage, hyalinization of dermal papillae, and necrosis of epidermal lesional tips were conspicuous early changes. Specimens taken more than 48 hours after rubbing showed a spectrum of changes which included: 1) loss of epidermal mass, 2) expansion and interconnection of keratin cysts, 3) thinning of the epidermis, 4) proliferation of strands from the epidermis, 5) an increase in size of epidermal cells, and 6) evidence of hair follicle changes including trichostasis spinulosa and, in one specimen, hair germ proliferation.[2] Dermal lymphocytic infiltration was variable, and only rarely involved the epidermis. The authors concluded that a patterned response of the seborrheic keratosis to trauma was present, and also suggested a relationship between seborrheic keratosis and the hair follicle [2]. These findings seem to be different from our data, generated in the context of a clinically inflamed seborrheic keratosis. We suggest that undefined immunological reasons may exist to explain the clinical *de novo* immune response to these structures.

Few studies exist addressing the immunophenotypic analysis of the immune response in inflamed seborrehic keratoses. Our study revealed strong reactivity in the inflammatory infiltrate cells for CD1a, CD68, LAT, and COX-2.

In addition, we also found strong expression of myeloid/histiocyte antigen within the infiltrate**.** The myeloid/histoid marker reacts with a human cytoplasmic antigen (L1-antigen or calprotectin). The calprotectin protein is a member of the S-100 family, and its subunits are termed S-100A8 and S-100A9. Calprotectin is expressed in granulocytes, blood monocytes, tissue histiocytes, squamous mucosal epithelia, and reactive epidermal areas [5, 7]. Our results suggests the possibly that lesional keratinocytes begin expressing the myeloid/histiocyte antigen as a chemoattractant factor for the other immune cells, including the CD1a homing molecule for skin Langerhans cells. Further, the increased number of CD1a and CD68 positive cells could be due to upregulation of other, unknown molecules produced as a result the immunological response in irritated seborrheic keratoses [6, 7].

In other diseases, it has been shown that one of the earliest activation events following stimulation of the T cell receptor (TCR) occurs as LAT promotes TCR signal initiation. The LAT (linker for activation of T cells) family of adaptor proteins plays an important role in the positive and negative regulation of lymphocyte maturation, activation, and differentiation.

In addition to the above markers, we found strong activation of COX-2, an enzyme responsible for the formation of prostanoids [8]. The prostanoids are part of a family of biologically active lipids, derived from the action of cyclooxygenases or prostaglandin synthases upon the twenty carbon essential fatty acids or eicosanoids. The best known function of prostaglandins and thromboxanes in cells is in modification of the inflammatory response [8].

In this case, we suggest that the seborrheic keratosis inflammation occurs via multiple, coordinated components including antigen presenting, antigen processing and end process immune response cells. Larger studies are needed to specifically define why the body reacts with seborrheic

keratoses, mounting a complex immune response.

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References

1. Berman A, Winkelmann RK. Inflammatory seborrheic keratoses with mononuclear cell infiltration. J Cutan Pathol 1978; 5: 353-360.
2. Berman A, Winkelmann RK. Histologic changes in seborrheic keratoses after rubbing. J Cutan Pathol 1980; 7:32-38.
3. Levine N. Irritated lesion. What does it mean when an inflamed scaly plaque becomes red-brown in color? Geriatrics 1999; 54:22.
4. Abreu-Velez AM, Howard MS, Hashimoto T, Grossniklaus HE. Human eyelid meibomian glands and tarsal muscle are recognized by autoantibodies from patients affected by a new variant of endemic pemphigus foliaceus in El-Bagre, Colombia, South America. J Am Acad Dermatol 2010;62:437-447.
5. Howard MS, Yepes MM, Maldonado-Estrada JG, et al. Broad histopathologic patterns of non-glabrous skin and glabrous skin from patients with a new variant of endemic pemphigus foliaceus-part 1. J Cutan Pathol 2010; 37:222-230.
6. Abreu Velez AM, Howard MS, Hashimoto K. Autoantibodies to sweat glands detected by different methods in serum and in tissue from patients affected by a new variant of endemic pemphigus foliaceus. Arch Dermatol Res 2009;301(10):711-718.
7. Abreu Velez AM, Howard MS, Loebl A. Autoreactivity to sweat and sebaceous glands and skin homing T cells in lupus profundus. Clin Immunol 2009; 132: 420-424.
8. Nakamura K, Yasaka N, Asahina A, et al. Increased numbers of CD68 antigen positive dendritic epidermal cells and upregulation of CLA (cutaneous lymphocyte-associated antigen) expression on these cells in various skin diseases. J Dermatol Sci 1998; 18: 170-180.
9. Dong S, Corre B, Nika K, Pellegrini S, Michel F. T Cell receptor signal initiation induced by low-grade stimulation requires the cooperation of LAT in human T cells. PLoS One 2010; 30;e15114.
10. Green GA. Understanding NSAIDs: from aspirin to COX-2. Clin Cornerstone 2001; 3: 50–60.