International Case Reports Journal
Short Communication

Keratoacanthoma: Understanding by Immune Responses

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SHORT COMMUNICATION

Skin is called the "first line of defense" and an integral part of the innate immune system. It is one of the organs in the body that is vulnerable to physical or chemical insults, which can lead to inflammation and cancer. Keratoacanthoma is a type of skin cancer, also known as Squamous Cell Carcinoma (SSC). Keratoacanthoma (KA) is usually characterized by a centralized keratinous plug with a size of 1-2 cm in diameter with a low-grade, quickly scattering dome-shaped skin tumor [1]. Highly differentiated keratinocytes overlay to form this plug. KA has been a topic of great debate in the world of dermatology as well as oncology which can be attributed to rarity, classification methods, and comparability to other non-melanoma cancers of squamous cells. Skepticism has led to declassification and reclassification of KA in various ways. In contrast, despite the lack of complete understanding and sample size, KA has fascinated researchers and doctors alike due to its intriguing capacity for spontaneous regression, which takes about 9 months. Often regarded as a 'pseudotumor' with self-healing potential, the hyperkeratosis of the infundibulum is associated with KA and often develops in hair-bearing regions, including the mouth, gingiva, lip, and several other mucosal surfaces exposed to sunlight. KA has different subtypes arranged by histological assessments as; mucosal keratoacanthoma, solitary keratoacanthoma, giant keratoacanthoma, subungual keratoacanthoma, Keratoacanthoma Centrifugum Marginatum (KCM),generalized eruptive keratoacanthoma of Grzybowski, as well as several keratoacanthomas Ferguson-Smith syndrome [2,3].Older patients and men are more vulnerable to KA, and 40 percent of cases have been identified on the extremities [4]. There's been a long-running controversy on how to categorize KA, so different perspectives arise, like whether the KA is benign or malignant. Many also, on the other hand, have identified KA as cutaneous Squamous Cell Carcinoma (cSCC) with the propensity towards regressing spontaneously. Despite possessing violent characteristics such as perivascular and/or perineural intrusion, KAs are usually benign. As a consequence, many people consider KAs to be a mild type of SSC [5].

The immune system is essential in the surveillance and obliteration of neoplasms. The participation of cells of the immune system in the pathogenesis of KA is of paramount importance as heavy infiltration of lymphocytes is observed in all three stages of KA; proliferative, maturation, and involution [6,4,7]. These three stages of the KA are proliferative, which is characterized by rapid tumor growth; maturation, which requires essential changes in immune response within the tumor; and involution, which is marked by spontaneous tumor relapse and necrosis [8]. The importance of immune response in KA has been corroborated by observing aggressive KA subtypes in immune suppressed patients [9]. Curiously, the primary distinction of KA from other non-melanoma cancers of squamous cells is their exceptionally separated nature which may help immune reconnaissance mechanisms to recognize the tumor rapidly [10]. What makes KA extraordinary is simply the way that they display "recuperating" or unconstrained relapse. As it is with all malignancies, KAs also induce inflammation to some extent which involves the innate and adaptive immune response. The destiny of the inflammatory setting in thought is controlled by the battle between Th17/Tregratio, which employs pro-inflammatory as well as anti-inflammatory responses, correspondingly. The dome-shaped structure and center filled with keratinocytesmay give a moderate climate to the invasion of immune cells. Tumor-Invading Lymphocytes (TILs) are one of a kind, annihilating lymphocytes found in the tumor microenvironment. The adaptive immune cells, T and B cells, along with natural killer cells, are primary infiltrates [11]. Additionally, the infiltration of CD1a+ macrophages and Langerhans cells, including CD3+, CD20+,CD30+,CD34+ interstitial cells, CD45+, CD68+ cells, may explain the rapid inflammation and disruptive necrosis observed in KA, which may lead to spontaneous regression of KA lesions from inside out [7,12]. Moreover, lack of B cell infiltration and low levels of CD3+ FOXP3+ Tregs supports pro-inflammatory cascades aiding in rapid necrosis in the involution stage of KA [7,13]. [Figure 1]

However, these findings are reported on the basis of histopathological examinations of limited samples of KA patients, which may be subjected to experimental error and bias. This reveals the literature gap in KA and its mystic nature of regression. The CD4+/CD8+ T cell ratio appears normal in KA lesions indicates that a regulated and controlled T cell-mediated immune response is necessary to maintain equilibrium in order to destroy malignant keratinocytes [14].

Citation: *Nishant Vyas (2021) Keratoacanthoma:Understanding by Immune Responses. Int Case Rep Jour 1(2):1-3.*

Received Date: *25 May 2021;* ***Accepted Date:*** *28 May 2021;* ***Published Date:*** *31 May 2021*

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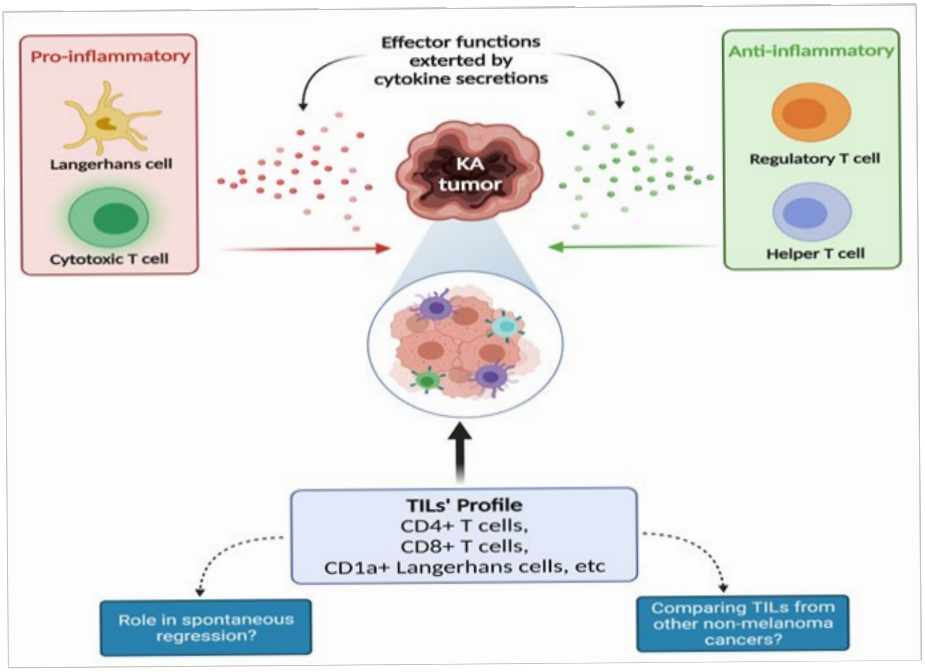

Figure 1: Understanding the role of TILs in KA. The distinction of KA from other non-melanoma cancers of squamous cells based upon TILs ratio and cytokine secretion profile in the tumor microenvironment. Pro-inflammatory functions are exerted by CD1a+ Langerhans cells along with CD8+ cytotoxic T cells. In contrast, the anti-inflammatory functions are exerted by regulatory and helper T cells. These effector functions are mediated by cytokines such as interleukins, interferons, and tumor necrosis factors High-throughput technologies such as flowcytometry with magnetic-activated cell sorting (MACS) may help in revealing a quantitative picture of pro and anti-inflammatory cascades and provide a deep insight into the destructive mechanisms; a hallmark of KA.

Newer technologies such as high-throughput genome sequencing and Flow cytometric assays may aid in the appropriate quantification of TILs and the cytokine secretion profile associated with the tumor-microenvironment in KA. Although histological evidence has paved the way in the right direction employing renewed approach with TILs might help better to characterize KA from other non-melanoma cancer of squamous cells. Understanding the underlying immune response and activation of pro as well as anti-inflammatory cascades may revolutionize the treatment of solid cancers. These strategies can also contribute to the creation of quantitative KA diagnostic tests, thus removing the possibility of misdiagnosis. In recent years, TILs have been found in the primary tumor, tumor-bearing lymph nodes, and visceral metastases of a number of cancers [15]. In addition, the quantification of TILs present in KA lesions can aid in the segregation of KA as a malignant condition from conventional Squamous Cell Carcinoma (SCC) by also considering histomorphological, clinical, and immunological differences. By employing Magnetic-Activated Cell Sorting (MACS) to isolate individual cell populations of TILs and flow cytometry may give a better understanding of their role in spontaneous regression, and this data can also be used to compare and contrast TILs from other SSCs and solid cancers. Moreover, profile TILs along with cytokine secretions are necessary to corroborate previous findings. Additionally, standardizing TILs isolation protocol may help create a diagnostic test not only for KA but other solid cancers too. Therefore it is of paramount importance that we should understand KA's distinctive property of spontaneous regression and find possible applications for similar malignancies.

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