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CD30+ cell population in common keratoacanthomas: a study of 21 cases

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Abstract

Many examples of epidermal pseudocarcinomatous proliferations associated to CD30+ lymphoid infiltrates are described in literature. Most of them have been interpreted as epidermal proliferations secondary to the lymphoid infiltrate. In this study, our purpose was to investigate the CD30+ cell population in keratoacanthomas of patients with no other cutaneous or hematological conditions. We randomly selected 21 cases of KA from our archives and performed an immunohistochemical study for CD30 in all of them. The quantity of CD30+ cells was graded according to a 5-tier system (from non-existent to evidence of groups of three or more CD30+ cells each: 0–4). In four cases, the inflammatory infiltrate could not be studied, since the lesions had been enucleated. From the other 17 cases, in 94.12% of them, the infiltrate was graded as 3 or 4. Only one case was graded as 1, and interestingly, this case corresponded to a keratoacanthoma in regression. We also studied the percentage of CD30+ cells in the infiltrate in each case, obtaining a mean of 2.89%. We conclude that CD30+ cells are a common component of the inflammatory infiltrate of normal keratoacanthoma. We also wonder if the cases described as either lymphomas or lymphomatoid papulosis with keratoacanthomatous changes are nothing more but simple keratoacanthomas. Lastly, we see this CD30+ infiltrate as a source of investigation to understand why keratoacanthomas spontaneously regress, instead of progressing to a metastasizing squamous cell carcinoma.

***Keywords*:** keratoacanthoma, CD30, epidermal hyperplasia, lymphomatoid papulosis, anaplastic large cell lymphoma.

Introduction

It has been claimed in literature that a relationship between CD30+ lymphoproliferative disorders and certain epidermal proliferations exists [1].

Nevertheless, the lymphoid disorder is presented as the "cause", while the epidermal change is usually seen as the "result or consequence" [2]. This has led to certain terms in literature such as primary cutaneous CD30+ anaplastic large-cell lymphomas mimicking keratoacanthoma (KA) [3] or CD30 anaplastic large cell lymphoma with keratoacanthoma-like pseudocarcinomatous hyperplasia [2].

When CD30+ atypical cells have been found in the dermal infiltrate of a keratoacanthomatous lesion, a diagnosis of lymphomatoid papulosis (LyP) has also been favored [4].

Therefore, we found it interesting to investigate the CD30+ cell population, in common keratoacanthomas, in patients with no other cutaneous or hematological alterations.

Material and methods

Twenty-first KAs were randomly selected from our archives.

All cases were examined under the microscope in order to confirm the original diagnosis.

None of the patients had any hematological alterations or any other cutaneous lesions.

In all these cases, we performed an immunohistochemical study with the monoclonal mouse anti-human CD30 antibody of DakoCytomation (clone Ber-H2; code N1558), and with the Dako REAL EnVision detection system.

We evaluated the immunostaining according to the following scheme: 0 = no CD30+ cells; 1 = occasional CD30+ cells; 2 = CD30+ cells which are more than occasional but still appear non-grouped; 3 = CD30+ cells in groups of 3 or less cells each; 4 = CD30+ cells in groups of more than 3 cells each. When two or more patterns of immunostaining were observed (other than 0), only the most frequent in the biopsy (and not the highest value) was the one considered.

Moreover, we have estimated the percentage of CD30+ cells in the infiltrate, following the same semiquantitative method that has been described by Cepeda LT *et al.* [5].

Results

Table 1 shows the clinical details of the patients concerning their age, gender, and location plus size of the lesion. It also shows the pattern of immunostaining, which were observed in each biopsy, as well as the percentages of CD30+, cells in each case.

None of the patients had any other cutaneous disorder, and especially, none of them had any CD30+ cutaneous condition, such as lymphomatoid papulosis or CD30+ lymphoma of any type.

Table 1 – Clinical data of the patients from whom keratoacanthomas were studied. *The CD30 immunostaining pattern evaluated was as follows: 0 = no CD30+ cells; 1 = occasional CD30+ cells; 2 = CD30+ cells which are more than occasional but still appear non-grouped; 3 = CD30+ cells in groups of 3 or less cells each; 4 = CD30+ cells in groups of more than 3 cells each. **In these cases, the infiltrate could not be evaluated: the lesions had been enucleated. ***Curiously, this case presented a morphology of regressing keratoacanthoma. ****They were evaluated according to the method described by Cepeda LT *et al.* [5]

Case	Gender	Age	Location of the lesion	Size of the lesion	CD30+ cells, pattern*	% of CD30+ cells (%) ****
1.	Male	80	Chest	1.3 cm	4	3..34
2.	Female	81	Nose	0.8 cm	**	**
3.	Female	79	Cheek	0.4 cm	**	**
4.	Female	83	Forehead	1 cm	4	2.23
5.	Male	78	Forehead	1 cm	3	1.86
6.	Female	72	Forehead	1 cm	4	10.54
7.	Female	94	Cheek	1.9 cm	4	2.48
8.	Male	66	Forehead	1 cm	4	1.36
9.	Female	83	Cheek	1.5 cm	4	3.47
10.	Female	103	Cheek	3 cm	4	3.10
11.	Male	71	Nose	0.5 cm	4	2.48
12.	Male	71	Forehead	1 cm	4	4.09
13.	Female	90	Cheek	1 cm	**	**
14.	Female	88	Cheek	1.2 cm	**	**
15.	Male	74	First finger, right hand	1.4 cm	3	2.60
16.	Female	85	Hand	3 cm	4	2.10
17.	Male	81	Cheek	1.3 cm	4	3.34
18.	Female	92	Chest	1 cm	1 (***)	0.24 (***)
19.	Female	101	Hand	2 cm	4	2.60
20.	Female	86	Arm	1.5 cm	4	2.48
21.	Male	73	Cheek	0.4 cm	4	0.86

In 17 cases, an inflammatory infiltrate was seen (Figure 1) as it has classically been described in KA in textbooks.

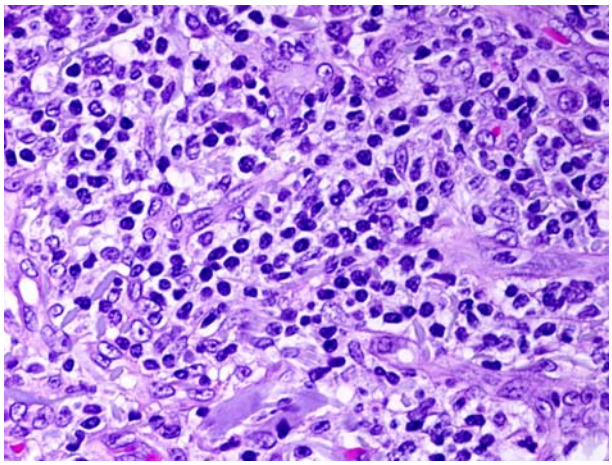

Figure 1 – ***A close view of the atypical infiltrate that was seen around the keratoacanthomas***

In the other four cases, the infiltrate could not be evaluated because the lesions had been enucleated, and therefore, very little stroma was present in the biopsy. The CD30 immunostaining was membranous and paranuclear, as it is usually seen in activated lymphocytes (Figure 2, middle and bottom), and the cytological details could be appreciated in these stains, showing that the nuclei were atypical, with prominent nucleoli in many cases.

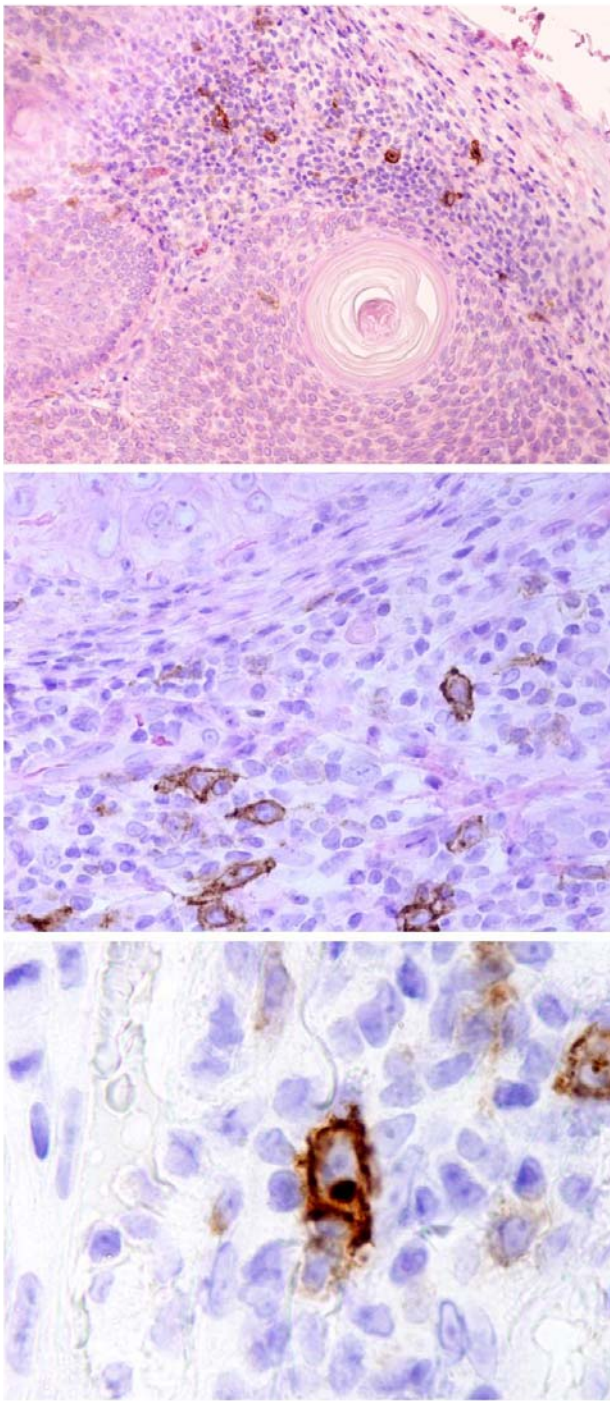

Figure 2 – ***Immunostaining for CD30 showing how many CD30+ cells were easily found in the infiltrate (top). The pattern of immunostaining that was seen in most cases showed grouping of more than three positive cells (middle). The immunostaining was membranous and paranuclear (bottom)***

From the 17 cases with an inflammatory infiltrate, in 14 cases (82.35%), the CD30 immunostaining was graded as 4 (Figure 2, top), and in two cases, it was

graded as 3: that makes 94.12% of the evaluated cases, which had a significant CD30+-rich cell infiltrate. Interestingly, the other 5.88 % was represented by case 18 (graded as 1). In this latter case, the keratoacanthoma was morphologically in regression. Excluding that latter case, the mean of the percentages of CD30+ cells in the infiltrates was 3.06%, while when that case was included, the mean of the percentage of CD30+ cells was 2.89.

Discussions

In literature, a relationship between CD30+ lymphoproliferative disorders and epidermal proliferation has been claimed [1]. The latter has been associated to cases of CD30+ large cell lymphoma [2, 4, 6, 7], cutaneous T-cell lymphoma of mycosis fungoides-type [8], and lymphomatoid papulosis [1, 4, 9].

It has mainly been suggested that the lympho-proliferative condition acts as a cause, and the keratoacanthoma would be the result or consequence [1]. This has been based on the hypothesis that the lymphoid cells produce either cytokines, epidermal growth factor-like molecules or other substances that induce the epidermal proliferation [1]. However, one wonders why the number of lesions KA-like are not more numerous in these patients. Our results might be a morphologic indication that the CD30+ infiltrate might be secondary to the keratoacanthoma rather than a primary event.

The diagnosis of CD30+ large cell lymphoma has well defined quantitative criteria: more than 75% of the cells of the infiltrate should stain for CD30. On the contrary, the diagnosis of LyP can sometimes be based on scattered CD30 positive cells [10], which might be difficult to find. In the WHO-EORTC report on the classification for cutaneous lymphomas [11], for instance, no criteria were given regarding the percentage of the inflammatory cells, which is necessary to make a diagnosis of LyP. On the contrary, it was admitted that "the histologic picture of LyP is extremely variable" and that "in LyP type A lesions, scattered or small clusters of large,…, CD30+ cells are intermingled with numerous inflammatory cells,…". It is not necessary either, in order to make a diagnosis of LyP, that "most" of the atypical cells (even if they are scattered) express CD30: some teams have already demonstrated that in LyP cases, the expression of CD30 by the atypical cells ranged from 25% to more than 90% [12].

Some of the cases described in literature seem to support the point defended by us. Guitart J and Gordon K, for instance, presented a case of KA above a LyP-infiltrate. Nevertheless, they do not mention what the percentage of CD30+ cells is in the infiltrate, and they do not show any images of the CD30 immunostaining either [9]. Even farther, they favored the infiltrate in their case as part of the KA, rather than a variant of LyP! ("the atypical lymphoid infiltrate" "is part of the reactive inflammatory infiltrate normally seen in keratoacanthomas, rather than an unusual variant of LyP." "... it is reasonable to believe that a keratoacanthoma arising from a patient with LyP is likely to have atypical lymphocytes within the reactive infiltrate"). This latter interpretation would be in consonance with our findings.

Scarisbrick JJ *et al.* presented a series of six cases in which one of their patients had an initial diagnosis of multiple eruptive KA [4]. They reinterpreted these lesions as "pseudocarcinomatous change in lymphomatoid papulosis" after "large atypical CD30+ cells were identified in the dermis". We wonder if taking into account our findings, this case would be better considered as multiple simple KAs.

Some groups have studied the percentage of atypical CD30+ cells in benign cutaneous infiltrates, although they did not investigate KA [5]. The mean percentage of these cells was 4.8% in their benign cases. Our results are in consonance with theirs, suggesting that the amount of CD30 cells does not differ from the one in other benign inflammatory infiltrates.

Another consideration seems interesting to us. It has been debated for a long time if KA is a type of squamous cell carcinoma (SCC) or not. Many authors defending the benignancy of KA emphasize the spontaneous regression of the lesions. Many groups, including ours [13–16], have defended that the inflammatory infiltrate plays a crucial role in that regression, so KA could develop into a deeply infiltrating SCC if the regression process does not properly work [17]. For instance, it is well known how systemic immunodeficiency in transplant recipients is a source of risk for developing SCCs [18, 19], and a deficient immunologic state has been associated to cases of metastasizing KA [20, 21]. Old age, as a contributor to a poor immunologic state, has also been associated to cases of KA with metastases [22]. Although many of the inflammatory cells have been investigated in relationship with this spontaneous regression of KA [15, 16, 23–25], we think that our results offer a clue on CD30+ lymphocytes playing a role in the benign evolution of KA. This is also in consonance with some findings from previous reports that showed how T-cells from the inflammatory infiltrate in KA were activated, based on the expression of interleukin 2 receptor by the lymphocytes [23]. It could also explain why a lymphocytic infiltrate in tumors is not always a synonym of good prognosis [26].

Conclusions

Our results show how CD30+ cells are a common component of the inflammatory infiltrate of KA. Therefore, this fact should be taken into account before rendering a diagnosis of lymphomatoid papulosis with keratoacanthomatous changes. We also think that CD30+ population might provide, in the future, some answers about the spontaneous-regression phenomenon that is so characteristic in KA.

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