Case Report

Gingival Anaplastic Large-Cell Lymphoma Mimicking Hyperplastic Benignancy as the First Clinical Manifestation of AIDS: A Case Report and Review of the Literature

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Received 24 April 2013; Accepted 26 May 2013

Academic Editors: M. Ashkenazi, M. A. Polack, and A. Scribante

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This paper presents an unusual case of gingival ALCL, which mimicked a benign hyperplastic lesion that occurred in a 57-year-old white man representing the first clinical manifestation of acquired immunodeficiency syndrome (AIDS). The patient was referred to the Dental Clinic of PUCPR complaining of a lobulated nodule on the gingiva of his upper central incisors. The presence of advanced chronic periodontitis and dental plaque raised suspicion for a benignancy. An excisional biopsy was performed, and large pleomorphic cells with an abundant cytoplasm, sometimes containing prominent nucleoli and “Hallmark” cells, were observed through hematoxylin and eosin staining. The tumor cells showed strong CD30 expression, EMA, Ki-67, and LCA, and negative stain for p80NPM/ALK, CKA/E/AE3, CD20, CD3, CD56, and CD15. The final diagnosis was ALCL (ALK-negative). Further laboratory tests revealed positivity for human immunodeficiency virus (HIV). The patient was submitted to chemotherapy, but four months after diagnosis, the patient died due to pneumonia and respiratory failure. Oral anaplastic large-cell lymphoma (ALCL) is a rare disorder. Only 5 cases involving the gingiva have been reported, and to our knowledge, this is the first case reported of the ALCL, which mimicked a hyperplastic benignancy as the first clinical manifestation of AIDS.

1. Introduction

Malignant lymphomas (MLs) are a large group of neoplasms affecting the lymphoid system and are subdivided into two main groups: Hodgkin’s and non-Hodgkin’s lymphomas (NHLs) [1]. ML is considered an opportunistic neoplasm because it frequently affects immunocompromised patients. The prevalence of ML has increased considerably with improved acquired immune deficiency syndrome (AIDS) survivorship [2, 3]. NHLs appear in 3% of HIV-seropositive patients [4]. The NHLs may be present outside the lymphoid system, in which case they are called extranodal [5]. This type of lymphoma is located at an extranodal site in 40% of cases [5] and its extranodal presentation occurs in almost 75% of human-immunodeficiency-virus- (HIV-) seropositive patients [2]. Furthermore, only 2% to 3% of these extranodal cases occur in the oral cavity [6].

In the group of NHLs, mature T cell and natural killer (NK) cell neoplasms make up only 12% of NHL cases worldwide [1]. Within this heterogeneous category, anaplastic
large-cell lymphoma (ALCL) is found [7, 8] and is listed in the Revised European-American Classification of Lymphoid Neoplasms (REAL) as an independent entity [9]. A couple of ALCL cases have been reported, although some were the B-cell phenotype now classified as an anaplastic type of diffuse large B-cell lymphoma [10]; therefore, these cases were excluded from the present review. ALCL is characterized by proliferation of the anaplastic large lymphoid cells with abundant cytoplasm and strong expression of CD30 antigen; however, its final diagnosis is a challenge for oral pathologists [8, 11–17]. Two distinct clinical entities of ALCL are recognized by the World Health Organization (WHO) lymphoma classification: cutaneous and systemic lymphomas [1, 5]. The cutaneous ALCLs are characterized by indolent growth and may show spontaneous remission and good prognosis [18, 19]. The systemic ALCLs can be ALK-positive or -negative [18]. The ALK-positive ALCLs usually occur in male pediatric patients and show a good prognosis taking into account their affective response to chemotherapy, whereas the ALK-negative ALCLs occur in elderly patients and present a poor prognosis [18, 20].

ALCL especially affects the skin of the body [6]. This T-type lymphoma in the oral cavity is an extremely rare disorder characterizing 1% of lymphomas overall [19]. From the scientific literature, we found around 15 cases of ALCL in the oral cavity [2, 6, 8, 11–17, 21, 22]. Only 5 cases of ALCL located in gingiva have been reported in the literature [12, 17, 22], and our case is the fourth reported occurrence of ALCL in the oral cavity of a HIV-seropositive patient [2, 11]. Besides, this paper is the first to present an unusual case of oral ALK-negative ALCL that mimicked a benign hyperplastic lesion as a first clinical manifestation of AIDS.

2. Case Report

A 57-year-old white man was referred to the Dental Clinic of PUCPR complaining of an asymptomatic hyperplastic lesion on the gingiva of his upper central incisors, which had grown significantly in the last two months. The patient was a nonsmoker and his medical history did not reveal other relevant information. The extraoral examination showed a small swelling of the upper lip and absence of cervical lymphadenopathy. The intraoral examination showed advanced chronic periodontitis and the presence of a lobulated reddish nodule, pedunculated, measuring around 2.5 cm on the gingival area between both upper central incisors which had mobility and accumulation of dental plaque (Figure 1). The lesion did not have an ulcerated surface, and palpation revealed a soft consistency with bleeding on the surface. Panoramic radiography showed a significant resorption of bone mainly in the anterior area of the maxillary, compatible with advanced chronic periodontitis (Figure 2).

Taking into account that the first impression of the lesion revealed clinical characteristics of a benignancy, as the pedunculated nodule, circumscribed, freely moveable, the presence of dental plaque, and advanced chronic periodontitis, we initially suspected that it could be related to a reactive hyperplastic lesion. These lesions include pyogenic granuloma, focal fibrous hyperplasia, peripheral giant cell granuloma, and peripheral ossifying fibroma. Therefore, considering these main hypotheses, an excisional biopsy of the nodule was performed under local anesthesia. Furthermore, the patient was referred for periodontal treatment.

Hematoxylin and eosin-stained sections showed a lesion characterized by a diffuse proliferation of lymphoid tumor cells underneath an epithelium (Figure 3(a)). The slices also showed large pleomorphic cells with an abundant cytoplasm, sometimes containing prominent nucleoli. “Hallmark” cells with eccentric, horse-shoe, or kidney-shaped nuclei were also observed (Figure 3(b)). The tumor cells frequently demonstrated mitotic figures. Immunohistochemical analysis using a streptavidin-biotin protocol [14] was performed with the antibodies: CKAE1/AE3, CD20, CD3, CD30, Ki-67, epithelial membrane antigen (EMA), CD56, leukocyte common antigen (LCA), p80 NPM/ALK, and CD15. The tumor cells showed strong CD30 expression with a membrane and Golgi distribution in the majority of tumor cells (Figure 3(c)). Ki-67 positive stain was observed in 90% of tumor cells (Figure 3(d)). Positive stain in tumor cells was also identified for EMA and LCA. Negative stain was identified for p80 NPM/ALK, CKAE1/AE3, CD56, and CD15. The tumor was a null-cell type (negatively stained for CD20 and CD3). Based on clinical, histological, and immunohistochemical findings, the final diagnosis was extranodal ALK-negative ALCL.

The patient was referred to a specialized oncology hospital where further laboratory and imaging tests showed positivity for HIV, negativity for both hepatitis B and C, normal full blood count proportions of white and red blood
cells and platelets, and absence of lymphadenopathies and metastasis. The following chemotherapy protocol consisted of six cycles of CHOP (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 2 mg, and oral prednisone 100 mg) for five days [23]. However, four months after diagnosis, the patient died due to pneumonia and respiratory failure.

3. Discussion

This case report presents a rare case of ALCL in an extranodal site of a Brazilian male HIV-seropositive patient. Since ALCL was first described as a clinical entity by Stein et al. (1985) [20], this lesion was classified as Ki-1+ ALCL and currently as Ki-1 (CD30) [17], which corresponds to a cohesive proliferation of large pleomorphic cells that express CD30. The ALCL is subdivided according to the immunohistochemical features in precursor T cells or null cells, in 60% and 25% of the cases, respectively [2]. Therefore, immunohistochemistry is imperative for the correct diagnosis of ALCL considering that the cells are positive for CD30 antigen and several other markers such as EMA that is present in slightly more than 50% of cases [2]. LCA is usually positive but may be used negative in 30% to 40% of cases [2]. In most cases, other markers such as Ki-67, CD3, and CD45RO (T-cell phenotype), TIA-1 (T-cell intracytoplasmic antigen-1), perforin, granzyme B, and p80NPM/ALK will be positive [6, 17].

The clinicopathologic features of ALK-carrying ALCLs were first investigated by Shiota and Mori [24]. The authors found that ALK-positive is a distinctive entity clinically and pathogenetically and should be differentiated from ALK-negative. Indeed, based on the most recent findings, the WHO classification currently considers two ALCL types, negative and ALK-positive [25, 26]. The tumors that show a positive reaction for ALK have greater cell proliferation and can show a relatively better prognosis [19]. Recently, studies have proposed that proteins such as aberrant fusion protein (NPM-ALK), JAK-STAT, and PI3K/STAT may be a potential target in ALK-positive lymphomas [26–28]. The findings about specific antigens also suggest that ALK represents an ideal tumor antigen for vaccination-based therapies of ALCL and other ALK-positive tumors [29]. On the other hand, the cases of ALK-negative ALCL show an inaccurate behavior with a relatively unfavorable prognosis [18]. To make the diagnosis of ALK-negative ALCL, there must be a large cell predominant population with abundant cytoplasm and pleomorphic, embryo or hallmark nuclei or wreath-like giant cells, and strong CD30 expression with a membrane and Golgi distribution in virtually every cell with a highly anaplastic T-cell phenotype [17, 19]. As the current case did not express ALK, it was classified as an ALK-negative ALCL. In addition, the tumor did not show expression of NK or T-cell markers; therefore, it was classified as a null cell lymphoma. ALK-negative ALCL normally occurs in adults.
| Age | Gender | Oral area | Clinical findings | Radiographic findings | HIV | Diagnostic hypothesis | ALK | References |
|-----|--------|-----------|-------------------|----------------------|-----|-----------------------|-----|------------|
| ND  | ND     | ND        | ND                | ND                   | ND  | ND                    | ND  | Takahashiet al. [8] |
| 36  | M      | Retromolar trigone | Mass with ulcerated surface Enlargement surrounding a crateriform ulcer Scaly, swollen, and bleeding gingival surface | Diffuse radiolucency with poorly margins | +    | Nonspecific infection | ND  | Hicks et al. [2] |
| 42  | M      | Retromolar trigone | Mass involving the nasal cartilage and floor of the orbit Periodontitis (deep pockets) and redness of the gingiva | Bone resorption adjacent to teeth 11, 12, and 13 | −    | −                     | ND  | Hicks et al. [2] |
| 12  | F      | Gingiva    | Well-delimited ulceration | −                   | ND  | −                     | ALCL | Willard et al. [11] |
| 12  | M      | Hard palate | Mass involving the nasal cartilage and floor of the orbit | Bone resorption causing teeth displacement | +    | Gingivitis | ND  | Papadimitriou et al. [21] |
| 75  | F      | Upper gingiva | Mass with ulcerated surface | Bone resorption | ND  | −                     | Periodontitis | Rosenberg et al. [12] |
| 61  | M      | Lower gingiva | Mass with ulcerated surface | Bone resorption | ND  | −                     | Eosinophilic granuloma | Rosenberg et al. [12] |
| 48  | M      | Upper lip   | Mass with ulcerated surface | Bone resorption | ND  | −                     | Nonspecific infection | Chandu et al. [13] |
| 76  | F      | Upper lip   | Mass with ulcerated surface | Bone resorption | ND  | −                     | ALCL | Chim et al. [14] |
| 65  | F      | Hard palate, buccal mucosa, and floor of the mouth | Mass with ulcerated surface | Bone resorption | ND  | −                     | − | Present case |
| 77  | M      | Left side of soft palate | Mass with ulcerated surface | Bone resorption | −    | −                     | Lymphoma, salivary gland neoplasm, or necrotizing sialometaplasia | ND  | Savarrio et al. [6] |
| 77  | M      | Tongue     | Mass with ulcerated surface | Bone resorption | ND  | −                     | Nonspecific infection | Notani et al. [16] |
| 76  | F      | Upper and lower gingiva | Mass with ulcerated surface | Bone resorption | ND  | −                     | Chronic marginal periodontitis | Matsumoto et al. [17] |
| 34  | F      | Upper gingiva | Mass with ulcerated surface | Bone resorption | ND  | −                     | Lymphomatoid papulosis, fungal infection, or traumatic ulcer | − | Grandhi et al. [22] |
| 53  | M      | Tongue     | Mass with ulcerated surface | Bone resorption | ND  | −                     | Reactive hyperplastic lesion | − | Grandhi et al. [22] |
| 57  | M      | Gingiva in maxillary incisor area | Mass with ulcerated surface | Bone resorption | +    | −                     | Present case | Present case |

ND: not described; F: female; M: male; +: positive; −: negative; *includes pyogenic granuloma, focal fibrous hyperplasia, peripheral giant cell granuloma, and peripheral ossifying fibroma.
with CHOP (cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, vincristine 2 mg, and oral prednisone 100 mg from the first to the fifth day of chemotherapy) [23]. This CHOP regimen was administered every 3 weeks for a total of six cycles. Several studies demonstrate the high rate of complete remission (70%–95%) and 70%–85% long-term overall survival [23]. However, unfortunately, in the current case, the patient died.

4. Summary

In our case, it is important to highlight that the rapid growth of the lesion in the last two months reported by the patient and the presence of dental plaque and advanced chronic periodontitis indicated a reactive process in the gingiva. For this reason, the first decision to make an excisional biopsy of the lesion was kept. It is also important to stress that, if it was known that the patient was HIV-positive, our conduct would be completely different. Unfortunately, the final diagnosis was a malignant lesion.

We presented an unusual case of ALK-negative ALCL on the gingiva associated with advanced chronic periodontitis that mimicked some clinical features of a hyperplastic gingival benignancy, which manifested in a 57-year-old HIV-seropositive man. ALCL is a systemic malignant disease characterized by the extranodal type which rarely occurs in the oral cavity as the first manifestation of acquired immunodeficiency syndrome. Thus, we emphasize the importance of an accurate clinical, including HIV investigation, histological, and immunohistochemical analysis of oral lesions to establish the correct diagnosis of those lesions which in daily practice are considered benign.

Disclosure

The authors declare no conflict of interests concerning this paper. The authors have full control of all primary data of their paper. This paper is not supported by any institutional or corporate affiliation.

Acknowledgments

The authors thank Ana Paula Camargo Martins and Marina Viola Azevedo for their most valuable laboratory technical assistance.

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