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Primary mandibular ALK-positive anaplastic large cell lymphoma in a young child: A case report in oral surgery

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Abstract

Non-Hodgkin lymphomas constitute a large family of malignant diseases that frequently affect children. One of them, systemic anaplastic large cell lymphoma, is described by the WHO as having two subtypes: ALK positive and ALK negative anaplastic large cell lymphoma. These are rare, especially when they appear in a primary extranodal form. Lack of awareness of these extranodal manifestations can lead to delayed diagnosis with, sometimes, dramatic consequences. Here, we report the case of a young boy presenting intra-oral and cervical swellings, initially diagnosed as infectious cellulitis with a dental origin, before being referred to an oncohematology department. Analysis revealed an ALK positive anaplastic large cell lymphoma and appropriate treatment could be initiated. Extra-nodal manifestations, particularly oral, are little-known forms of lymphoma, especially in children. It is therefore essential to raise awareness among practitioners about the detection of extra-nodal and particularly oral manifestations of these rare lymphomas.

Keywords: Anaplastic large cell lymphoma; Pediatric lymphoma; Primary oral lymphoma; Oral cancer; Gingival cancer; Head and neck cancer; Case report.

Abbreviations: ALK: Anaplastic Lymphoma Kinase; ALCL: Anaplastic Large Cell Lymhoma; MDD: Minimal Disseminated Disease; NHL: Non Hodgkin Lymphoma.

Introduction

Anaplastic Large-Cell Lymphoma (ALCL) is a rare Non-Hodgkin's Lymphoma (NHL) (less than 10% of all NHLs) that occurs most frequently in children and young adults [1,2]. There are 2 types: cutaneous ALCL and systemic ALCL. The latter includes 2 subtypes according to the expression of Anaplastic Lymphoma Protein Kinase (ALK): the ALK-positive and ALK-negative subtypes. This T-cell lymphomas are histologically characterized by the proliferation of CD30-positive large lymphocyte cells. Its diagnosis is often delayed, complicating patient care, especially since they are considered aggressive [1,2]. Its main symptoms are chronic lymphadenopathy, severe fatigue, night sweats, fever and weight loss. Interestingly, primary extranodal manifestations (particularly oral mucosal manifestations) are regularly reported in the literature, with even greater delays in diagnosis [3,4]. Primary ALCL of the oral cavity is very rare with approximately 30 cases reported in the literature. Herein we present the case of an initial oral manifestation of an ALK-positive ALCL in a young boy. This is, to the best of our knowledge, the youngest case reported in English literature.

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Case presentation

A 7 years and 9 months old child was referred to our oral pathology consultation by his pedodontist for a left cervical swelling associated with a left mandibular gingival ulcerated mass present for the past two months. The swelling persisted despite avulsion of deciduous lower left canine under antibiotics following an initial diagnosis of odontogenic cellulitis, several weeks of antibiotic therapy and various medical and dental consultations.

Medical history was unremarkable. The anamnesis indicates a painful limitation of the extension of the left arm of concomitant appearance with oral lesions, as well as a feeding difficulty without deterioration of the general state, nor weight loss. There had been a single loss of consciousness 3 weeks previously.

Extraoral examination revealed large, firm, painful and fixed left swelling, extending from the mandibular angle to the chin and causing limited cervical rotation and an opening mouth limited to 3 cm (Figure 1A). Intraoral examination revealed a reddish ulcerous necrotic mass on the lower gingiva, located on either side of the deciduous canine alveolus, extracted two months before (Figure 1B). Palpation of the buccal swelling and the left lingual floor is firm and painful. On one hand, 2D and 3D radiographies showed discrete and superficial bone resorption of the mandible. On the other hand, the X-ray of the left arm revealed lysis of the humeral epiphysis cortical bone (Figure 1C) and the cervical ultrasound showed two left submandibular lymphadenopathies (27x17 and 11x20 mm). Routine laboratory studies did not show any abnormalities. A biopsy of the mandibular mass was performed to rule out hematologic malignancy. Anatomopathological examination exhibited an infiltrate of medium to large lymphoid cells with eosinophilic and reniform nuclei. Immunohistochemistry showed that these tumoral lymphoid cells are positive for CD30, ALK in a nuclear and cytoplasmic pattern, CD25, EMA, Granzyme B (partial), but were negative for CD3, CD5, CD20. The Ki67 proliferation index was 70%. Additional examination, useful for staging-procedure, performed in a hematology pediatric department, revealed cervical, cutaneous, digestive, bone and pulmonary involvement. The bone marrow was intact but there was a positive peripheral Minimal Disseminated Disease (MDD).

Based on clinical, MRI and histopathological findings, a diagnosis of stage IV primary ALK-positive anaplastic large cell T/NK lymphoma of the mandible was made.

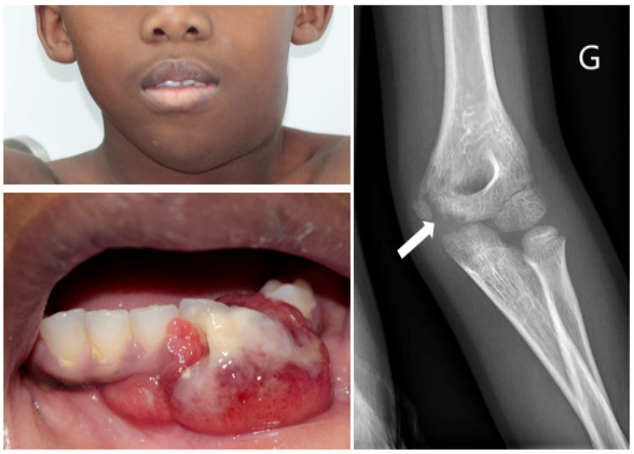

Figure 1: Clinical and radiographical features of primary mandibular ALK-positive anaplastic large cell lymphoma. **(A)** Extraoral examination showing a left cervico-mandibular swelling, **(B)** Intraoral examination showing a reddish ulcerous necrotic mass on the lower left alveolar ridge of the mandible, **(C)** Radiography of the left arm, showing an osteolysis of the of the cortical bone of the humeral epiphysis.

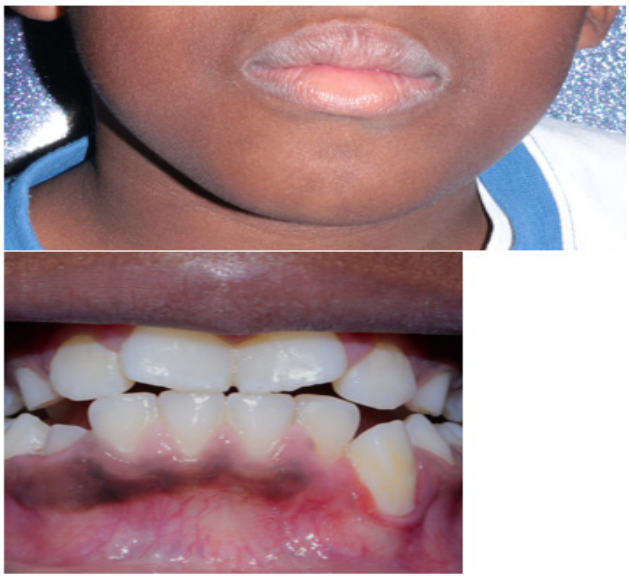

Figure 2: Clinical features of primary mandibular ALK-positive anaplastic large cell lymphoma after one year of treatment: **(A)** Extraoral examination showing the regression of the left cervico-mandibular swelling, **(B)** Intraoral examination showing the regression of the reddish ulcerous necrotic mass on the lower left alveolar ridge of the mandible.

Treatment: A first-line treatment of polychemotherapy, according to the ALCL 99 protocol (Course P: dexamethasone 5 mg/m²/d, cyclophosphamide 200 mg/m²/d, methotrexate 15 mg, aracytine 30 mg and hydrocortisone hemi-succinate 15 mg; course AM1: dexamethasone 5 mg/m²/d, methotrexate 3 g/m², ifosfamide 800 mg/m², cytarabine 150 mg/m², etoposide 100 mg/m²; course BM1: dexamethasone 5 mg/m²/d, methotrexate 3 g/m², cyclophosphamide 200 mg/m², doxorubicine 25 mg/m²)was initiated [5]. Tolerance was rather poor with the presence of nausea/vomiting, abdominal pain and asthenia. The first courses of chemotherapy led to a good clinical response and a partial morphological response on the cervico-thoraco-abdomino-pelvic scanner and mandibular MRI. However, given the persistence of a positive minimal residual disease (0,14%) at two months, sign of poor disease control, long-term targeted therapy with an ALK inhibitor (alectinib 150 mg twice a day for seven days and then 150 mg morning and 300 mg evening) was initiated allowing the negativation of MDD after 1 month of treatment, with a good compliance and no specific adverse event.The patient also showed regression of the cervical masses as well as the gingival nodule (Figures 2A,B).

Discussion

ALCL is a subgroup of T-cells NHL, first described by Stein et al. (1985). There are two systemics subtypes: ALK-positive ALCL, and ALK-negative ALCL, account for less than 10% of NHL. The main clinical presentation of ALCL is peripheral lymph nodes as-

Table 1: Among the sixteen cases reported in the literature proposing differential diagnoses, 11 initially evoke purely benign diagnoses.

Author	Age/ gender	Time before diagnosis (days)	Location	Clinical features	Radiographic findings	Biological tests	Differential diagnosis	ALK status
Hicks et al. [9]	36/M	60	Retromolar trigone	Ulcerated mass	Poorly defined radiolucency	NA	Infection	-
Hicks et al. [9]	42/M	75	Retromolar trigone	Ulceration	Alveolar heeling	NA	Pericoronitis, bacterial, fungal or viral infection	NA
Willard et al. [10]	12/F	365	Lower right gingiva	Ulcerated swelling, easily bleeding	Bone resorption	NA	Gingivitis and then Papillon LeFevre Syndrome, peripheral giant cell granuloma, histiocytosis, X, Wegener's granulomatosum, and osteogenic sarcoma	NA
Savarrio et al. [12]	77/M	21	Soft left palate	Ulcerated mass	NR	Normal	infection (abcess) and then lymphoma, minor salivary gland neoplasm or necrotising sialometaplasia	NA
Matsumoto et al. [13]	76/F	330	Upper and lower gingiva	Gingival swelling	None	Elevated CRP	Periodontitis, infection and then malignant disorders	-
Terada et al. [14]	74/F	NA	Upper left gingiva	Swelling of the left maxillary gingiva	Normal	Normal	Granulation tissue	-
Grandhi et al. [1]	34/F	21	Upper anterior gingiva	Ulcero-necrotic mass with erythema	NA	NA	lymphomatoid papulosis, other lymphoproliferative disorder, deep fungal infection, and traumatic ulcer	-
Rozza de Meneses et al. [4]	57/M	60	Gingiva	Reddish multilobulated nodule	Anterior maxillary bone resorption	HIV, HCV and HBV positive	Pyogenic granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma	-
Yoon et al. [15]	70/F	NA	Upper right and lower left gingiva	Reddish erythema around implants	Bone resorption	Elevated Sedimentation rate, leucocytosis	malignant disorders	-
Narwal et al. [8]	48/M	60	Hard palate	Rapidly bleeding swelling	Discrete bone resorption	Normal	Pyogenic granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma, and even pleomorphic adenoma	-
Lapthansupkul et al. [11]	55/F	30	Left hard palate	Multilobular mass	Osteolysis of left maxillary	NA	malignant neoplasms, including squamous cell carcinoma, malignant salivary gland and lymphoid tumors	-
De Andrade et al. [7]	88/M	20	Alveolar ridge	Multilobular ulcerated swelling	Discrete well-defined superficial bone resorption	Normal	Reactive lesion or malignant primary or metastatic tumors	-
De Andrade et al. [7]	18/M	30	Submandibular region and floor of the mouth	Ulcerated swelling	Hyperdense area with necrotic center	NA	malignant mesenchymal tumor	+
Aizawa et al. [17]	15/M	395	Upper left gingiva	Gingival and buccal swelling	Bone destruction	Normal	Buccal cellulitis, maxillary sinusitis and peripheral periodontitis	+
Oya et al. [16]	38/M	NA	Upper right gingiva	Diffuse swelling with ulceration	Irregular bone resorption	NA	Osteomyelitis	+
Present case	7/M	90	Lower left gingiva	Ulcero-necrotizing nodule	Discrete bone resorption	Normal	Cellulitis and then hematologic malignancy	+

sociated with extranodal disease and B symptoms (fever, night sweats, asthenia and weight loss) [1,2]. While primarily originating in lymph nodes, extra-nodal involvement (with or without lymph node) is also frequent in NHLs, including ALCL, and often results in high grade at diagnosis [3,4].

ALK-positive ALCL commonly affect male patients in their first decades, frequently in childhood, unlike ALK-negative ALCL which affect elderly patients [1,3,4]. Pediatric ALCL are frequently ALK positive due to the existence of a chromosomal translocation within the NPM1-ALK oncogene [6].

Within systemic ALK-positive ALCL, extra-nodal involvement is commonly cutaneous, pulmonary, digestive, hepatic or in the bone [7]. While ALK-positive intra-oral involvement is less frequent than ALK-negative, both remain a rare localization of ALCL (<1%, approximately 30 cases in the English literature). They are mainly located on the gingiva/alveolar ridge or the palate. In our case, the oral manifestations are locally aggressive, as described in the literature as an ulcerated painful nodule or mass associated with underlying bone resorption [4,7].

The diagnostic workup in patients with suspected ALCL includes a biopsy of sufficient size, MDD evaluation in blood, bone marrow aspirates, and lumbar puncture [2]. Microscopic analy-

sis shows a proliferation of large atypical lymphoid cells with abundant cytoplasm and eccentric horseshoe or kidney-shaped nuclei, which is the case for our patient. The characterization of the cells involves the study of immunohistochemical markers that show a strong expression of CD30. ALK expression account for 50% of systemic ALCL and, is the result of a t (2;5) chromosomal translocation. In contrast, expression of other markers such as CD2, CD5, CD3, CD45, or cytotoxic markers such as TIA1, Granzyme B, and perforin is more variable [2]. These markers are not specific, and this disease can therefore easily be confused with poorly differentiated squamous cell carcinoma, melanoma, Hodgkin lymphoma, or anaplastic diffuse large B-cell lymphoma [1,7].

Treatment includes a combination of chemotherapies leading to good overall survival (70%) but extremely aggressive and associated with major toxicities. However, there is a relapse rate of approximately 30%. Recently, targeted therapies have come on the market, notably anti-ALK drugs such as alectinib. They can be administered in the long term or transiently before allogeneic hematopoietic stem cell transplantation [2]. These treatments achieve a good control of the disease with lesser adverse effects but remain second-line treatments (for children with a relapse of an ALCL or for consolidation).

ALK-positive ALCL is a distinct entity, having a better prognosis than ALK-negative ALCL [4,7]. In the present case, the young patient was able to have a rapid remission four months after diagnosis and, at one year follow-up, he is in remission but still under treatment, with no evidence of disease.

Young age, chemotherapy treatment as well as the extranodal head and neck primary site involvement are known to have a more favorable prognosis [3]. Our patient management required second-line treatment, probably because of the advanced stage of the pathology.

The rarity of ALCL and ignorance of the possibility of oral manifestations of this pathology may explain the delay in diagnosis and thus the advanced stage at diagnosis of oral ALCL. Indeed, the median diagnosis is 60 days, for a pathology that can be aggressive. This delay in diagnosis may also be linked to the clinical presentation, which mimics a benign tumour or locoregional infection, as reported by various authors [4,8]. Among the sixteen cases reported in the literature proposing differential diagnoses, 11 initially evoke purely benign diagnoses (Table 1). The diagnosis of malignancy is generally made at a later stage, after failure of 1st-line treatment, or is discovered incidentally during biopsy, which is usually performed in a specialized hospital department.

It also seems that, in children, the delay in diagnosis is greater than in adults, median 365 days (range [90-395]) versus 45 days (IQR [23-60]) while the potential harm is more important. However, it should be noted that the median is calculated on only 3 pediatric cases. Extra-oral manifestations facilitate the evocation of a diagnosis of malignancy. However, although they are regularly prescribed, first-line biological tests seem to contribute little to the diagnosis because they do not show any abnormality (6/9) or non-specific variations suggestive of an inflammatory syndrome (2/9) (Table 1). Thus, despite the clinical presentation frequently suggesting benign diagnoses, it is essential to carry out additional examinations to confirm the diagnosis, particularly in case of failure of an initial therapy adapted to the benign diagnosis made as first intention.

Conclusion

It is essential to recognize warning signs and symptoms of this rare disease, even if the lesion appears benign and in an unusual form like an intra-oral manifestation, to avoid any loss of chance for the patient, especially children.

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