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*RESEARCH ARTICLE*

# ANAPLASTIC LARGE CELL LYMPHOMA ALK NEGATIVE OF THE MANDIBLE AS THE FIRST CLINICAL MANIFESTATION OF ACQUIRED IMMUNODEFICIENCY SYNDROME

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## *Abstract*

Anaplastic large cell lymphoma (ALCL) is a distinct subtype of peripheral T-cell lymphoma (PTCL) characterized by CD30 expression and accounts for less than 5% of all non-Hodgkin's lymphomas. People infected with the human immunodeficiency virus have an increased risk of developing high-grade non-Hodgkin's lymphoma. But the appearance of ALCL in HIV-positive people remains a rare manifestation. Extranodal involvement is common in the skin, bones, soft tissues, lungs and liver. Extranodal ALCL rarely occurs in the oral cavity as a first manifestation. Histological and IHC analysis are necessary to exclude other malignancies associated with acquired immunodeficiency syndrome.



## Introduction:-

Anaplastic large cell lymphoma (ALCL) is a subgroup of non-Hodgkin's T-cell lymphomas (NHLs) that accounts for 1% to 8% of all NHLs and 12% of all T-cell lymphomas [1-2] . It is characterized microscopically by the proliferation of large anaplastic lymphoid cells that strongly express the CD30 antigen [3-4]. Although,the acquired immundeficiency syndrome is usually associated with aggressive B-cell non-Hodgkin's lymphomas, the risk of developing PTCL is also increased in the setting of HIV infection. To date, the occurrence of ALCL in HIV-positive people is limited to a few case reports and small case series. We describe the case of a newly diagnosed HIV-positive patient with confirmed ALCL pathology on a mandibular bulky mass in the hematology department of mohammed V military hospital, rabat, Morocco, and highlight recent findings in the literature.

**Case Presentation**

We report the case of a 57-year-old man referred for evaluation of a painless soft tissue mass on the left alveolar crest of the mandible since two months. Extraoral examination revealed facial asymmetry involving the left body of the mandible. The intraoral examination revealed an irregular surface mass on the postero-inferior alveolar ridge on the left side, measuring 8*10 cm. The mass was ulcerated and soft in consistency, bleeding easily, and covered in yellow and red mucus, responsible for an almost total dental avulsion. His medical history is unremarkable. The radiological assessment showed a lytic lesional process centered on the left mandible with a tumoral appearance. Biopsy of the mass revealed strong and diffuse expression of anti-ACL and anti-CD30 antibodies, weak and focal expression of anti-EMA. Ki67 proliferation index was evaluated at 95% .Immunehistochemisry with antibodies: CD3, CD5, CD20, CD138, MPO, CD1a, ALK, EBV, CD79a, AE1/AE3, CD10, CD15 was negative. No cytogenetic analysis was performed. The final histological diagnosis was associated ALK-negative anaplastic large cell lymphoma.

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The FDG-PET-Scan revealed in addition to the left mandibular hypermetabolic mass, multiple pathological hyper-metabolic supra and subdiaphragmatic lymph nodes, pulmonary nodules , involvement of the left pleura, lever, spleen, bone and bilateral adrenal parenchyma.

[figures 1,2,3].

Complementary biological tests revealed positivity of the human immunodeficiency virus (HIV), with a viral load of 178,200 copies/ml. The patient started a treatement with highly active antiretroviral therapy (HAART).

Two months later, he had fiever and his general condition deteriorated considerably. The CD4+ cell count was 67/mm3 and the HIV viral load was 355,000 copies/mL at that timepoint. Lactatdehydrogenase (LDH) was 5 times higher than normal. Despite receiving chemotherapy (CHOP regimen, i.e. cyclophosphamide, doxorubicin, vincristine and prednisone), the patient's condition worsened afterwards and he died after a few days of acute respiratory distress.

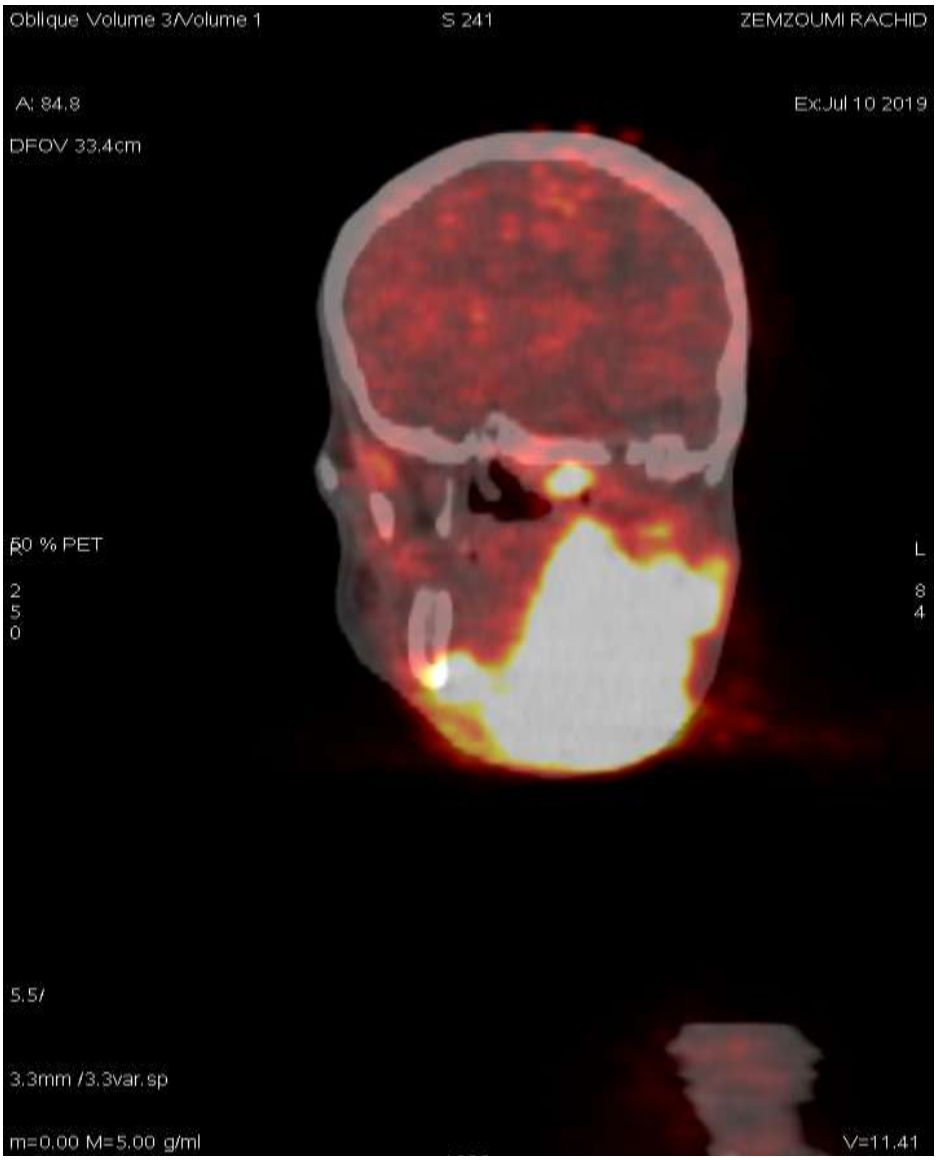


**Figure 1**:- FDG-PET-CT images showing increased increased uptake of FDG in left mandibular bulky masse.

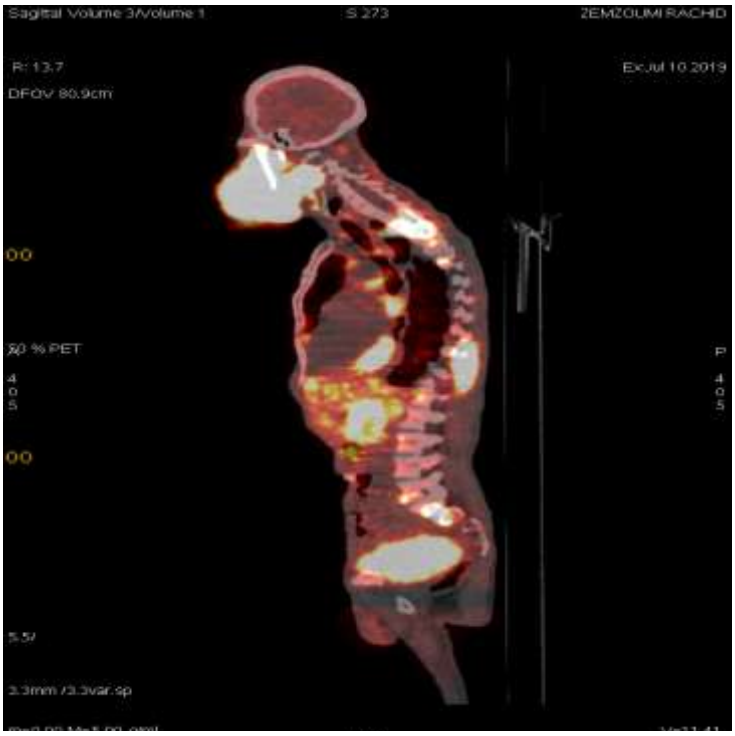


**Figure 2**:- FDG-PET-Scan (sagittal plane), showing a voluminous left mandibular hypermetabolic mass , supra and sub diaphragmatic lymph nodes hypermetabolism , pulmonary nodules , involvement of the left pleura, lever , spleen , bone and bilateral adrenal parenchyma (stade IV).

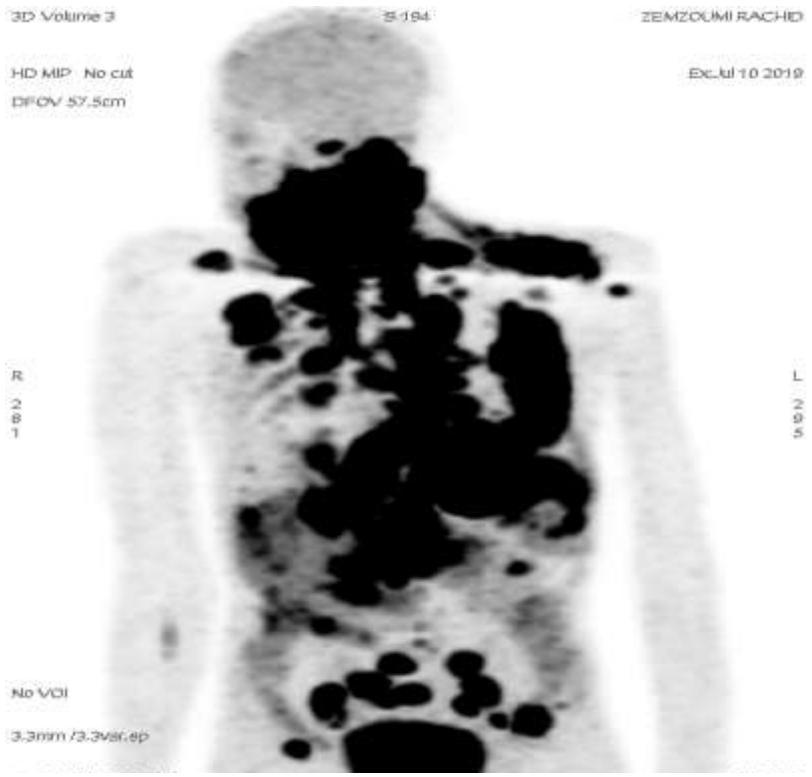


**Figure 3**:- FDG-PET Scan ( coronal plane) showing in addition to the left mandibular hypermetabolic mass , supra and sub diaphragmatic lymph nodes hypermetabolism , pulmonary nodules , involvement of the left pleura ,lever ,spleen , bone and bilateral adrenal parenchyma ( stage IV).

## Discussion:-

Anaplastic large cell lymphoma (ALCL) was first described by Stein and colleagues in 1985. The 2016 update of the World Health Organization (WHO) classification of hematological malignancies finally defined ALK- ALCL as an established diagnostic entity [5]. According to the previously published International Peripheral T-cell Lymphoma Project report, ALK-ALCL accounts for approximately 5 % of peripheral T-cell lymphoma (PTCL) diagnoses worldwide, with some geographic predilection [6]. In the United States, the incidence of rates is the highest in non-Hispanic black and white patients and the lowest rates in Asian and Pacific Islander patients [7]. In both reports, the median age at diagnosis was similar (58 years and 56 years, respectively).

ALK-negative anaplastic large cell lymphoma (ALK(-) ALCL) is a rare CD30-positive T-cell lymphoma that presents a major diagnostic challenge. It affects individuals in a wide range of age and a variety of nodal and extranodal sites. ALCL can mimic clinically, morphologically and immunohistochemically many other hematologic and non-hematologic malignancies . Lack of expression of pan-T cell markers and a spectrum of histological features can be misleading [8]. ALK-negative ALCL is a more aggressive and less reactive disease, with studies suggesting 5-year overall survival rates of 49% versus 70% for ALK-positive ALCL [9].

NHLs occurring in the context of HIV disease are mainly of B lymphocyte origin. Nevertheless, T-cell NHL in the context of HIV disease has already been previously described. In a cohort of 429 AIDS-related lymphomas, 11 cases 2.6% of T origin were reported [10]. In another cohort of 6,788 NHL in the context of HIV, 1.4% had T-cell lymphomas [11]. T-ALCL is a rare event in HIV infection and usually present aith an advanced disease (stage III or IV). In addition extranodal involvement is common in this cohort of patients, like the case we present [12, 13].

The apparent poor prognosis of ALK-negatives is explained by more aggressive characteristics and a more advanced international prognostic index [14]. The prognosis for HIV-positive ALCL is usually very poor. Thus, with the limited available data, most of what we know about ALCL in the HIV-positive patient population is based on a comprehensive review of 37 patients with HIV-associated ALCL. This case study demonstrated that ALCL was predominantly ALK negative, with an average patient age of 38 years and an average CD4+ count of 83 cells/mm3. Out of these cases, 78% of patients presented with advanced disease (stage 3/4), with extranodal involvement including the lungs, liver, bone marrow, spleen and myocardium. Median overall survival was only 5 months. The administration of chemotherapy and the early stages of presentation were identified as good prognostic factors, while the use of HAART showed a statistical improvement of survival in HIV-associated ALCL patients [12, 15]. In the review by Castillo et al., the majority of these patients received a CHOP-like chemotherapy. The most common causes of death were lymphoma progression 37% and opportunistic infections 31% [12]. Oral involvement of ALCL is rare and, to our knowledge, only 34 cases of ALCL have been published in the English literature to date [16-17].

Regarding treatment, chemotherapy options are usually based on CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like therapies. Only 30% to 50% of cases achieve stable complete remission with the use of standard treatment regimens, and a 30% to 40% 5-year survival rate is noted in systemic ALK-negative cases [18]. Intensive chemotherapy with autologous stem cell transplantation could be an interesting approach, since a recent survey published by the EBMT has demonstrated identical results for HIV-positive patients and HIV-negative patients [19]. Other promising research is focusing on anti-CD30 monoclonal antibodies, with a preliminary positive test response in previously treated ALK-negative patients [20]. Undoubtedly, the emergence of new targeted therapies will increase our ability to treat and manage ALCL in the future.

## Conclusions:-

ALCL in HIV patients is a rare event, the oral manifestation is an even rarer entity. The microscopic features may mimic other malignancies and therefore it is always necessary to correlate the morphological and immunohistochemical analyses with local and systemic symptomes to establish the diagnosis of ALCL in every case of an oral mass.The prognosis is often very poor with standard treatments. Thus, alternative approaches should probably be used.

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