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# Midline Destructive Syndrome in a Patient with HIV, Case Report, Review and Approach Proposal

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## Abstract

**Midline destructive syndrome (MDS) is a clinical of diverse etiology that may appear in immunocompromised and immunocompetent subjects. The purpose of the present work is to describe the case of a 68-year-old man with human immunodeficiency virus infection and CD4 lymphocytes with 666 cells, type 2 diabetes mellitus and well metabolic control. He began 3 months earlier pain and increased volume in the palate and left maxillary region and non-painful bilateral submandibular adenopathies, fever, unexplained weight loss and night sweats. A CT scan showed a tumor lesion at the level of the lower jaw with extension towards the nasopharynx. Serology for Epstein Barr was negative. Histopathological finding study with immunohistochemistry demonstrated diffuse large B-cell lymphoma with colonization by hyphae. This case highlights the need for a comprehensive and systematic approach to this pathology, for which we propose a stepwise approach.**

**Keywords:** ***Lymphoma; Midline destructive syndrome; Acquired immunodeficiency syndrome; Human immunodeficiency virus***

## 1. Introduction

Midline Destructive Syndrome (MDS) was first-described in 1897 [1]. It was not until 1922 when Stewart reported 10 cases of a chronic destructive process in the facial midline. Since then, there have been multiple ways to call the syndrome, including idiopathic midline granuloma, lethal midline granuloma, polymorphic reticulosis, and Stewart's syndrome, among others. This reflects the variability behavior and the lack of homogeneous nomenclature [2].

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The approximate MDS prevalence is estimated at 6 out of every 10,000 habitants, with variations from one country to another. It can develop at any age, although , it predominates between the fifth and sixth decades of life [3].There are tumor, immune, traumatic, infectious and idiopathic causes. The most common disease causes are granulomatosis with polyangiitis and Extranodal NK/T cell lymphoma. In patients with Acquired immunodeficiency syndrome (AIDS), the syndrome's prevalence and the diseases more common than the provoke are unknown. The clinical features are common to all the diseases that cause it and it is distinguished by an ulcerated lesion in the nose or nasal passages and invasion of neighboring structures, including the upper part of the upper respiratory tract, the ethmoid, the vomer, the infra and supra-palatine regions and the maxillary sinuses, and may also have distant manifestations [4].

Medical history is the cornerstone in the initial approach. Locally, patients may present with intermittent nasal discharge, epistaxis, nasal congestion, facial pain, and soft tissue edema. They can also present systemic clinical manifestations, such as hemoptysis, paresthesia, hearing loss, and edema, which suggest to autoimmune etiology, or fever and B symptoms that lead to infectious or neoplastic diseases. The traumatic history leads to suspicion of giant cell granuloma of the midline or cholesterol granuloma. Nonetheless, it is important to consider that different etiologies may coexist at the time of clinical presentation, which makes diagnosis difficult. Sarcoidosis is most common in female patients between the fourth and fifth decades of life. Eosinophilic granuloma, which is a form of Langerhans histiocytosis, usually appears in men younger than 10 years of age. T-cell / Natural Killer lymphoma is more common in East Asia, especially in the Chinese population. In many occasions it has been associated with the presence of Epstein Barr virus (EBV) [5-7].

The diagnostic approach must include a thorough physical examination since in each of the diseases there will be characteristic clinical data. Common to all of them is the possibility of finding a nasal septum ulcer, epistaxis, maxillary fistulas, involvement of adjacent soft tissues, and even if there is alteration of structural stability, saddle deformity can be found in the nose. The necessary laboratory studies should be guided by the suspected diagnosis and by the cost-benefit. Initial laboratory tests include a blood count to assess the white blood cell count or the presence of anemia or eosinophilia, acute phase reactants such as C-reactive protein, and erythrocyte sedimentation rate. Systemic vasculitis must be ruled out, therefore assessing renal function is of vital importance, as well as anti-neutrophil cytoplasmic antibodies (c-ANCA and p-ANCA) [8].

Another essential study is culture and biopsy of the lesions. Culture should include aerobic, anaerobic, and mycobacterial microorganisms. Biopsy should be performed from different regions, including those appear free of disease, immunohistochemical and flow cytometry studies must be performed, since it can help to distinguish specific cell and identify other intracellular and cell surface antigens. In up to 5%-15% the underlying etiology is not found [9]. The biopsy can also help rule out other immunological causes since each of them has a characteristic pattern as well as other less common causes such as IgG4-associated disease [10].

In patients with HIV there are a few reports of MDS causes, since unlike other clinical situations of immunocompromise, the viral status may not be a determining factor in the diagnostic algorithm. The following is a presentation of a case which etiology was lymphoma and subsequently a proposal for a study approach is set forth according to the immunological status of patients with HIV.

## 2. Case Report

We present the case of 68-year-old man with an AIDS, whom had undetectable viral load and a CD4 lymphocyte count of 666 cells. Long standing type 2 diabetes mellitus with adequate metabolic control. He began 3 months before being referred with palate pain and left maxillary region enlargement (IMAGE 1, panel A and B). He also had non painful hardened bilateral submandibular lymphadenopathy, fever, diaphoresis and weight loss.

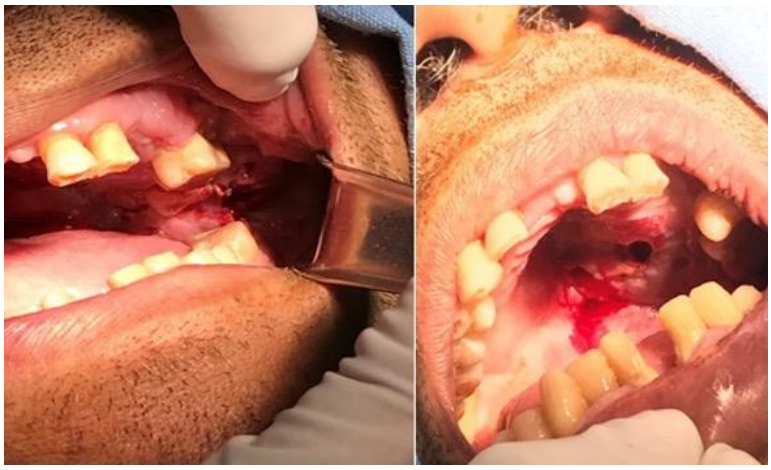

IMAGE 1. **Panel A and B: Location of the lesion on the palate after biopsy.**

A head and neck CT scan (IMAGE 2, panel A and B) showed a tumor lesion in the lower jaw which extended to the nasopharynx, bilateral submandibular and cervical adenopathies. Initial laboratory tests were normal. EBV serology was negative. Histopathological analysis of the palate biopsies showed, under light microscopy, subepithelial proliferation of large cells with marked nuclear atypia, evident nucleolus and scant cytoplasm, arranged in a diffuse pattern (IMAGE 3, panel A and B); where abundant hyphae and fungal spores positive for histochemical periodic acid Schiff staining were identified. Immunohistochemistry showed positivity for CD45 and CD20, and negativity for CD3, smooth muscle actin (SMA) and CKAE1 / AE3; reporting as diffuse large cell lymphoma immunophenotype B (IMAGE 4).

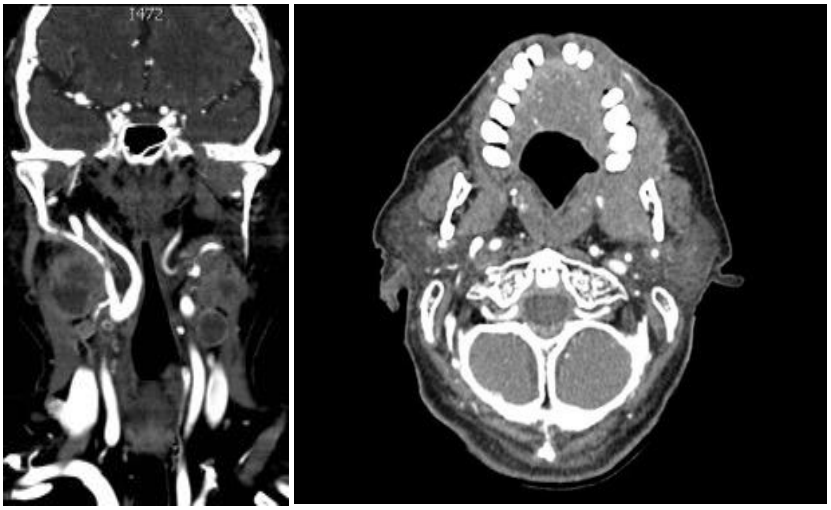

IMAGE 2. **Panel A and B Simple tomography. Injury in the left maxilla which conditions bone destruction. As well as multiple cervical and submandibular lymphadenopathies with heterogeneous density.**

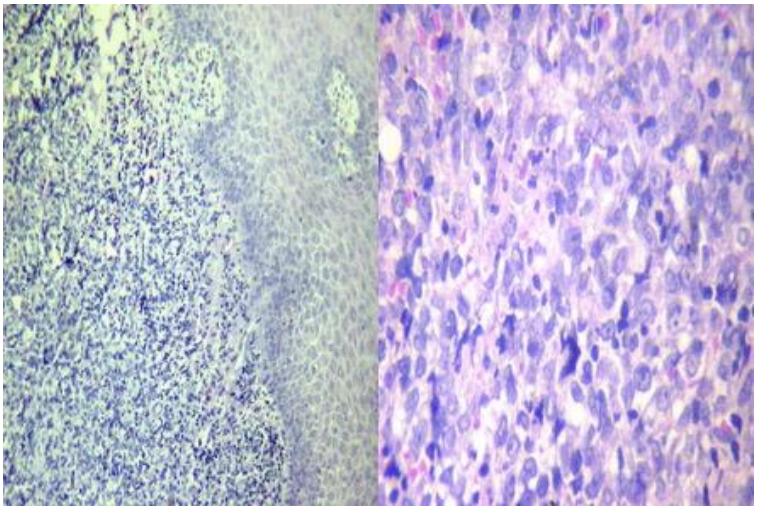

IMAGE 3. **Panel A and B. Subepithelial proliferation of large cells with marked nuclear atypia, evident nucleolus and scant cytoplasm, arranged in a diffuse pattern.**

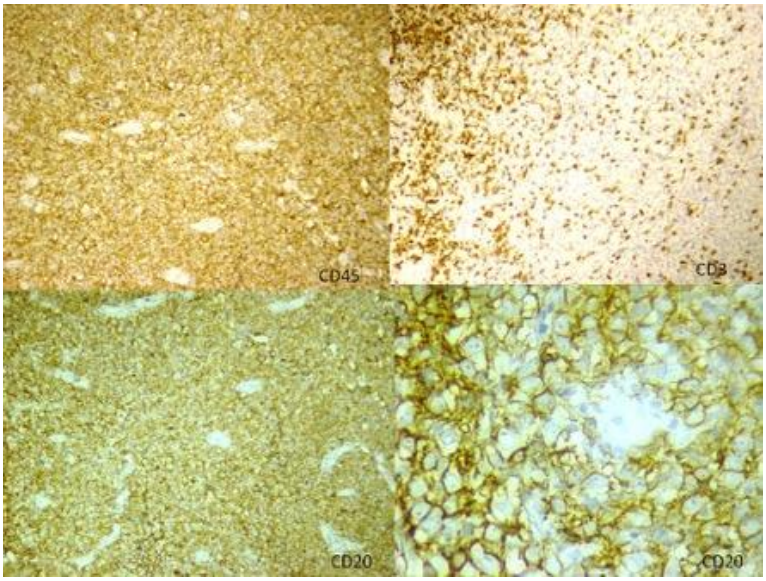


IMAGE 4. **Positive immunohistochemical markers in neoplastic cells (CD45, CD20) and reactive lymphocytes (CD3).**

## 3. Treatments, Evolution and Monitoring

He refused to receive chemotherapy treatment and died three months after establishing the diagnosis.

### 3.1 Differential diagnostics

#### 3.1.1 Patients with Human Immunodeficiency Virus (HIV) Infection

Histopathologic classification of midline destructive lesions has undergone substantial revision over the last two decades. Historically, destructive midfacial lesions, other than those caused by trauma, toxic agents, or infectious or neoplastic processes,

were categorized under multiple pathologic labels that did not reflect specific clinicopathologic entities and provided little guidance in disease management [11].

In the case of patients diagnosed with HIV infection, it is necessary to initially assess the patient's immune status in order to guide diagnosis. Patients with HIV infection develop a wide variety of neoplasms, frequently associated with their CD4 count. Most HIV-associated neoplasms are caused by oncoviruses such as Herpes Virus 8 (HV8), EBV, high-risk human papillomavirus (HPV), hepatitis B virus (HBV), Hepatitis C virus (HCV) and Merkel cell polyomavirus. With a CD4 lymphocyte count <200 cells / mL, opportunistic infections or a tumor of a more aggressive lineage such as Burkitt's lymphoma should be suspected initially. The etiology of B-cell non-Hodgkin lymphomas, that lead to destructive midline syndrome in patients with HIV, has been the subject of debate due to the lack of clarity regarding its origin and the role that HIV plays [12].

In FIG. 1, we propose a diagnostic approach to patients with HIV, taking into account the immune status of the patient. We don't consider the levels of viral load, since up to now what has shown a role in the genesis of tumors or the presence of certain infections is the immune status. Anyhow the role of the interaction between HIV, EBV and the patient's immune dysregulation must be considered, which play a fundamental role [13,14]. It is believed that in HIV patients there is a deficiency of immune surveillance, the pathogenesis of some B cell lymphoma in AIDS may involve initial polyclonal expansion of the B cell population due to reactivation of EBV with subsequent emergence of a transformed monoclonal population characterized by chromosomal rearrangement and disordered regulation of c-Myc oncogene [15-18]. The viral load cut-off point where there is an association in the genesis of different tumors is not known with certainty. Another disease which could resemble a lymphoma or disease related to infiltration by IgG 4 is diffuse infiltrative lymphocytosis syndrome or diffuse infiltrative lymphocytosis syndrome (DILS), which has only been described in patients with HIV. This present signs similar to IgG4-associated disease and Sjögren's syndrome, with parotid enlargement, sicca symptoms, and lung disease, for which it should be considered as a differential diagnosis [19].

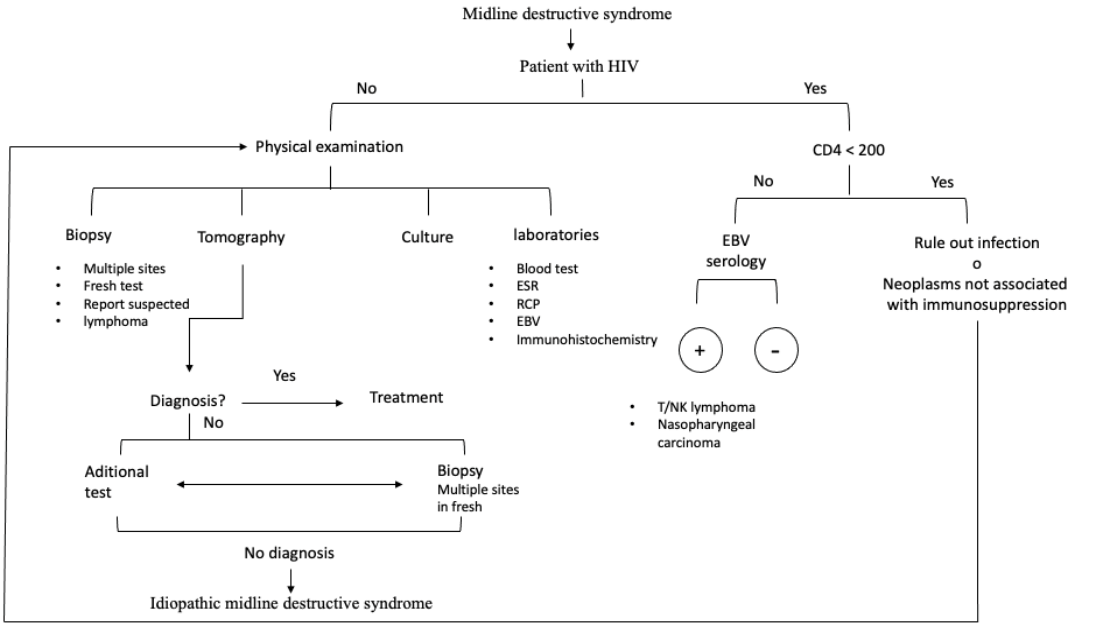


FIG. 1. **Proposal for the diagnostic approach to destructive line syndrome in a patient with HIV.**

Another type of tumor that can be influenced by the presence of EBV is nasopharyngeal carcinoma, which on some occasions could manifest as a destructive syndrome of the midline, so it should be considered. If after the macroscopic analysis of the biopsy there is a diagnostic doubt, it is necessary to consider carrying out immunohistochemistry, which will guide us more specifically towards the type of neoplasm we are facing [20].

## 4. Discussion

### 4.1 Lymphoma, HIV and midline destructive syndrome

MDS is a rare entity, and rare described in patients with HIV infection. The diagnosis is predominantly one of exclusion and knowing the immunological status of the patient with the TCD4 lymphocyte count can help to establish a likely etiology to initiate timely treatment. particularly in patients with HIV infection, in whom the diagnostic approach is essential for proper management. The use of an algorithm can facilitate early diagnosis.

Therefore, HIV alone may be capable of inducing a T-cell neoplasm, however, the genesis of the tumor could also be influenced by the type of HLA of the infected patient and the degree of immunosuppression of the patient, as previously commented. If the etiology is infectious, treatment with antimicrobial or antifungal agents is required, however, when a tumor is identified, treatment is established according to the histology and the extent of the lesion [21].

There are few reports of cases of MDS, which have been described frequently with inflammatory causes such as Granulomatosis with polyangiitis in immunocompetent patients, and relation with causes like infectious such as mucormycosis, and other generally fungal etiologies, as well as viral infections such as EBV in immunosuppressed patients. The latter has found an association with the development of diffuse B-cell lymphoma, and T / NK cell lymphoma. In patients with HIV, neoplastic causes such as lymphoma with compromised immune status with viral load and CD4 count have been previously described, unlike our case, which although the cause was diffuse B-cell lymphoma CD4 count was normal. In the context of the patient with normal CD4 lymphocytes, there is a greater possibility of a less aggressive tumor or disease of immunological origin not related to the patient's underlying disease. The role of EBV is controversial since not all malignant lesions with B cell tumors have found genetic material that could establish a relationship between HIV and EBV.

Nevertheless, it is necessary to take into account that these patients have chronic antigenic stimulation, inflammation and dysregulation of cytokines (even with HIV control and preserved CD4 + counts), which makes them susceptible to the development of lymphoma and other neoplasms. Also, people at risk of HIV infection have higher rates of oncovirus infection [22,23].

## 5. Key Points Learning Messages

- SDLM is an entity common to several pathologies in immunocompetent and immunocompromised subjects.
- Due to the diversity of the pathology in patients with HIV-AIDS, the initial clinical approach should consider the CD4 + lymphocyte count.
- In patients with <200 CD4 + lymphocytes, opportunistic infections should be ruled out first.
- In patients with> 200 CD4 + lymphocytes, EBV should be investigated first and lymphoma or carcinoma should be ruled out.

- The complete study should include imaging studies, cultures and, where appropriate, biopsy.

## 6. Intellectual Property and Conflicts of Interest

The authors state that we have actively participated in the process of research, information gathering, writing and review of the manuscript. The members of the internal medicine service participate in the diagnostic approach, treatment and in-hospital follow-up from admission to discharge of the patient. We state that we obtained written approval from the patient and family members to write and publish the information regarding the clinical case. We omit names and other information that could lead to the identification of the patient or relatives. The local ethics committee verified the content of the manuscript and approved its publication. The final review of the article was performed by the attending physician Guillermo Flores. The authors declare no conflicts of interest. We assign the copyright to Clinical Case Reports: Open Access.

## 7. Abbreviations

MDS: Midline Destructive Syndrome; HIV: Human immunodeficiency virus; EBV: Epstein Barr virus; SMA: Smooth muscle actin; HV8: Herpes Virus 8; HPV: Human papillomavirus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; DILS: Diffuse infiltrative lymphocytosis syndrome

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