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CLINICAL CASE

Clinical spectrum of a syndromic diagnosis: Lethal midline granuloma

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Abstract

A 73-year-old man presented to the emergency department for 2 months of erythema, warmth, and blushing on the tip of the nose, with progression to ulcerative and granulomatous tissue and posterior necrotizing compromise of the nasal septum, despite antibiotic schemes. A diagnosis of lethal midline granuloma was made, a disease with a wide spectrum of etiological diagnostic possibilities and usually a poor prognosis. A biopsy sample confirms a NK/T-cell lymphoma. The patient did not accept the proposed chemotherapeutic treatment. He requested voluntary discharge and later died.

Keywords: *Extranodal NK-T-cell lymphoma. Lethal midline granuloma. Colombia.*

Espectro clínico de un diagnóstico sindrómico: granuloma letal de línea media

Resumen

Un hombre de 73 años ingresó al servicio de urgencias por dos meses de eritema, calor y enrojecimiento de la punta nasal, con posterior progresión y compromiso granulomatoso y necrotizante del tabique nasal. Se realizó diagnóstico de granuloma letal de la línea media, un síndrome clínico con un amplio abanico de opciones diagnósticas y generalmente un pobre pronóstico. La biosia confirmó un linfoma de células T natural killer (NK-T). El paciente no acepta tratamiento quimioterápico y posteriormente fallece.

Palabras clave: *Linfoma extranodal de célula NK-T. Granuloma letal de línea media. Colombia.*

Introduction

Lethal midline granuloma, also called lethal midline injury, is an infrequent entity first described by McBride in 1897, previously known as Stewart's granuloma or polymorphic reticulosis acording to Prasad and Gonzales[1,2], which is characterized by the presence of an ulcerous necrotizing injury with a strong inflammatory, angiocentric, and angiodestructive component that is very aggressive and highly lethal, which also compromises the tissues of the upper respiratory tract, the oral cavity, and the midline of the face[3]. With the advancements made in immunohistochemistry, it was possible to categorize most of the cases previously designated to the NK/T-cell extranodal lymphoma, a term that was introduced by the European lymphoma classification in

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2001 and was accepted by the World Health Organization in 2008. The term "lethal midline granuloma" has been used as a synonym, thus failing to acknowledge the large number of pathologies that can show this kind of behavior[4].

Etiological prevalence is variable according to each patient's risk factors, together with the additional specific symptomatology of the subjacent disease[5]. The age of manifestation oscillates between the fourth and fifth decade of a lifetime, with rapidly growing mucous injuries. The differential diagnosis is wide; other tumorous entities must be discarded, such as nasopharyngeal carcinoma, melanomas, other types of lymphoma, and viral, bacterial, parasitic, and mycotic infections. When faced with the presence of this kind of injury in the nasal mucus with a subacute or chronic course, as well as the presence of systemic symptoms, autoimmunity or chronic exposure to inhaled toxic compounds such as cocaine must be considered. Appropriate anamnesis, a physical examination, and a histopathological study are essential for a definitive diagnosis (Table 1)[6,7].

The clinical evolution of the patient with empirical treatments is an important marker when it comes to defining opportune scheme changes. We hereby present the case of a man with a nasal inflammatory injury who showed no response to the antimicrobial treatment, with a histopathological study that documented and NK/T-cell lymphoma.

Table 1. Differential diagnosis of the lethal midline granuloma

Neoplasms	Hodgkin and non-Hodgkin's lymphoma	
	Nasopharyngeal carcinoma	
	Melanoma	
	Sarcoma	
Infections	Viral	Epstein–Barr
	Bacterial	Tularemia
		Tuberculosis
		Lepra
		Mycobacteria
		Syphilis
		Klebsiella pneumoniae and *Klebsiella rhinoscleromatis*
	Fungal	Actinomycosis
		Mucormycosis
		Candidiasis
		Histoplasmosis
		Blastomycosis
		Coccidioidomycosis
		Rhinosporidiosis
		Aspergillosis
	Parasitic	Leishmaniasis
		Myiasis
Inflammatory	Granulomatosis with polyangiitis	
	Eosinophilic granulomatosis with polyangiitis	
	Sarcoidosis	
Idiopathic	Idiopathic midline destructive disease	
Traumatic	Cholesterol granuloma	

Clinical case

A 73-year-old man resides in an urban area in the Department of Huila, Colombia, with only a bilateral glaucoma as background, which led to amaurosis and mild functional dependence. At the time of admittance, he informs of a 2-month evolution of erythema, warmth, and blushing on the tip of the nose, which was considered to have an infectious origin. In light of the above, he received two different antibiotic schemes, with no sign of recovery. The injury progressed, becoming ulcerative and granulomatous in the left nasal vestibule, with a rapid evolution and subsequent, necrotizing compromise of the nasal septum, which is associated with purulent secretion (Fig. 1).

During the physical exploration, with normal vital signs, as well as during the physical examination, except for scabby hemorrhagic injuries in the vestibule and the edge of the nasal cavities, with a compromised columella, wide anterior septal perforation, easily bleeding granulation tissue, and non-fetid mucopurulent secretion, no lymphadenopathies or local or cervical masses were identified.

Given the lack of response to antimicrobial treatment, as well as the rapid evolution, a lethal midline granuloma was considered. The imaging studies confirmed the extensive local compromise (Fig. 2), with laboratory tests that discarded immunosuppression and autoimmunity. The pathological study confirmed an NK/T-cell lymphoma and an immunohistochemistry with positive markers for CD2, CD3, CD7, and CD56, and negative markers for CD 79 A, as well as

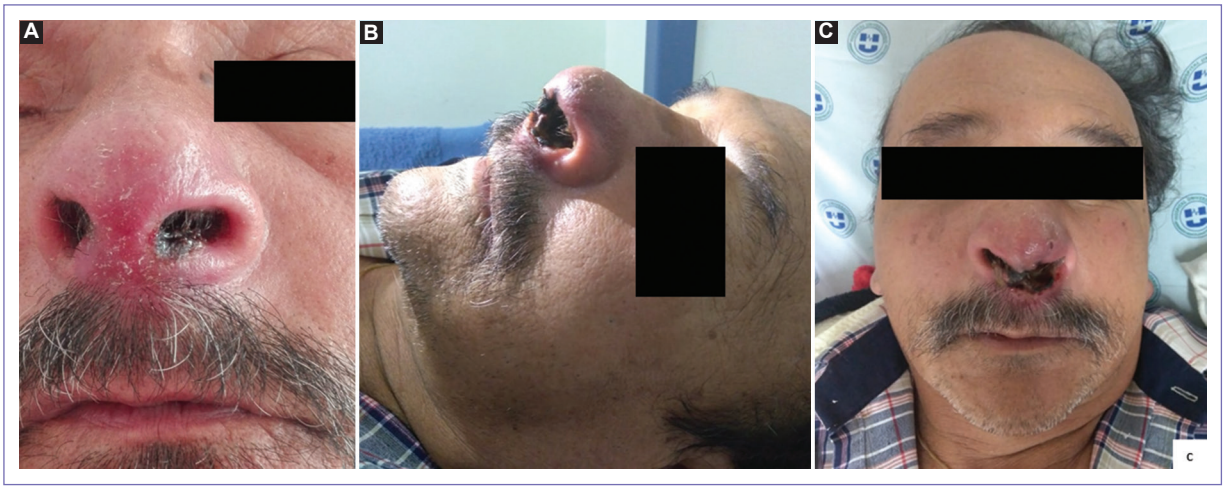

Figure 1. Clinical evolution. **(A)** Day 0, erythema in the nasal tip and columella; **(B, C)** day 60, perforation and necrosis of the nasal septum.

the presence of the Epstein–Barr virus (EBV) by hybridization.

A polychemotherapy treatment was proposed to the patient, who did not accept and was released with a loss of follow-up.

Discussion

The extranodal NK/T-cell lymphoma (ENKTL) is an aggressive, predominantly extranodal neoplasm of NK cell or T-cell lineage. It is characterized by an angiocentric and angiodestructive growth, in addition to the coagulation necrosis process, and it is significantly associated with the EBV[8].

ENKTL lymphomas represent between 5% and 10% of all non-Hodgkin's lymphomas, with a high prevalence found in Asia and Latin America (Mexico 40% and Peru 13%), in contrast with 4% and 6% in the United States and Europe[9]. The manifestation age median is around 50 years old, predominantly in the male gender, with a man-woman ratio of 2:1[10].

Most ENKTL (60-90%) are originated in the upper aerodigestive tract, although it has been described in extranasal regions (nasal and extranasal lymphomas share the same histopathological characteristics), including the skin, lungs, muscles, the gastrointestinal tract, bone marrow, and testicles[8,9].

The risk factors associated with the manifestation of this lymphoma have a genetic background related to the development of tumor cells of the NK/T lineage, where a positive association is found with HLA-A26, as well as a negative one with HLA-B52. There is also a weak association with the consumption of salted fish, exposure to chemical pesticides and solvents, and, in a lower proportion, immunosuppression. ENKTL is universally associated with infections by EBV with significant physiopathological implications, thus suggesting the demonstration of the pathogen for diagnosis[11].

The EBV infects B and epithelial cells, and it can also infect some T/NK cells. In some individuals who are genetically predisposed in association with the aforementioned risk factors, along with an unclear pathophysiological process, infected T/NK cells evade the host's immunity and survive. It is believed that the EBV can infect from B and T/NK cells, which are activated and express integrins that may act as receptors or acquire CD21 molecules through synaptic transfer. These ectopic receptors allow for the bonding of the virus with these cells, which are why they do not express the main antigens against cytotoxic T lymphocytes and can evade host community thanks to the intervention of viral oncogenes, mutations in the host's genes, or epigenetic modifications. A second model has been proposed, was aging and long-term exposure to environmental factors could induce genetic mutations in T/NK cells[11]. In these patients, cytogenetic anomalies are also observed, such as the deletion of the 6q chromosome, where suppressor genes such as PRMD1, FOXO3, HACE1, and PTPRK, which may also contribute to the genesis of these tumors[12].

In clinical terms, the local symptomatology is extensive. There is nasal affectation with a facial or orbital edema, diplopia, nasal obstruction, and rapid septal

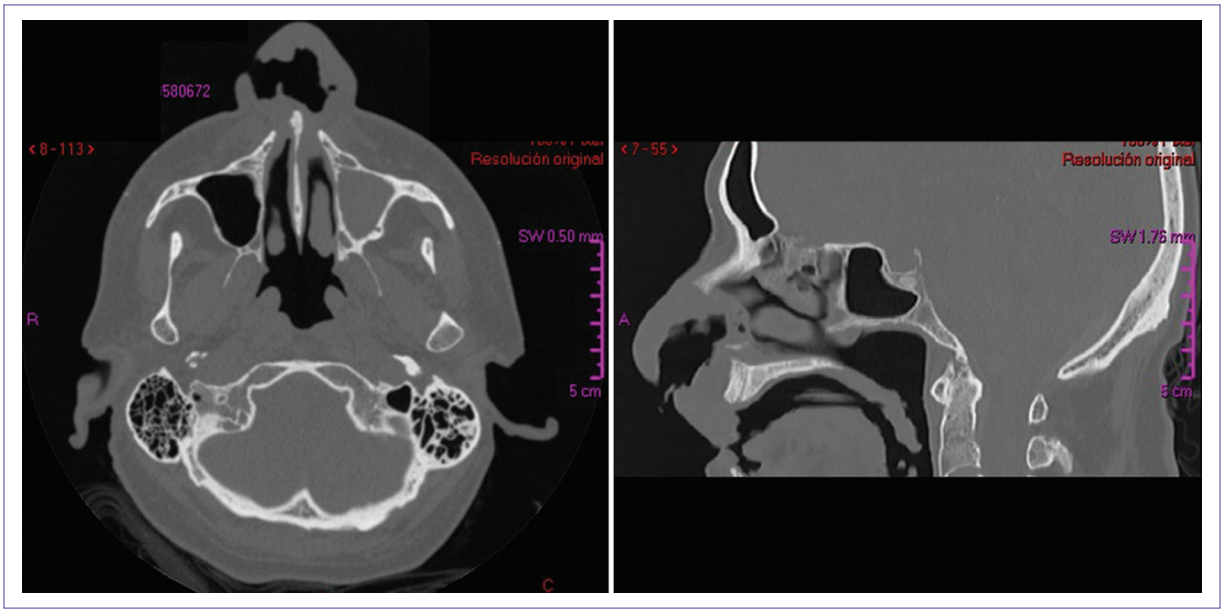

Figure 2. Computerized axial tomography of the face, where wide septal perforation is evidenced, as well as edema on the soft tissues of the nasal tip and periseptal area IV, mucoperiosteal thickening of the left maxillary sinus with calcification areas, and a sclerotic reaction of the lateral wall of the left maxillary sinus.

perforation or palatal ulceration associated with purulent nasal secretion (especially when there is bacterial superinfection). Patients may also show other manifestations such as subtle macular injuries or patches resembling mycosis fungoides, B symptoms, hemophagocytosis, and damage to multiple organs in advanced stages. Clinical characteristics are not specific and overlap considerably with infections, inflammatory and autoimmune disorders, and even with other neoplasms, thus making their diagnosis difficult. This is why histopathological studies are essential. Biopsies often show extensive necrosis with a lack of viable cells, whose morphology is poorly preserved. Therefore, the need for consecutive biopsies is not infrequent to achieve a definitive etiologic diagnosis[8,13,14]. Performing PET/CT scans for extranasal NK/T-cell lymphomas are important, given that many cases have hidden primary injuries, which modify the prognosis[12].

Demonstrating NK/T-cell markers and the presence of the EBV are paramount for the diagnosis. These tumors express CD2, superficial CD3 (–), cytoplasmic CD3ε (+), CD56 (+), and cytotoxic molecules (perforin, granzyme B, and TIA1)[12,15]. The plasmid DNA of the EBV at the time of diagnosis provides a measurement of the lymphoma's burden, in addition to allowing for a real-time evaluation of the treatment and its aftermath. Detectable EBV DNA reflects a residual disease[13].

Therapy and prognosis depend on the stage at the time of diagnosis. For early stages (I/II), the current standard is a combination of chemotherapy based on dexamethasone-etoposide-ifosfamide-carboplatin or etoposide-ifosfamide-dexamethasone-L-asparaginase and radiotherapy. Other chemotherapy regimens such as L-asparaginase-vincristine-prednisolone or gemcitabine-L-asparaginase-oxaliplatin have been used for this pathology with high remission rates. For Stage III/IV nasal lymphomas and non-nasal lymphomas, chemotherapy treatment is based on L-asparaginase in association with other chemotherapeutic agents. For disseminated disease cases, the SMILE protocol (dexamethasone, methotrexate, ifosfamide, and L-asparaginase) achieves the best results, although it has been associated with severe neutropenia with frequent serious infections. Autologous and allogenic blood-forming stem cell transplant has been explored as a therapeutical option in advanced or recurring chemosensitive NK/T lymphomas[12,15,16]. Other treatment strategies, especially for recurring or refractory cases, include the use of pembrolizumab and nivolumab[17,18].

Prognosis is variable but generally poor, especially in extranasal cases, where 5-year survival is around 40% compared to early stages, in which it may reach 70%. However, relapses after 10 years are frequent. Adverse risk factors include being older than 60 years

of age, a high level of circulating EBV DNA, an advanced stage at the time of diagnosis, and unfavorable international prognostic index, dissemination toward lymphatic ganglia, bone and skin invasion, the presence of EBV-positive cells in the bone marrow, and high levels of lactate dehydrogenase[14,16,19].

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of the data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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