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Nasal Type T/NK-cell Lymphoma: a rare case presenting as a palatal ulcer

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Title: Nasal Type T/NK-cell Lymphoma: a rare case presenting as a palatal ulcer

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Abstract

Nasal-Type T/NK-cell Lymphoma are very rare clinical entities, highly aggressive and with a dramatic prognosis. The case of a 37 year-old immunocompetent man with the main complaint of a deep palatal ulceration is presented. The patient had a three month medical history of his symptoms being underestimated and misdiagnosed by physicians. The diagnosis of extranodal T/NK-cell lymphoma nasal type was achieved in fifteen days but the patient clinical status worsened severely. Head and neck specialists must consider these clinical entities from the early symptoms. Because of their highly aggressive behavior, earlier therapies should be started before completing the diagnostic pathway.

Keywords: Nasal Type T/NK-cell Lymphoma; T/NK cell NHL; Lymphoma; Peripheral T-cell and NK-cell lymphomas; oral ulceration

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Introduction

Lymphoma, or lymphatic cancer, is a broad term encompassing a variety of cancers of the lymphatic system. Lymphomas in humans are generally classified in two main groups: the Hodgkin lymphomas (HL), also known as Hodgkin disease, and the non-Hodgkin lymphomas (NHL). Non-Hodgkin lymphomas are divided into B- and T-cell neoplasms and NK-cell lymphomas (1,2).

Natural killer (NK) cells are a third lymphocyte lineage, in addition to B- and T-cells, that mediate cytotoxicity without prior sensitization. NK cells also have phenotypic and genotypic characteristics; they express the NK-related antigen CD56 and T-cell markers such as CD2 and CD3 epsilon, but their T-cell receptor (TCR) locus is not rearranged (1).

Included in the NHL group are the Peripheral T-cell and NK-cell lymphomas (PTNKCLs), a wide family of lymphomas with different clinicopathologic features, which represent only 10%-20% of all NHLs in the Western world (2).

PTNKCLs are defined as angiocentric lymphomas in the revised European American Lymphoma (R.E.A.L.) classification and include the “nasal” and the "nasal type" varieties, which are very rare clinical entities in the United States and Europe, but more common in Asia and Central America (3). Nasal T/natural killer (NK) cell lymphoma is a distinct clinicopathologic entity highly associated with Epstein-Barr virus (EBV) and with a very poor response to treatment and prognosis (5-year overall survival rate of 25%) (3-6).

Generally a variety of cells ranging from small or medium-sized cells to large transformed cells can characterize the broad cytologic spectrum of this entity. Tissue damage is a common morphological feature of this form and is due to both the cytotoxicity of the T/NK lymphoma cells as well as to angiocentricity (4,5,7).

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The characteristic immunophenotype of Nasal T/NK cell lymphoma is distinguished by a CD2 and CD56 positivity, but usually a negativity for surface CD3.

The presence of EBV in early diagnosis can be effectively evaluated by in situ hybridization.

The differential diagnosis includes lymphomatoid granulomatosis, blastic or monomorphic NK cell lymphoma/leukemia, CD56-positive peripheral T-cell lymphoma, and enteropathy-associated T-cell lymphoma (4).

Extranodal sites like the skin, the subcutis and the gastrointestinal tract can be affected by tumors with an identical phenotype and genotype. These extranodal forms should be referred to as nasal-type T/NK cell lymphomas (4).

Here, we present a rare case of a 37-year-old Caucasian man affected by nasal-type T/NK-cell lymphoma, referred to our institution with a 3 month delay between the development of the first symptoms and our first medical examination.

The purpose of this study is to update data on the clinical and histopathological findings of this rare disease, pointing out how misdiagnoses are responsible for therapeutic delays and consequently of a worse prognosis for these aggressive forms.

Case report

A 37 year-old Caucasian man was referred to our Oral Medicine Unit, Department of Head and Neck Diseases, Federico II University of Naples, with the main complaint of a wide symptomatic ulcerative lesion of the hard palate.

His familial anamnesis encompasses 3 uncles who had died of different forms of cancer in recent years (2 of lung cancer, and 1 of bowel cancer). The patient's medical history was negative and he was in apparent good health except for a weak hypercholesterolemia.

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His first referred symptoms were a moderate submandibular lymphadenopathy and weak fever starting 2 months before, for which reason he consulted the family doctor who requested hematological tests with the main suspicion of an EBV/CMV infection. The results of all the tests performed were negative and for one month the patient received a symptomatic therapy. Four weeks later the patient started to complain of a sense of nasal obstruction, with a breathing difficulty for which he consulted an otorhinolaryngologist who performed an endoscopic examination of the nasal cavities finding suppurative exudate and inflammation of the nasal floor and lateral/medial walls. It was diagnosed as severe maxillary sinusitis and therapy with corticosteroids through an aerosol and antibiotics was prescribed. After one month, without any improvement of the symptoms, the patient started to complain of the first oral symptom, a pain due to a swelling and ulcerated area in the median area of the hard palate. For this reason he consulted his dentist who advised him to undergo an oral medicine consultation at our hospital. Our first examination was performed soon after and the patient was presented with the clinical condition shown in Figure 1.

The patient, after providing his written informed consent, was hospitalized and examined by routine hematological tests which revealed a glucose level of 120 mg/dL (normal range, 60 to 110), a total cholesterol level of 200 mg/dL (normal value up to 190), a Triglyceride level of 218 mg/dL (normal value up to 180) and an iron level of 49 µg/dL (normal range, 55 to 160).

The physical examination showed a widespread ulcerative and proliferative lesion involving the hard palate, and marginally the soft palate and the left maxillary alveolar process (Figure 1). The lesion measured about 4 cm at its maximum diameter and showed a central zone of deep and extensive necrosis, with a surrounding area of hyperplastic tissue weakly brown coloured. Two incisional biopsies of the lesion were

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performed.

After 2 weeks, while the patient underwent a diagnostic pathway, the lesion presented with a considerably worse clinical evolution as shown in Figure 2.

At histology, scanning magnification revealed a dense and diffuse proliferation of pleomorphic small and medium sized lymphocytes within the entire chorion, with overlying extensive squamous epithelium ulceration. An angiocentric pattern of infiltration was evident. The predominant cell type was lymphocyte with round nuclei, one or more nucleoli and a scant cytoplasm. Numerous mitotic figures were seen and areas of necrosis were also present (figure 3A, 3B, 3C).

The neoplastic cells expressed CD2 and CD3; a weak expression of CD56 and granzyme B was observed (figure 3D). CD8 and CD30 were consistently negative. The tumor had a proliferative fraction (Ki-67/MIB1) approaching approximately 70-75%. The analysis of the presence of EBV was performed with the FISH (fluorescent in situ hybridization) technique (Dako PNA ISH EBERER PNA Probe) and revealed a widespread positivity for EBV.

A diagnosis of extranodal NK/T-cell lymphoma, nasal type was made.

The patient was immediately referred to the Hematoncology Department to complete the staging and start treatment of the disease. A head/neck and chest computed tomography (CT) scan and a total body positron emission tomography (PET) scan were negative except for the oral and left nasal cavity involvement. Chemotherapy was therefore started.

At present the patient has developed a palatal perforation with an oronasal fistula (figure 4).

The study has been approved by the Ethics Committee of the University “Federico II” of Naples. Appropriate written informed consent has been obtained from the patient

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included in the study.

Discussion

PTNKCLs are rare and heterogeneous forms of NHL that are usually characterized by a very poor clinical outcome. Furthermore, many subtypes are currently present in the World Health Organization (WHO) classification of PTCL (8).

As confirmed by our experience, the diagnosis of these forms is difficult for the general practitioner as well as for medical specialists, a difficulty compounded by the frequent underestimation/misdiagnosis of the first symptoms. Each failure in a diagnostic step is usually followed by a delay of several weeks for the patient to achieve the correct diagnosis and to undergo the specific therapy.

Because of the overall relative rarity of this condition, achieving the correct diagnosis can be a challenge also for many pathologists. In a recent study conducted before the most recent WHO classification the overall diagnostic accuracy among experts was found to be approximately 81% with a value ranging from 67% to 95% depending on the specific subtype (9).

In our case, prompt biopsies and relative histopathological examination led us to a fast diagnosis in only two weeks, but unfortunately the patient had already undergone a 3 month delay since the first medical examination.

The head and neck health care specialists may be called as the main actors in the diagnostic pathway of these rare diseases and, in presence of lack of response to first treatments, the physicians are obliged to increase immediately the level of suspicion. The first observation/waiting period must be not longer than two weeks, and should be followed by a fast histopathological examination in all the uncertain cases.

Further examinations such as a maxillofacial CT scan and a head and neck ultrasound

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test could be very usefull to have a presumed initial staging of the disease since the first visits.

Based on this experience, it is arguably not correct to wait even three days in respect of these forms of lymphomas in which the cytotoxicity and angiocentricity can produce such a fast and deep necrosis. The grievous impairment of the surrounding anatomical structures is the main complication that contributes to the already very poor prognosis.

Furthermore in these highly aggressive forms the possibility of starting a therapy before completing the diagnostic pathway should be evaluated. Starting an earlier therapy could make a significant difference in improving such poor survival rates.

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Figure legends:

Figure 1: Intraoral clinical aspect in patient with T/NK-cell angiocentric lymphoma at first examination. The hard palate and the alveolar process presented with an ulcerative and destructive lesion at the first examination with an extensive zone of necrosis.

Figure 2: The clinical aspect of the patient after 2 weeks.

Figure 3: Extranodal NK/T-cell lymphoma, nasal type. a) low magnification showing a dense and diffuse infiltrate of pleomorphic lymphocytes within the entire chorion with an angiocentric pattern of infiltration (hematoxylin and eosin, x25); b) prominent tumor necrosis was seen (hematoxylin and eosin, x100); c) medium-sized pleomorphic lymphocytes predominate (hematoxylin and eosin, x200); and d) most cells strongly express CD2 (CD2, x25).

Figure 4: The intraoral examination after 5 weeks shows a palatal perforation with an oronasal fistula.

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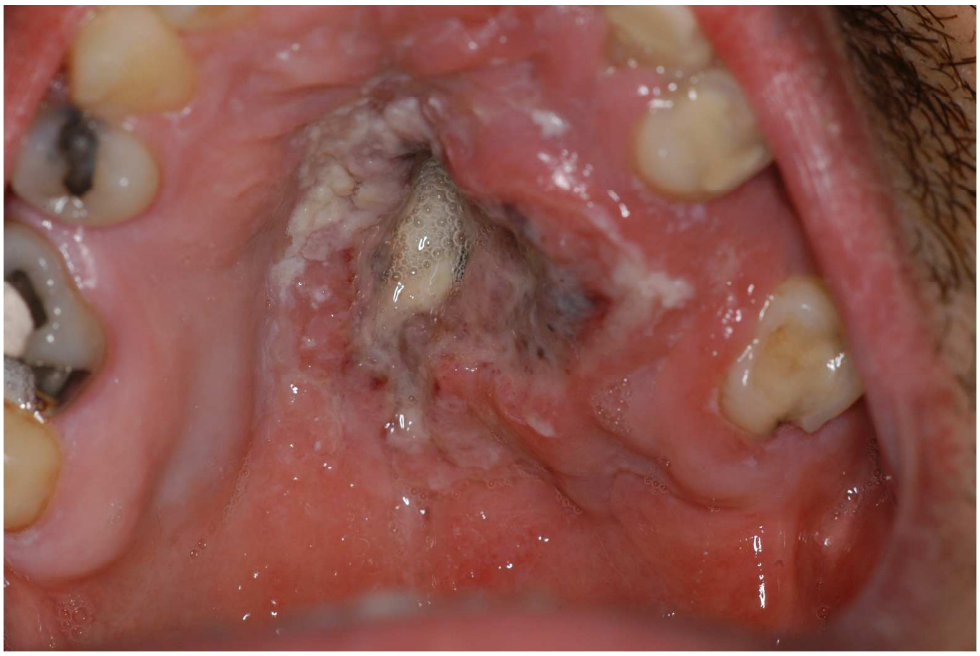

Figure 1
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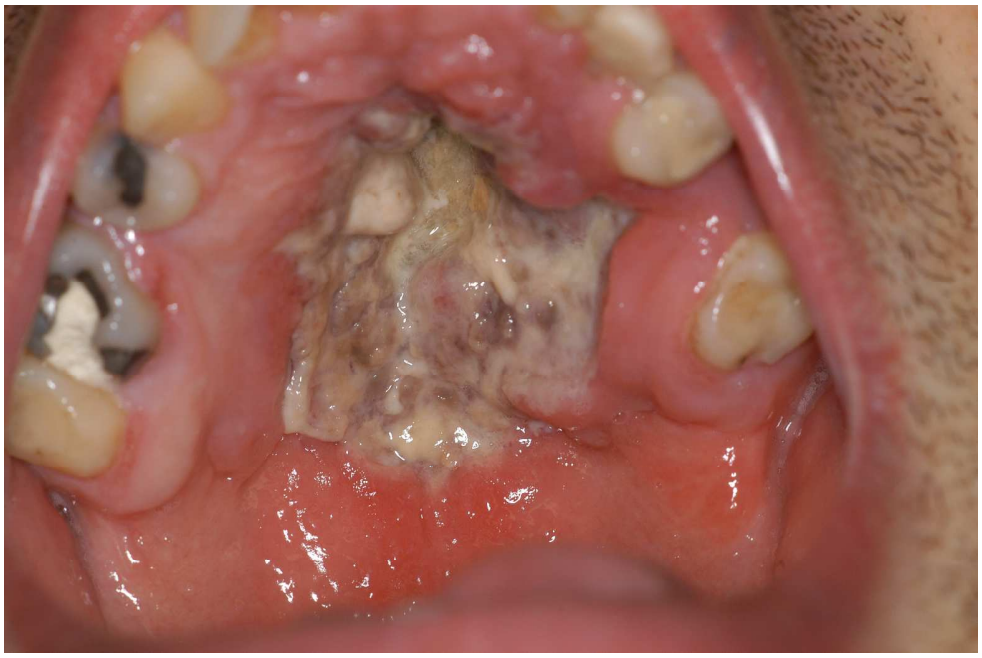

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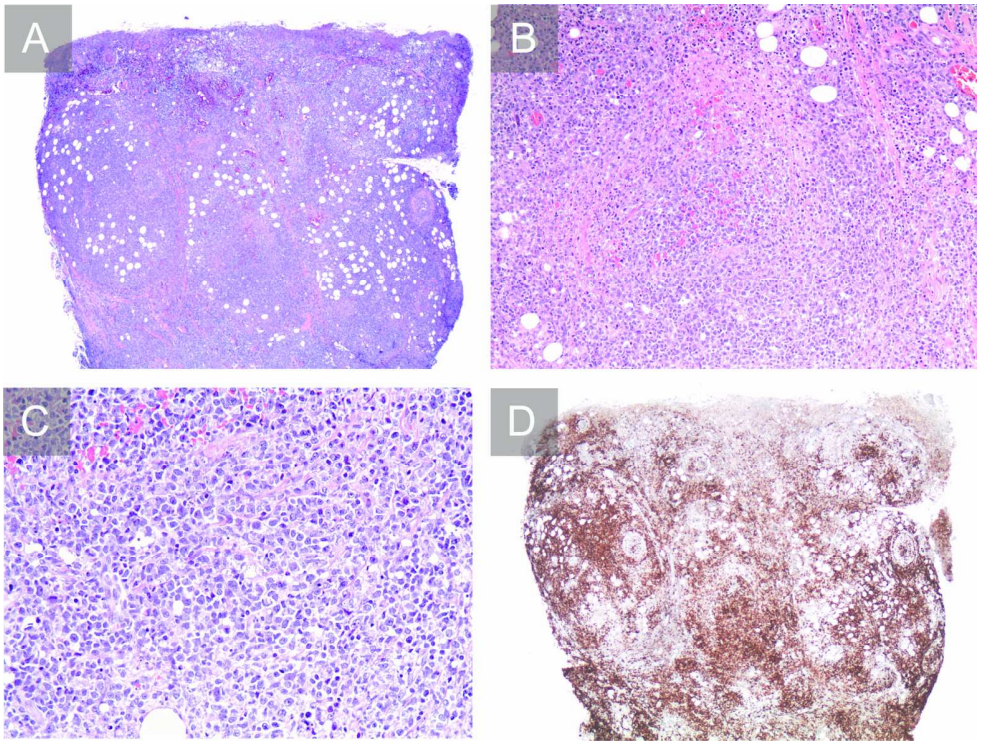

Figure 3
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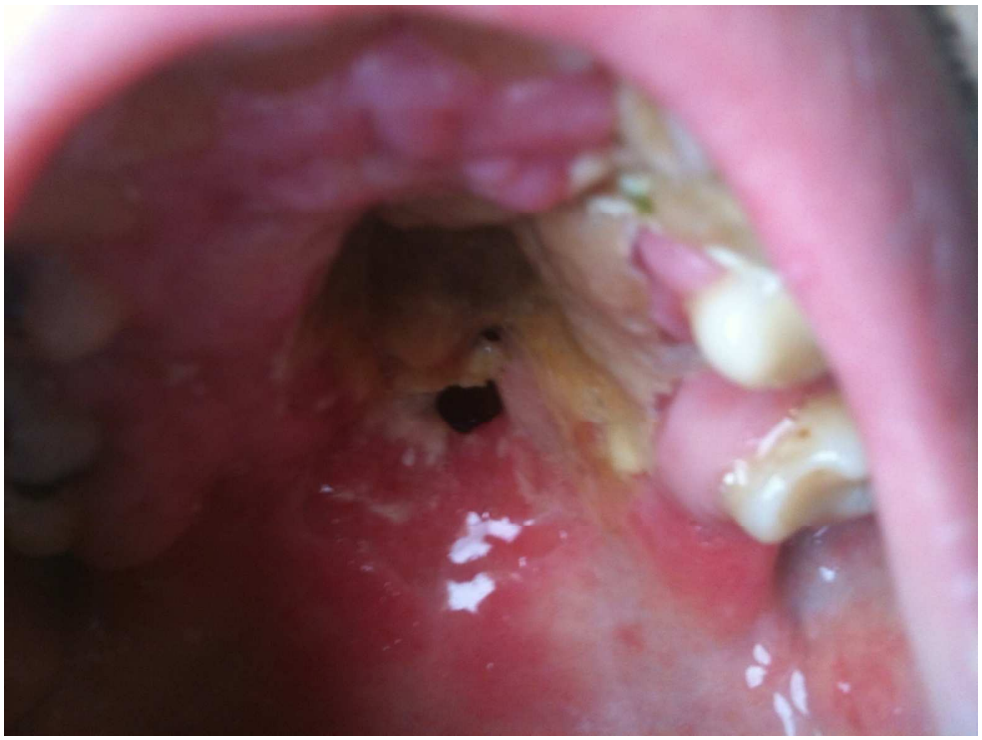

Figure 4
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