NK/T-cell non-Hodgkin lymphoma: Case report and review of the literature

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Abstract. Natural killer (NK)/T-cell lymphomas represent a rare type of lymphoid malignancy with mostly extranodal involvement, having NK cell or (rare) T cell lineage, classified by the World Health Organization into several subtypes which can involve the head and neck region, with the most frequent one being the nasal type. This article presents the case of a 31-year-old patient who presented at the Emergency Unit of Saint Andrew Emergency Clinical Hospital of Galati suffering from mycosis fungoides-like cutaneous lesions, associated with partial left eyelid ptosis of unknown etiology, as well as a poor health status with fever and respiratory failure. The final diagnosis was NK/T-cell non-Hodgkin lymphoma, possibly nasal type with medium sized T cells. The complexity of the rare diagnosis, associated with the unusual rapid patient evolution towards exitus 3 months after diagnosis, the intra-orbital metastatic involvement and the absence of a standardized treatment are case peculiarities, some of which are consistent with current literature data.

Introduction

Natural killer (NK)/T-cell lymphomas (NKTCLs) are non-Hodgkin lymphomas mostly extranodal, which are frequently of NK and of (rare) T-cell origin, being closely related to the Epstein-Barr virus (EBV). The World Health Organization (WHO) classifies NKTCL into nodal, extranodal (sometimes referred to as non-nasal)-cutaneous and other extranodal types, and disseminated (leukemic).

Nasal type NKTCL, previously referred to as lethal midline granuloma or angiocentric T-cell lymphoma, involves the upper aero-digestive tract with the nasal cavity, nasopharynx, paranasal sinuses, tonsils or palate. Non-nasal NKTCLs frequently involve the skin, testis or the gastrointestinal tract, but it can affect many other sites. The disseminated type, as the name implies, has the capacity to involve many organs, all the while having a leukemic phase (1,2).

The most frequent malignant intra-orbital tumor in adults is represented by lymphoma which can unilaterally determine eyeball protrusion, eyelid ptosis, diplopia, pupil anomalies and ocular discomfort.

The cutaneous manifestations of NKTCL are highly variable and can change as the illness progresses, varying from erythema, itching, eczematous eruption, pruritic plaques, lichenoid, to even nodular lesions.

Both intra-orbital and cutaneous manifestations were present in our case. Following careful and thorough investigations, our patient was diagnosed with NKTCL.

Case report

A 31-year-old patient presented at the Emergency Unit of Saint Andrew Emergency Clinical Hospital of Galati in March 2020 being transferred from the Infectious Diseases Hospital where he was assessed for respiratory failure, fever and acute pneumonitis. The patient presented with a poor health status with fever, bilateral pleurisy and marked ascites.

The patient provided informed consent before he was taken into consideration as a case study for possible journal publication. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Saint Andrew Emergency Clinical Hospital of Galati (approval no. 9436 from 28.04.2020).

The clinical examination revealed partial eyelid ptosis of the right eye and multiple cutaneous eczematous-type lesions localized on the thorax, abdomen, limbs and face. The lesions evolved into plaques and were found in different stages of evolution on different body sites, having a more or less

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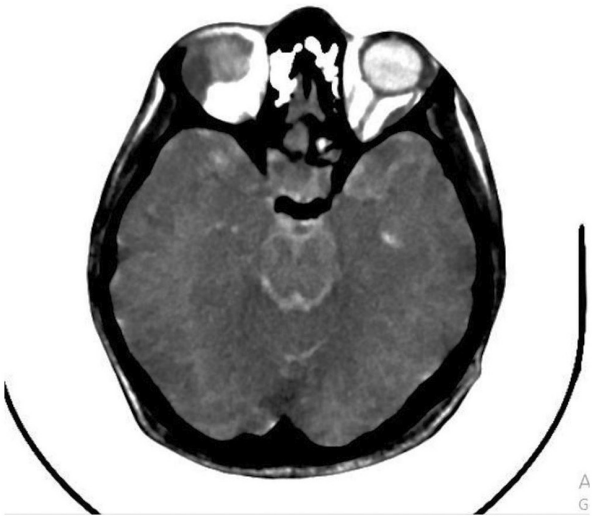

Figure 1. Cranial CT scan showing an intra-orbital tumor mass. CT, computed tomography.

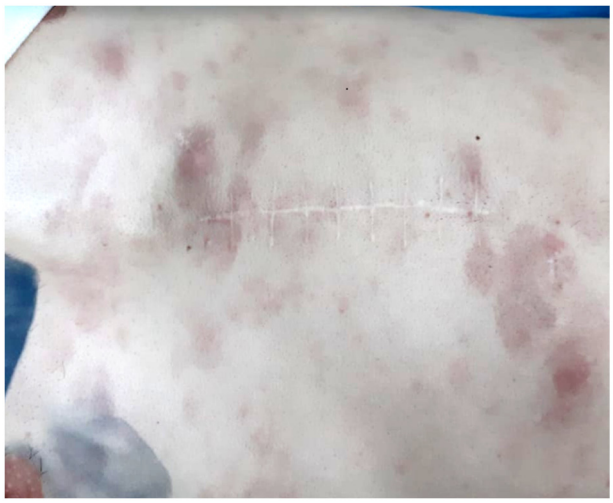

Figure 2. Clinical aspects of the skin lesions. Thoracic and abdominal lesions in different stages of evolution.

erythematous aspect. Some of the lesions acquired nodular features.

The patient's medical history revealed that the onset of the skin lesions was 3 months prior to this hospital admission, along with a progressive onset of partial right eyelid ptosis. The patient was underweight, had multiple tattoos on the arms and chest, denied alcohol and illicit substance consumption and was a non-smoker. He suffered from marked ascites, bilateral pleurisy and the inferior pole of the spleen could not be palpable.

Due to the patient's poor general health status, he was admitted to the Intensive Care Unit. The laboratory investigations revealed significant aspects.

The cranial computed tomography (CT) found a heterogeneous 20/11-mm mass located on the lateral wall of the right orbit, bilateral circumferential polypoid mucosal thickening of the maxillary sinuses and posterior nasal concha hypertrophy; no brain lesions were identified (Fig. 1).

The abdominal ultrasound measured a 139-mm spleen in its longitudinal axis and revealed large amounts of ascites. By analyzing the pleural liquid collected by aspiration, high values of lactic dehydrogenase (3,107 IU/l) were found and the smear identified frequent lymphocytes without the presence of any microorganisms (18,000 leukocytes/mm^3, 100% lymphocytes). Blood cultures returned positive for methicillin-resistant *Staphylococcus aureus* and the blood procalcitonin level was 30.65 ng/ml.

The complete blood count results revealed $9.46x10^3$ white blood cells with $7.27x10^3$ neutrophils, $0.95x10^3$ lymphocytes, $1.18x10^3$ monocytes, $0.01x10^3$ eosinophils and $0.05x10^3$ basophils; the hemoglobin level was low (11.9 g/l) and the platelets numbered $179x10^3/\mu l$. Peripheral blood smear revealed 5% unsegmented and 72% segmented neutrophils with 10% lymphocytes, 13% monocytes and no eosinophils, basophils or atypical lymphocytes.

Pleural puncture was performed. Microscopic examination of the pleural fluid revealed frequent leukocytes with a predominance of lymphocytes (18,000/mm^3), of which over 90% were small lymphocytes. This result raised the suspicion of non-Hodgkin's malignant lymphoma.

The bone marrow biopsy and aspiration revealed granulocyte suppression, plasmacytosis and eosinophilia, raising the suspicion of a T-cell non-Hodgkin lymphoma without medullar infiltration or any discharge into the peripheral bloodstream.

A skin biopsy was made from a tumor nodule and the pathology report revealed, on hematoxylin and eosin-stained slides, a focal hyperkeratotic epidermis with uneven granular layer, mild irregular acanthosis with discrete spongiosis, lymphocyte exocytosis and disproportionate epidermotropism, and interface vacuolar change with atypical lymphocytes along the dermo-epidermal junction. The superficial and deep dermis was characterized by a heavy infiltrate of atypical lymphocytes having irregular, cerebriform nuclei, with perivascular, perifollicular and intrafollicular location; the malignant cells also infiltrated the arrectorpili muscle. The histopathological diagnosis was peripheral NK/T cell lymphoma, no special type.

Immunohistochemistry studies were conducted as the differential diagnosis with mycosis fungoides was suspected. After careful investigation, the malignant proliferation was revealed to be made up of medium sized $CD3^+$ T cells with CD56 (NK marker) and isolated CD30 expression; the tumor cells were $CD4^-$ and $CD8^-$, negative for the blastic marker TdT (terminal deoxynucleotidyltransferase) and also for the B cell marker CD20. Isolated cells (under 5%) expressed CD30, an activated lymphocyte marker, while the cytotoxic activation marker, granzyme B, had no specific immunophenotyping expression.

Following results of the histopathology and immunohistochemistry, the final conclusion entailed the diagnosis of medium T/NK cell non-Hodgkin lymphoma, possibly nasal type. Its clinical and microscopic features are highlighted in Figs. 2-5.

The patient died 72 h after admission and was not tested for EBV; he proved to be HIV-negative. The lymphoma-specific treatment was not initiated.

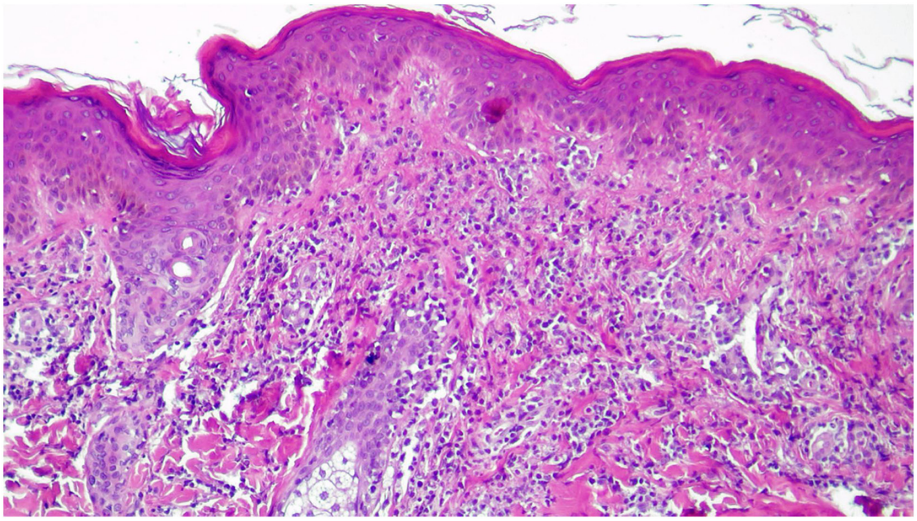

Figure 3. Skin biopsy. The superficial and deep dermis reveals an atypical lymphocytic infiltrate with irregular nuclei having perifollicular and angiocentric patterns, with disproportionate epidermotropism, col. H&E, magnification, x100. H&E, hematoxylin and eosin.

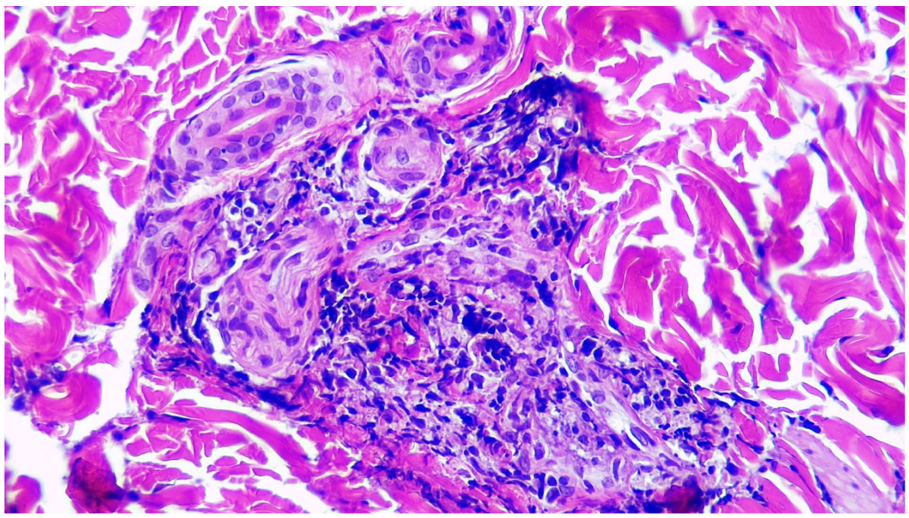

Figure 4. Perivascular and perineural disposition of atypical, medium-sized lymphocytes with oval/angulated, hyperchromatic nuclei, and associated apoptotic bodies, col. H&E, magnification, x200. H&E, hematoxylin and eosin.

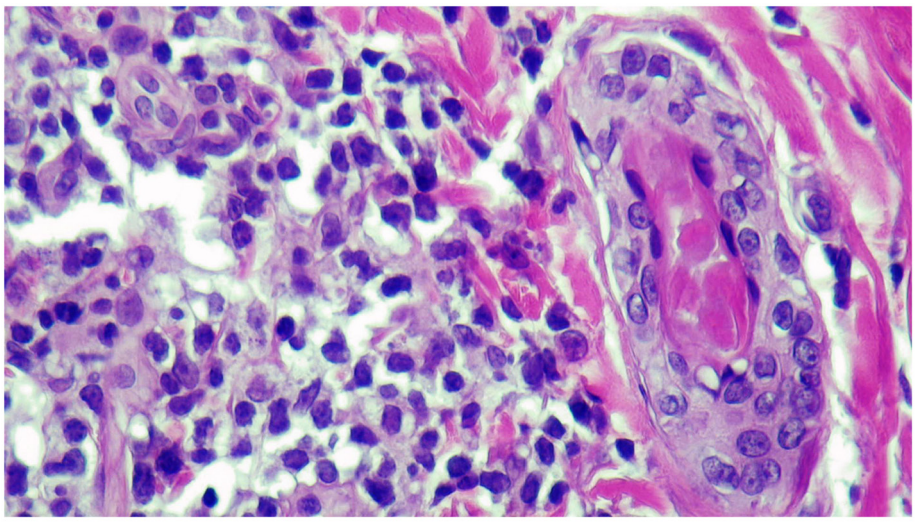

Figure 5. Atypical medium-sized lymphocytes with irregular, convoluted nuclei and inconspicuous nuclei, col. H&E, magnification, x400. H&E, hematoxylin and eosin.

Discussion

Natural killer (NK)/T-cell lymphomas (NKTCLs) are a rare and distinct type of malignant non-Hodgkin lymphoma (frequently extranodal lymphomas, most of them of the nasal type). They are identified in 12% of lymphoma patients, 68% of them having the nasal type, 26% extranasal type and 6% aggressive or unclassifiable type (3,4). A higher incidence is observed in Asia when compared with Europe (22 vs. 5%) with an average life expectancy of 8 months (5,6).

Nasal type lymphoma is frequently located in the upper aero-digestive tract: Nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx and larynx, being frequently associated with the Epstein-Barr virus (EBV) (7,8). Nasal type NKTCLs are, in almost 95% of cases, associated with EBV; the exact EBV pathway mechanism involved in the malignant transformation is not yet fully understood (6). The immunohistochemistry profile features $CD3^+$, $CD43^+$, $CD45RO^+$, $CD56^+$, EBV^-, $CD8^-$, Epstein-Barr virus-encoded small RNA-positive ($EBER^+$), with positivity for cytotoxic granular proteins (7-11).

The extranodal pattern of involvement seems to be connected with the CD56 marker, which is the neural cell adhesion molecule (NCAM) possessing hemophilic connection properties. The neoplastic cells are thus redistributed to other sites and evolve as new malignancy sites. The skin is the most common site for NKTCL dissemination (12).

NKTCL is rarely found in Caucasians or in the Western population, having a prevalence estimated at around 0.17-1.15% of all non-Hodgkin lymphomas, with 45% of these having NKTCL origin (5).

NKTCL appears most frequently in patients over the age of 60 years, although studies have shown that it can be found in both geriatric and pediatric patients. The mortality rate is higher than in other lymphomas and has poorer response rates to radiation and chemotherapy (3).

The general manifestations of NKTCLs include signs and symptoms located mainly in the face and neck regions: Facial pain, diplopia, visual impairment, eyeball protrusion, eyelid ptosis, pupil anomalies, nasal obstruction, refractory sinusitis, velo-palatal motor disturbances, cranial nerve neuropathies, intra-orbital and intrasinus masses. Other associations consist of respiratory failure and liver and spleen enlargement (7).

In our patient's case, the intra-orbital tumor mass was altering the ocular axis and was responsible for partial right eyelid ptosis, being considered an intra-orbital lymphoma metastasis. Unfortunately, biopsy was not performed in order to confirm this theory. Nevertheless, considering the previously described clinical aspects which were correlated with the laboratory investigations, we consider that the diagnosis of intra-orbital metastatic lymphoma can be supported.

In adults, lymphomas are the most frequent malignant intra-orbital tumors. They manifest as swellings with increase in intra-orbital volume causing mass-effect. Diplopia, eye motility disturbances and eyelid dysfunction appear due to the invasion or compression of orbital contents (13).

In regards to skin lesions, the differential diagnosis with mycosis fungoides must be made, being the most common cutaneous T-cell lymphoma. This type of lesion is more common in individuals younger than 20 years of age, with a sex ratio that favors males. It is an unusual manifestation of skin-associated $CD4^+$ T cells, which, in early stages, can resemble eczema or psoriasis (14,15).

In our case, some of the skin biopsy aspects that were found resembled mycosis fungoides: Atypical cerebriform lymphocytes in the dermis and epidermis, some of them in and around hair follicles (resembling folliculotropic mycosis fungoides) and epidermotropism with lymphocytes at the dermo-epidermal junction (sentinel sign). The differential diagnosis between NKTCL and mycosis fungoides was made with the help of immunohistochemistry studies.

Extranodal nasal-type NKTCLs are rare malignancies for which standardized therapy has not yet been established. To date, there are no randomized clinical trials which can clearly determine such a scheme. For these patients it is recommended that they enroll in clinical trials and that they receive treatment in highly specialized clinics (16).

The therapeutic strategy in this type of lymphoma requires collaboration between hematologists, oncologists, radiotherapists, neurologists, pathologists, and treatment needs to be individualized according to the site of the lymphoma (nasal or extra-nasal) and disease stage (17).

Patients in the first stage of disease evolution are stratified by age groups, by performance status and dependency level, by regional lymph node involvement and by the increased level of lactate dehydrogenase (1) (a situation which was present also in our patient's case).

Concerning nasal-type NKTCLs, one can use radiotherapy at a dose of at least 50 Gy, as single therapy, but this is associated with a high rate of local and distant recurrence. As such, combined therapy is recommended, using the CHOP treatment scheme (cyclophosphamide, doxorubicin, vincristine, prednisone); thus, the 5-year survival rate is increased from 20 to 80% (18,19).

For patients in the second stage of disease, in addition to radiotherapy and cysplatin, 3 cycles of DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) or sequential SMILE (etoposide, ifosfamide, methotrexate and dexamethasone) chemo-radiotherapy is suggested (20).

For stage four nasal-type lymphoma, and also any stage extranasal types, poly-chemotherapy with pegaspargase (with or without radiotherapy) can be administered (18).

Permanent re-staging is conducted according to imaging studies including CT, magnetic resonance imaging (MRI), positron emission tomography-computed tomography(PET-CT scan), endoscopy or repeated biopsies (5,21). Unfortunately, progression is registered even though treatment is applied (18).

Studies are being carried out which evaluate the beneficial role of stem cell transplantation in NKTCLs, but definitive conclusions cannot be yet drawn concerning this therapeutic alternative (22).

The case presented here describes the steps carried out in order to establish the diagnosis of nasal-type NKTCL, starting from the evaluation of neurological lesions (eye and eyelid mobility dysfunction) associated with suggestive skin lesions; all of these correlated with the cranial CT scan results which were suggestive for intra-orbital lymphoma dissemination.

The case was unusual as it presented with intra-orbital secondary dissemination of the primary NKTCL and as it

evolved quickly, with an exitus of approximately 3 months-a life expectancy much lower than that cited in other research (3), with positive blood cultures in the context of acute pneumonitis set in a background of immune suppression.

The intra-orbital mass could not be confirmed through biopsy as a lymphoma, but by correlating the clinical and laboratory data mentioned earlier, the orbital mass was suspected as being a lymphoma; this is also valid for the sinus involvement.

The cutaneous lesions which clinically and morphologically resembled mycosis fungoides, were confirmed to be NKTCL. An essential tool for diagnosis is immunohistochemistry which revealed the medium T cell tumor proliferation to be positive for CD3 and CD30 and negative for CD4, CD8 and CD20.

The diagnosis of lymphoma was also supported by the pleural liquid fine needle aspiration appearance.

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Availability of data and materials

Any further information concerning the case study is available from the corresponding author upon reasonable request.

Author's contributions

ML, AT, DCV and EN contributed to the study design, analyzed and interpreted the patient's clinical data regarding the hematological disease, and prepared the manuscript. EN performed the histological examination of the cutaneous biopsy. VS, AT, AF, VZC, GS, MP and EME contributed to collecting the relevant literature, data analysis, reviewed and critically interpreted the information. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Approval from 'Saint Andrew' Emergency Clinical Hospital Ethics Committee (Decision no. 9436 from 28.04.2020) was obtained. Informed consent for participation in the study or use of the patient tissue was obtained from our participant.

Patient consent for publication

Informed consent for publication was obtained from our patient.

Competing interests

The authors declare that they have no competing interests.

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