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Epstein-Barr Virus Positive Natural Killer/T-Cell Nasal Type Lymphoma Case Report

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1. Abstract

We describe the case of a patient admitted to the ward with a diagnosis of pyelonephritis. The subsequent appearance of fever and the consequently performed investigations have resulted in a relatively rapid diagnosis of nasal-type NHL, a rare disease whose late detection leads to facial tissue destruction.

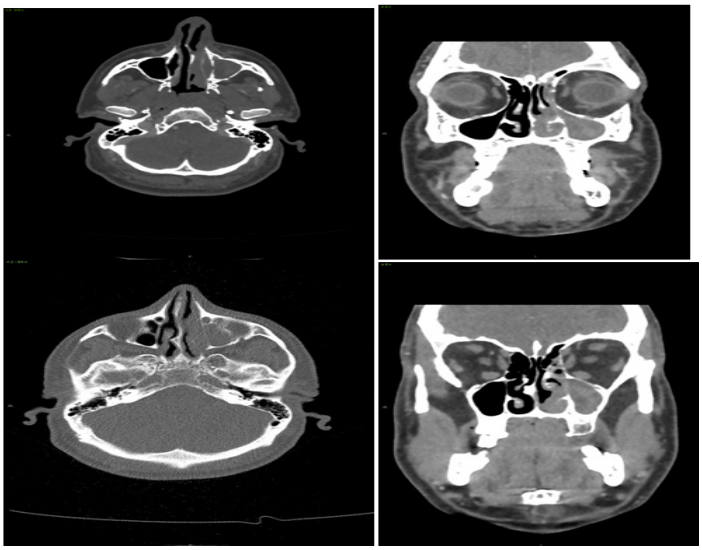
2. Keywords:
Extranodal NK/T cell lymphoma, EBV, orphan disease.

3. Introduction

In the most recent World Health Organization classification of lymphoid neoplasms, the eponym Extranodal NK/T-cell lymphoma of nasal type has replaced the many other terms with which this neoplasm was previously described [1] including lethal midline granuloma, midline malignant reticulosis, polymorphic reticulosis, angiocentricimmunoproliferative lesion, and angiocentric lymphoma. It typically involves the nasalregion, butmay affect otherextranodalsites, suchasskin and gastrointestinaltract [4]. This is a malignancy that is often diagnosed with delay, when destruction of the nose and infiltration of the surrounding tissues is advanced.

4. Case Report

Male patient, 46 years old, ex-smoker, is admitted for abdominal pain and fever (TC > 38 °C, septic type). He had already been managed with antibiotics in the two days before the hospitalization without success. On entry to the ward there is pain in the right renal loggia, with positivity of Giordano's maneuver.
In the emergency room he was tested for chest X-ray, ultrasound of the abdomen and finally, since no noteworthy alterations were found, also for CT scan.



In the CT images we can appreciate the presence of isodense tissue entirely occupying the left maxillary sinus, which widens the maxillary ostium and invades the nasal cavity, which, in turn, appears to be obliterated. No evident structural bone alterations are noticeable.

The latter showed a small adenoma of the left adrenal gland, and "an area of inhomogeneous post-contrastographic enhancement of about 35 x 25 mm, constantly and disomogeneously hypodense, to be ascribed to a nephritic focus, associated with tenuous suffusion of the neighboring cell".
Right pyelonephritis was therefore diagnosed and empirical therapy with Tazobactam and Ciprofloxacin was started. On the tenth day the fever disappeared. Among the required laboratory tests, particular attention was focused on EBV-DNA positivity (4,001 copies).

On day twenty the patient began to complain of pharyngodynia, discomfort on swallowing and non-specific pain in the neck, right side, as well as serotine fever. Numerous blood cultures were performed, all of which were negative. He underwent a CT scan of the cervical spine which revealed degenerative osteodiscitis with mild canal stenosis.

World Journal Of Hematology And Oncology

Subsequently, the patient began to complain of pain in the left maxilla. He was examined by the otorhinologist, who diagnosed Fothergill's disease and prescribed corticosteroids for six days.

Despite the apparent improvement in symptoms, a CT scan of the facial mass was requested, which revealed "phlogistic isodensity of the left maxillary sinus, ipsilateral ethmoidal cells, left nasal polyposis".As the fever persisted, an ultrasound examination of the renal folds was requested: it showed that the pyelonephritis had completely resolved. An echocardiogram was also performed, which was negative for endocardial vegetations.

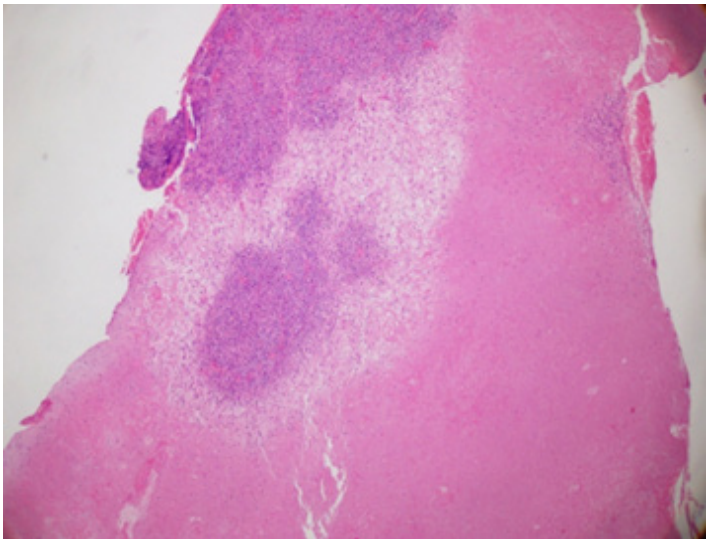


Image n. 1: histological biopsy preparation): small sample magnification (EE 40x):
extensive necrosis is observed with focal residual areas of vital neoplasm.

After examining the TAC of the facial massif, the otorhinolaryngologist performed a rhinofibroscopy and finally formulated the hypothesis, shared by the infectious pathologist, of mucopurulent maxillary sinusitis to be differentiated from a possible fungal sinusitis. A FESS antrostomy of the left maxillary sinus with biopsy was performed. On the following day, crustose lesions appeared in the left nasal fossa and slight swelling of the half-face.

The pathologist described the biopsy as follows: the morphological picture shows fibrin-necrotic tissue with large, atypical cells with little cytoplasm and irregular vesicular nuclei with small nucleoli that are sometimes evident. An attempted immunohistochemical study showed positivity for CD3, CD2, CD43 and CD30, weak positivity for LCA and negativity for CD20, CD79a, CD4, CD5 and ALK. Proliferation index around 80-90 % in large cells. Picture suggestive but not fully conclusive of a T cell lymphoproliferative process (non-Hodgkin's lymphoma, T cell, CD30+).

Subsequently the haematologist, having seen the biopsy, diagnosed "lymphoproliferative disease with extranodal localisation in the maxillary sinus with negative CT scan for other localisations" and recommended PET-CT. The latter examination showed exclusive hypercapitation in the left maxilla. A second biopsy was recommended. In the meantime the EBV DNA values increased significantly (14,586 copies).The second biopsy finally led to the diagnosis of EBV-positive nasal type NHL.

The bone marrow biopsy excluded bone marrow invasion and therefore confirmed the exclusive localization in the left maxillary sinus. For the EBV infection, the infectivologist recommended IgG therapy and then treatment with Rituximab. The haematologist prescribed therapy with Cisplatin (20 mg/sq.m. days 1-4), Dexamethasone (15 mg/sq.m. i.v. days 1-5), Gemcitabine (800 mg/sq.m. i.v. on day 1 and day 8), Peg-Asparaginase (2500 i.m. on day 1 and repeated every 3 weeks).

As a result of asparaginase, the patient developed mild pancreatitis and pulmonary microthromboembolism [35, 36, 40]. He is currently undergoing follow-up in the haematological ward of the Cardarelli Hospital and, finally, he has undergone a bone marrow transplant.

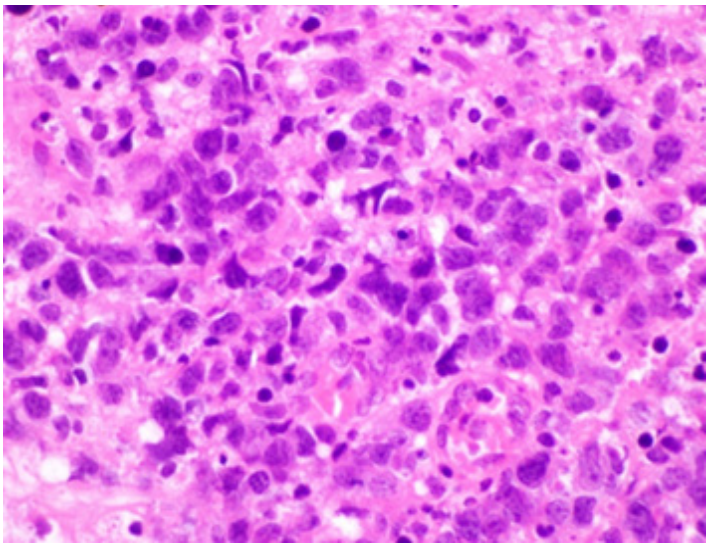


Image n. 2: High magnification (EE 400x): large cells with poor cytoplasm and irregular nuclei with evident small nucleoli.

5. Discussion

Extranodal NK/T-cell lymphoma, nasal type, is a clinical entity, first described in 1933, comprising ulcerative and necrotic lesions preferentially arising in the nasal cavities and sinuses (70%), but which can also arise at the expense of Waldeyer's ring (38%), thoracic cavity (14%), larynx, hypopharynx (10%) and mandible or cheek [2, 27]. Prevalence and incidence are variable: the disease is rare in the Caucasian population, and has a much higher incidence in Asia and Latin America [3, 5, 6, 10, 14, 17].

A genetic predisposition to its development is possible [14]; but more importantly, it has been reported that social and cultural factors may influence its incidence [19]. The patients are aged between 40 and 50 years and are predominantly male [2].

Association with EBV infection is possible, in which case the prognosis is often poor with an average five-year survival rate of between 38% and 85%(2,5). However, EBV-DNA monitoring may be important for the assessment of response to therapy [12].

The diagnosis is usually late or even post-mortem: the patient's symptoms are often referred to persistent sinusitis [11]. However, a distant

World Journal Of Hematology And Oncology

localisation is also possible, with gastrointestinal or thoracic involvement [4,13]. In about 10% of cases there may be bone marrow invasion [3].
In terms of diagnosis, important information comes from CT and MRI scans, but biopsy remains essential, although in some cases even the use of multiple biopsies has not been conclusive [4,18].
Granulysin, a cytolytic protein expressed in cytotoxic T and natural killer (NK) cells, has recently been presented as a promising marker for the diagnosis [29, 42]. It is a member of the saposin-like protein (SAPLIP) family of proteins and displays lytic activity. It is synthesized as a 15-kDa molecule, and portions are then cleaved at the amino and carboxy termini to produce a 9-kDa form. The 9-kDa form is sequestered in cytolytic granules, while the 15-kDa form is constitutively secreted; however, the recombinant 9-kD form cannot avoid perforins to promote killing of intracellular pathogens [29b].

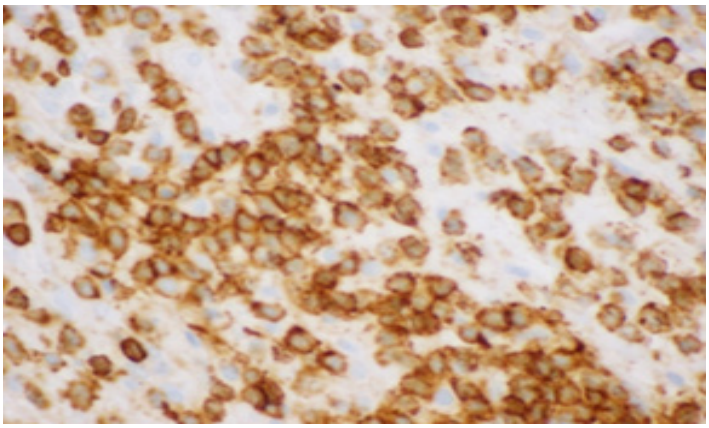


Image n. 3: Immunohistochemical positivity for CD30 and CD56

In contrast to other lymphomas, treatment regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine and predsinone) have a poor effect on ENKTL patients because the malignancy expresses high concentrations of Glycoprotein P, which allows multiresistance to antracyclines [21, 30, 31, 32]. Treatments with ifosfamide and metrotrexate and etoposide have been described as effective in patients with EBV-positive lymphomas [33, 34]. Currently L-asparaginase-based cycles are able to induce a therapeutic response in more than 80 % of patients with refractory or relapsed ENKTL [35, 36].
However, the side effects, including serious ones, of the drug should not be underestimated:anorexia, nausea, vomiting, anaemia, hepatopathy, leucopenia and infection, fever, allergic reactions, pancreatitis.
The role of radiation in early-stage disease has been established by several prospective studies. However, it may also be beneficial in some patients with advanced disease,irrespective of initial treatment [6].

Concurrent chemoradiotherapy was found to improve the outcome of localized ENKTL. The so called DeVIC regimen (dexamethasone, etoposide, ifosfamide, and carboplatin) administered with radiotherapy was reported to have a 77% complete response rate [38].
Although radiotherapy and chemotherapy administered concomitantly had prove to reduce risk of disease relapse, efficacy is burdened by an increase in haematological and non-haematological toxicity.
Radiotherapy with weekly cisplatin for 4 weeks, followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone showed a comparable complete response rate [39]. Furthermore cisplatin, acting as radiosensitizer, allows to reduce the radiation dose by around 40 Gy. Concurrent chemoradiation can be also followed by two cycles of VIDL (etoposide, ifosfamide, dexamethasone, and L-asparaginase), which reported to have a near 90% CR rate [40].
Sequential chemo-radiotherapy approach was also evaluated with the SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) followed by radiotherapy [41].

6. Conclusions

The case described is interesting for various reasons. The patient was hospitalized for pyelonephritis.
As is known, in most cases, pyelonephritis is a complication of a urinary tract infection (in these cases an ascending etiology is invoked). In some cases, in patients suffering from endocarditis, from odontogenic abscesses, or sepsis, bacteria can reach the kidney and produce pyelonephritis (in these cases a descending etiology is invoked).
In our patient, suffering from nasal type NHL and in which there was also an infectious and inflammatory component in the left maxilla, the cause of pyelonephritis was most likely caused by a descending infection, starting from the left maxilla.

After the resolution of the pyelonephritis, and after a period of absolute well-being, a low-grade fever appeared.
The low-grade fever was the only symptom for a few days and only later the patient began to complain of non-specific pain in the neck and then pain in the left jaw.
We must say that the patient's cheek was normal and began to become edematous only after the first biopsy. In a classic way, the biopsy revealed the EBV.The diagnosis in this patient was early and was made possible by the desire to understand the cause of the fever and the knowledge that, if the patient had been discharged according to guidelines, the diagnosis would have been made with considerable delay. The patient was therefore treated early and clinically at present he is in complete remission.The disease, as mentioned before, is considered rare in Italy [37].

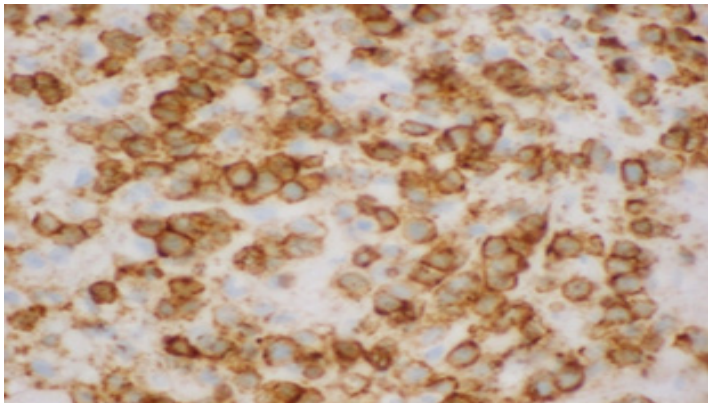


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Image n. 4: Immunohistochemical positivity for CD30 and CD56

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World Journal Of Hematology And Oncology

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