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A CASE REPORT ON EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA (ENKTCL) IN A CAUCASIAN ADULT

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Abstract

Peripheral T-cell lymphomas (PTCLs) are uncommon entities, accounting for fewer than 10% of all non-Hodgkin lymphomas. Initial evaluation of PTCLs includes history and physical examination, computed tomography (CT) of the chest, abdomen and pelvis or positron emission tomography (PET)/CT imaging, a marrow aspirate and a biopsy.

Extra nodal NK/T-cell lymphoma (ENKTL) represents approximately 5% of PTCLs. Although the disease typically appears as a localized tumor at the initial diagnosis with a low (favorable) International Prognostic Index (IPI) and without B-symptoms, recurrence and frequent relapses are the main threats to the course of ENKTL. For this reason, patients with stage 1 of the disease have a worse outcome compared to those who initially appear with a tumor mass at other locations.

We hereby present a case of a 38-year-old male patient, who firstly appeared with a localized mass in one of the testicles. Despite properly treating the condition with first-, second- and third-line chemotherapeutics plus adjuvant radiotherapy, the patient has had a total of two relapses in the past 4.5 years. After the last given regimen, the patient has been disease-free for three months, which is not an encouraging time given the cumulative side effect of polychemotherapy and the aggressiveness of the disease itself.

Keywords*:* natural killer/T-cell lymphoma, testis,^{18}F-FDG PET.

Introduction

Non-Hodgkin lymphomas (NHLs) are a group of histological and biologically heterogeneous malignancies that originate from the lymphoid system.

The annual incidence of these diseases in Europe and North America ranges from 14 to 19 cases per 100000 inhabitants [1].

Extra nodal natural killer/T-cell lymphoma (ENKTCL) is a type of NHL that is typically aggressive and mainly affects the nasal cavity and nasopharyngeal region. These malignancies were previously known as *lethal midline granuloma* due to the central facial region involvement and the fast progressive course of the disease. However, in some patients the disease can manifest with distant nodal or extranodal involvement such as the Waldeyer ring, gastrointestinal tract, genitourinary organs, lungs, thyroid, skin and testes. Compared to ENKTCL of nasal type, primary testicular ENKTCL is very rare and has a lower age of onset and faster clinical progression, with tumor cell dissemination occurring early in the disease [2].

According to the World Health Organization (WHO) classification of lymphoid malignancies, these lymphomas are referred to as extra nodal NK/T-cell lymphoma to reflect their cellular origins from both NK-cells and T-cells.[3].

NK-cells are typically regarded to be part of the innate immune system, implying that they can proliferate rapidly in response to antigens without prior sensitization, and that their lifespans are short without a long-lived memory population. In contrast, T-cells are educated in the thymus through exposure to different antigens and develop into memory T-cells after antigen-driven proliferation, which are characteristic of the adaptive immune system [4].

Treatment outcome of ENKTCL is best achieved with combined chemotherapy and radiation therapy. CHOP-based (Cyclophosphamide-Doxorubicin-Prednisolone-Vincristine) therapy is an option, but asparaginase is considered as a very active agent in this disease, especially when combined with gemcitabine, oxaliplatin and radiotherapy [5].

Another intensive chemotherapy regimen, SMILE (Dexamethasone-Methotrexate-Ifosfamide-L-asparaginase-Etoposide) also contains asparaginase as a potent enzyme which was initially identified in 1963. Back then, asparaginase, referred to as AS Nase -was considered an effective antileukemic agent. Clinical testing with bacterial-derived AS Nase commenced in 1966, and in 1978, *E. coli*–derived AS Nase received approval in the United States for the treatment of acute lymphoblastic leukemia. Afterwards, following many other clinical trials, asparaginase found further use in the treatment of many other hematological malignancies, including ENKTCL.

The main side effects from the asparaginase-based protocols are pain or swelling at the injection site, nausea or vomiting (may be severe), pancreatic impairment with stomach cramps, loss of appetite, weight loss, headache, drowsiness, skin rash, irritability, etc.

When the side effects overcome the cost-benefit risk, it is suggested to switch to a different regimen which does not contain asparaginase. This approach is also an option in clinical cases of relapsed/refractory ENKTCL.

Case Report

We hereby present a case of a 38-year-old Caucasian male, who initially appeared in 2019 with painless left testicular enlargement over the course of several months. The patient reported a history of iatrogenic diabetes mellitus, hypertension, and lower limb thrombosis (two months ago) as comorbidities present at the time of diagnosis.

Elective left-sided orchifuniculectomy was performed, and the obtained operative material was duly sent for a pathohistological analysis. The findings were consistent with peripheral testicular natural killer T cell lymphoma.

The physical examination of the patient did not show organomegaly or signs of haemorrhagic syndrome on the skin and mucous membranes, but the patient complained of a bloody cough. The ESR was 70/-, Hb=13.9 g/dL, WBC=13x10^3/uL, PLT=378 x10^3/uL. In peripheral blood samples, neutrophils 0.73, lymphocytes 0.21, eosinophils 0.02, monocytes 0.04 were present, with no recorded pathological elements. From the indicated biochemical analyses, the following results were obtained: D-dimers=3.650 mg/L, LDH=477 u/L, AST=42 u/L, ALT=120 u/L, glycemia=7.2 mmol/L, total protein=84 g/L, total bilirubin=12.8 μmol/L.

The patient was referred to a pulmonologist who suggested that CT angiography of the chest should be done, which showed massive, acute, arterial PTE of central and lobar types, acute thrombi on both pulmonary arteries, interlobular branches bilaterally for both lower lobes, saddled thrombus and multiple subpleural infarction zones.

Afterwards, the patient was admitted to the Pulmonary Ward until stabilization of the thromboembolic condition (there he was treated at the Intensive Care Unit with Enoxaparin and extensive supportive care). He was sent back to our Clinic of Haematology with prescribed Acenocumarol. Immediate PET/CT scan was scheduled.

The results were as follows: metabolic activity in pleural thickening at the right lung level (SUVmax=2.7): Increased metabolic activity at the level of the left inguinal ligament (reactive change at the site of surgery) (SUVmax=6.0). Diffusely increased metabolic activity in the bone marrow, reactive. (SUVmax=2.6).

Due to the absence of bone marrow involvement in the diagnosed disease, the collegium at our Clinic decided to initiate treatment according to the SMILE protocol (started on 21.1.2020) as follows: amp. Methotrexate i.v. a 4200mg/day 1, amp. $NaHCO_3$ N. V+V before and after Methotrexate, amp. Calcium folinate No IV/day 2-4, amp. Etoposide a 200mg/day 2-4, amp. Ifosfamide a 3gr/day 2-4, amp. Sodium 2-mercapto ethane sulfonate (MESNA) a 4grams/day 2-4, tbl. Dexamethasone an 8 mg 5x1/day 2-

4, amp. L-Asparaginase a 10000 i.e./day 8,10 and 12. Due to acute pancreatitis with elevated a-amylase, lipase, and non-measurable glycaemic values, the L-Asparaginase therapy was discontinued.

A conciliary endocrinologist and a gastroenterohepatologist were called in and symptomatic and supportive therapy was initiated, as well as insulin therapy, after which the condition and the laboratory values returned to normal. A consultative ophthalmologist was also called in for an examination because of the patient's complaints of blurred vision. The patient was given therapy with sol. Potasium 3x1 in both eyes and tbl. Vitamin C a 500mg 2x1.

In March 2020, the treatment was continued with therapy following the DeVIC regimen (amp. Dexamethasone a 4mg 5+5amp/3 days, Carbolplatin a 400mg/day 1, Etoposide 140mg/days 1-3, amp. MESNA, amp. Ifosfamid 2 grams /days 1-3) due to Asparaginase intolerance at the first treatment attempt. The patient was given Acenocumarol and other symptomatic/supportive treatment when discharged from hospital.

Afterwards, the patient was regularly monitored on an outpatient basis at the Clinic of Hematology, with no signs of relapsing disease. In February 2021, a control PET/CT scan, was scheduled. The following findings were obtained: pleural thickening in the right postererobasal region, with no pleural effusion.

There was an increased uptake of FDG (SUV max=11.5) along the intestines, possibly due the therapy with antidiabetics. Metabolically active lesion in gastric cardia projection (SUV max=4.7, d=22mm) which was suspected to be an underlying ulcus ventriculi. There were no signs of active metabolic lesions connected to the haematological diagnosis.

A year later (April 2022), the patient appeared for a regular control with subcutaneous lesions in the region of the right shoulder and right forearm, painless on palpation and with no present discoloration of the surface skin, which was an indication for another PET/CT scan.

The liver SUV max was 3.4, but there was diffusely increased metabolic activity along the small intestine, colon, and rectum present, and more importantly, metabolically active subcutaneous tumor lesions (SUV max=16.8, d~50mm) in the right upper arm were detected. A biopsy was performed in addition to a relapse of the NK lymphoma. This relapse of PET SCAN with malignant features with high FDG uptake in the right upper arm was the reason for re-evaluation and therapy. The patient was immediately hospitalized and treated according to ESHAP protocol. Throughout the hospitalization, the patient was afebrile, with no signs of bleeding, clinically stable, with no major side effects from the administered therapy.

The second cycle of the regimen was given according to the NCCN (National Comprehensive Cancer Network) protocols. Meanwhile, in the course of August, the patient was referred to radiation therapy with a three-dimensional conformal approach in the right upper arm and forearm area (6 MB -a TTD 30 Gy).

A control PET/CT scan was conducted in September the same year with the following conclusion: the PET/CT scan compared to the previous scan in April had a complete regression of the described subcutaneous lesions, but there was an increased metabolic activity in gastric fundus projection and throughout the small intestines and the colon, which was further correlated with gastro/colonoscopy. There was no evidence of other metabolically active lesions.

Upon the noted remission of the disease, the patient was referred for a stem cell transplant, but the patient refused it. Nonetheless, the patient underwent regular controls at our Clinic. In May 2023, he was referred for a follow-up PET scan following the completed radio/chemotherapy. The conclusion was that the PET/CT did not show metabolically active lesions with malignant features. There was only an increased metabolic activity in gastric projection with metabolic progression.

A few weeks after obtaining the PET/CT scan results, the patient again appeared with soft tissue swelling on the right forearm. The noted tissue was excised. The pathohistological findings indicated another relapse of PERIPHERAL T-CELL LYMPHOMA NK -/ -T-CELL LYMPHOMA. The macroscopic finding was described as an oval skin excision of 1.6x1.3x1cm. A cross-section showed whitish tumour tissue.

The sections were stained with N.E. and immunohistochemically for CD20, CD3, Ki-67, and CD30. The microscopic findings were as follows: microscopically, the specimens showed an ulceratively altered epididymis under which dermal and subcutaneous adipose tissue was infiltrated by a malignant

lymphoid population that is CD3+, CD20-, CD30-, with a high proliferation of Ki-67+ (>80%). Given the previous findings, the changes were considered to be a part of a divergence of the underlying disease (NK/T cellular peripheral lymphoma).

The patient was re-referred for initiation of therapy, and a decision to conduct treatment according to the GDP protocol was adopted. A total of 6 cycles were administered, with an adjuvant radiotherapy of the affected area. The treatment finished in March 2024.

An MRI of the right wrist involving the bones of the carpus and metacarpal bones and of the right forearm in the distal portion was made in June 2024: fibrous thickening of the radial side box with adjacent interstitial reticular lymph edema was noted and there were no signs of a residual, recurrent tumor in the superficial adipose tissue.

There was presence of nodular change with signaling values of adipose tissue resembling a fat lobe, with a longitudinal diameter of 1 cm, transverse diameter of 5 mm at a distance from the styloid process within a radius of 5.5 cm.
Since then, the patient has been undergoing regular follow-ups at the Clinic.

So far, there are no evident symptoms/clinical signs/hematological disturbances. The patient's last hemogram in September 2024 had normal reference values of hemoglobin, white blood cells and thrombocytes, with no increased sedimentation rate, LDH or CRP.

Discussion

Most lymphomas in the testicular region are disseminated from extra-testicular lymphomas. In primary testicular lymphoma (PTL), the testis is the only involved site at presentation, with no involvement of other nodes or organs. Compared to ENKTCL of nasal type, primary testicular ENKTCL is much less reported and has a lower age of onset and rapid clinical progression [6].

Our Report on an adult male patient is consistent with the previous reports found in literature, considering the age of onset (a 38-year-old male patient) and the clinical progression and the number of relapses noted despite the given regimens.

As opposed to other types of lymphomas, the treatment for primary testicular NK/T-cell lymphoma is not well established, but radical orchiectomy is the commonest initial therapy, with radiation or chemotherapy used as an adjuvant treatment modality in select cases [7].

Astonishing achievements have been made in the last two decades in our understanding and treatment of NK/T-cell lymphomas. With non-anthracycline and L-asparaginase-containing regimens, up to 90% of good-risk stage I/II patients may achieve durable remission [8].

On the contrary, according to *Zhang WL et al.* [7], all known patients previously described as case reports in literature showed a relapse soon after diagnosis despite aggressive treatment, indicative of an extremely poor prognosis. In our case, the patient's last progression free survival after the last treatment lasted only 3 months, despite the initial remission which was almost a year long.

The poor prognosis of the disease is due to frequent relapses, as well as gastrointestinal bleeding, chemotherapy side effects, and possible CNS involvement, as shown by ongoing clinical studies.

This highly aggressive course and poor prognosis have led some investigators to recommend bone marrow or peripheral stem cell transplantation and consolidation chemotherapy to combat this fatal condition, as proposed by Liang R et all [9]. This option was also considered in our case but was unfortunately declined by the patient.

Conclusion

In conclusion, primary testicular NK/T-cell lymphoma is a very rare, extremely aggressive entity characterized by short periods of remission, i.e., frequent relapses despite intensive surgery, chemotherapy, and radiotherapy approaches.

This case presents detailed clinical and pathological features of a patient diagnosed with ENKTCL to inform and remind diagnosticians and prescribers of appropriate diagnostic approaches. It also aims to encourage further research in order to develop more effective treatment strategies for the purpose of improving survival rates in patients with primary testicular NK/T-cell lymphoma.

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