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Case Report

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Orbital T-Cell Lymphoma – A Challenging Case

Pedro Manuel Baptista[1,2*], Catarina Castro[1], Luísa Regadas[1], Maria Araújo[1]

[1]Ophthalmology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal

[2]Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Porto, Portugal

***Corresponding author**

Pedro Manuel Baptista MD, Centro Hospitalar Universitário do Porto, Largo Prof. Abel Salazar 4099-001 Porto, Portugal. Tel: 00351-917868372. E-mail: pedroyybaptista@gmail.com

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Lymphomas are malignant tumors arising as clonal proliferation of either B-lymphocytes, T-lymphocytes or, less commonly, of natural killer (NK) cells and are divided into 2 major categories, namely Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). While the first is of B-lymphocyte origin, the second is a heterogeneous group of lymphomas of different clonal origin consisting of both B-cell, T-cell and NK-cell lymphomas [1]. Orbital lymphomas constitute 50–60% of ocular adnexal lymphomas and the vast majority are of B-cell origin (97%).

Within the rare prevalence of orbital peripheral T-cell lymphoma PTCL, the most common type is the natural killer T-cell lymphoma (NKTL), accounting for 65% [1]. The extranodal Natural Killer/T-cell lymphoma, nasal type (N-NKTL) is a very rare subtype of NKTL with unique epidemiological, etiologic, histologic, and clinical characteristics. The main clinical course is characterized by a rapid local progressive necrotic lesion in the nasal cavity with subsequent distant metastases [2]. As an angiocentric and polymorphous lymphoreticular infiltrate is the characteristic histological finding, the disease has been previously called polymorphic reticulosis [3]. It is proved that this lymphoma is originated from either NK- or γδ T-cell, both of which express CD56 and the Epstein-Barr Virus (EBV) has been recognized to play an etiological role in N-NKTL and was included as a diagnosis criteria by World Health Organization (WHO) classification [4-7].

When mature PTCL don´t met the WHO criteria for a specific entity diagnosis, they called not otherwise specified (PTCL-NOS). This is a diagnosis of exclusion, comprising several disease entities that differ in biology, clinical presentation, and outcome and accounting for up to 11% of all orbital lymphomas [1].

Case-Report

A 70-year-old woman with previews nasal surgery due to chronic rhinosinusitis came to the emergency department of Centro Hospitalar Universitário do Porto, in May 2017, with complaints of left periorbital edema with one week of evolution (Figure 1). In the previous three months, she had two episodes of orbital cellulitis associated with chronic rhinosinusitis, treated with cycles of oral antibiotic, without complete improvement (patient refused hospitalization). On ophthalmological examination, best corrected visual acuity was 20/20 (Snellen) and there were no signs of chemosis, proptosis or ocular movement limitation. After a CT-scan (Figure 2) and an anterior rhinoscopy, the patient was hospitalized with the diagnosis of acute exacerbation of chronic rhinosinusitis with associated post-septal cellulitis. Intravenous antibiotic and steroids in a tapering scheme were started and, on the 9th day of hospitalization, substantial symptomatic improvement was noted. After complete resolution, the patient was discharged, and an elective review of previous nasal surgery including turbinoplasty and ethmoidectomy was done.

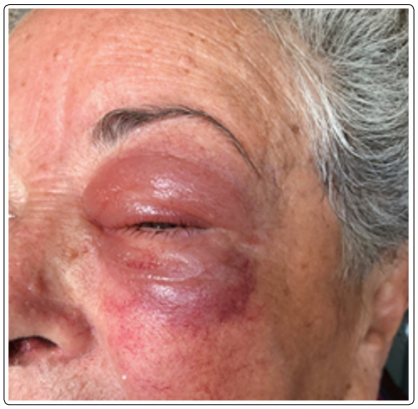

Figure 1: External appearence at first evaluation, with periocular inflamatory signs, May 2017

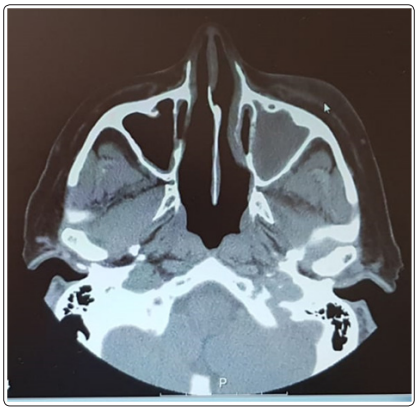

Figure 2: CT-scan at first evaluation, with signals of rhinosinusitis with associated post-septal cellulitis, May 2017

In June 2017, the patient presented with a new mild acute exacerbation and started an ambulatory nine-day course of oral antibiotic and steroids in a tapering scheme. The response was poor and 3 weeks later presented with exuberant periorbital edema, this time with abundant mucopurulent discharge, chemosis and painful but no restricted ocular movements. The patient refused a new hospitalization and was discharged against medical advice with a new course of oral antibiotic and steroids followed by a tapering schedule.

One month later, a new recurrence was seen, this time associated with exuberant left facial edema, proptosis and evident left adduction and elevation restriction. After an eight-day course of intravenous antibiotics and steroids, the control CT-scan showed reduced inflammation but suggested an orbital abscess (Figure 3) that was excluded by a maxillofacial surgeon. On the 14th day of hospitalization, the patient only had elevation restriction and was discharged with a request for a thorough clinical and analytical study with ophthalmology, otorhinolaryngology and maxillofacial surgery appointments.

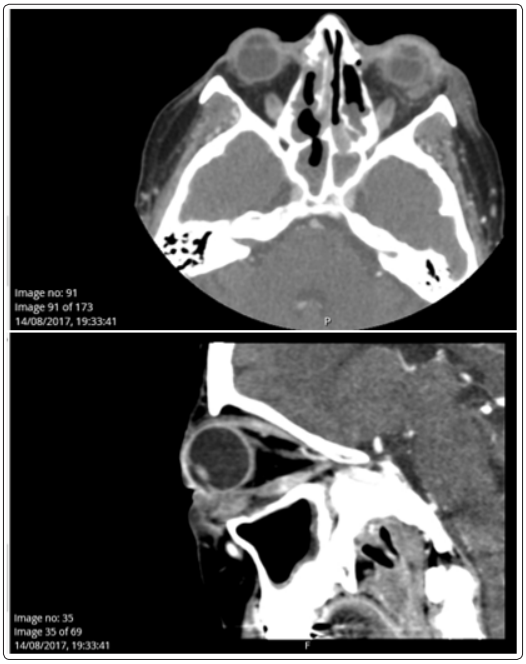

Figure 3: CT-scan suggesting an infraorbital abscess, August 2017

Even before the appointments - October 2017-, the patient returned to the emergency department with complaints of purulent rhinorrhea and edema of the left infraorbital area, with proptosis or chemosis and maintained elevation restriction. On the 9th day of hospitalization with systemic antibiotics and steroids treatment the CT-scan excluded the presence of the suspected infraorbital abscess but highlighted an enlarged inferior oblique muscle, which maintained similar on the 17th day despite overall clinical improvement (Figure 4). At this point some differential diagnosis hypothesis were lifted in a patient with recurrent acute exacerbations of chronic rhinosinusitis associated with cellulitis and with response to antibiotics and steroids: myositis, thyroid eye disease, orbital pseudotumor, IgG4-related disease, infectious process or a neoplastic condition. The patient was forwarded to outpatient clinic follow-up in order to perform an etiologic study. In the ophthalmology appointment 3 weeks later, elevation restriction was maintained, associated with diplopia, with no pain. The thyroid study and serum IgG4 were normal and was decided to perform both an extraocular muscle and nasal polyps' biopsies. The blood counts showed only mild leukocytosis and reactive-C protein elevation.

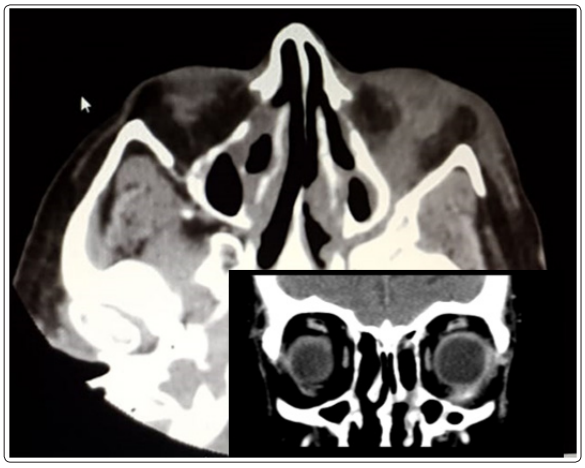

Figure 4: CT-scan, excluded the presence of the suspected infraorbital abscess but highlighted an enlarged inferior oblique muscle, October 2017

During the extraocular muscle biopsy procedure, fibrosis of the inferior rectus was verified and the inferior oblique appeared thick and infiltrated. Despite the material was considered inadequate for proper cytometric analysis, a diagnosis of PTCL-NOS was proposed by the pathologist, as the sample was negative for the CD56 or EBV. (Figure 5). The polyp's biopsy showed no signs compatible with lymphoma. However, a second biopsy was performed and the flow cytometry exam was compatible with a diagnosis of a N-NKTL: 99% of T Lymphocytes were found, with a population (90%) with CD2+, CD5+, CD8+, CD28+, CD38+ and CD56+; cytotoxic granules with T-cell restricted intracellular antigen (TIA-1), granzyme B and Perforin; negative CD4, CD7, CD11, CD16, CD57.

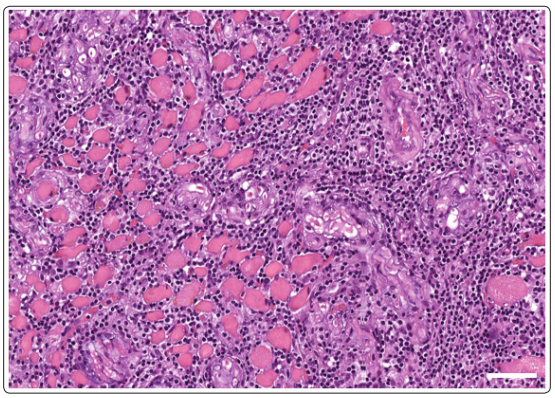

Figure 5: Representative image of peri-ocular muscle extensively infiltrated by neoplastic lymphocytes. Magnification bar = 50 µm. Image kindly provided by the Anatomic Pathology Service, Pathology Department, Centro Hospitalar e Universitário do Porto.

In the neoplasm staging, the PET scan showed an hypercaptation in the left amygdala and two hypermetabolic lesions in the right superior pulmonary lobe. The EBV was negative in the peripheric blood but positive in the cerebrospinal fluid. The thoracic CT-scan showed subpleural parenchymal abnormalities and nodular formations, of millimetric dimensions, without calcifications, in the right superior pulmonary lobe. The bronchofibroscopy showed immunofluorescence with presence of some T lymphocytes with activation characteristics but without the disease phenotype.

A multidisciplinary team meeting was performed to decide the treatment plan and the patient started 20 sessions of 2Gy curative radical radiotherapy in the left periorbital region, with reasonably

good tolerance. The pulmonary changes were monitored with a PET-CT-scan. A whole-body PET-CT-scan of March 2019 (Figure 6) shows good response to the treatment without hypermetabolic foci. The patient is keeping vigilance without evident progression, despite a suspicious focus of elevated metabolic activity described as inflammatory origin in a recent exam (Figure 7). In July 2020, cotton wool spots and hemorrhage areas were detected in the fundoscopy exam. The cystoid macular edema in the spectral domain-optical coherence tomography (Figure 8) and peripheric nonperfusion areas and macular leakage in the fluorescein angiography accounted for the diagnosis of Radiation Retinopathy. The patient underwent Argon laser pan-retinal photocoagulation in the ischemic areas and a cycle of intravitreal Bevacizumab injections (Figure 9). Currently, the ocular status is stable, with BCVA of 20/63 (Snellen), some complaints of dry left eye and periorbitary discomfort in the left side.

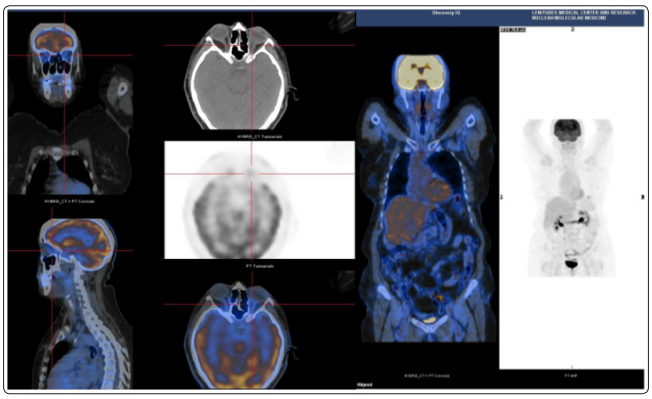

Figure 6: PET-CT-scan, with absense of suspect hypermetabolic foci, March 2019

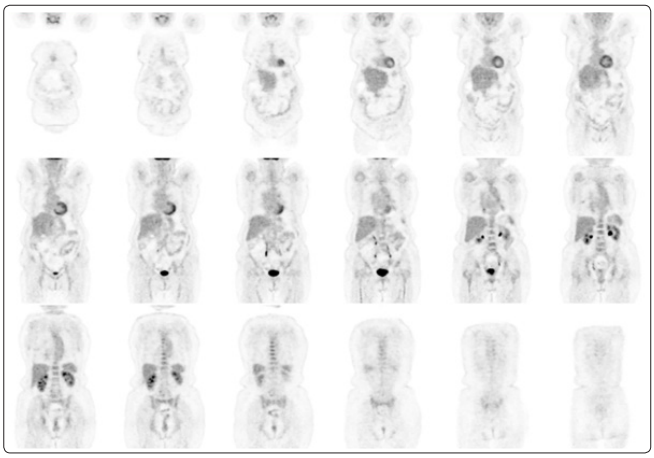

Figure 7: PET-CT-scan, showing a suspicious focus of elevated metabolic activity described as inflammatory origin, February 2020

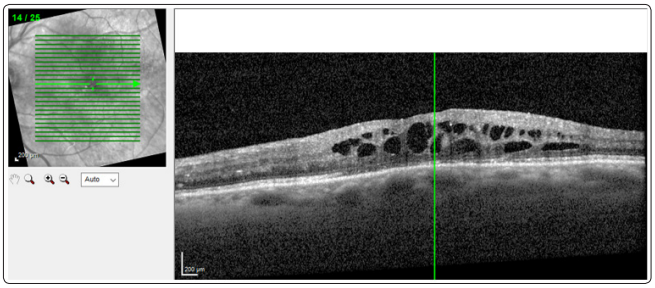

Figure 8: Spectral domain optical coherence tomography showing cystoid macular edema, July 2020

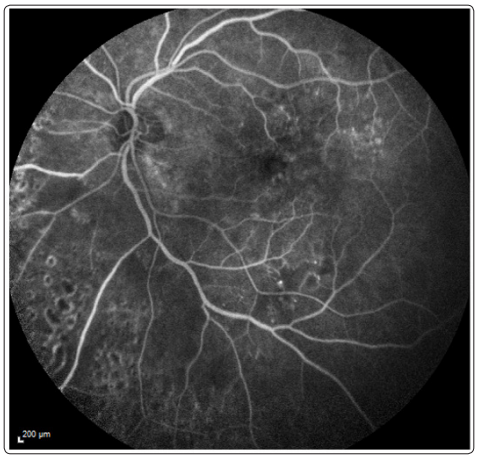

Figure 9: Fluorescein angiography after initiation of panretinal photocoagulation, August 2020

Discussion

Despite very rare, the NKTL and the PTCL-NOS are the two most common orbital T-cell lymphomas. The N-NKTL is a distinctive form of NKTL, more common in Asian populations, initially found as progressive ulceration and necrotic granuloma in the nasal cavity, palate, and nasopharynx with secondary invasion of the rounding tissues such as hard plate, pharynx, facial skin, paranasal sinus, and orbits [5,8]. Then develops extensive destruction of midline structures (lethal midline granuloma), accompanied with metastization for lymph nodes and distant tissues such as liver, lung, digestive tracts, and bone marrow [9].

According to the 2008 WHO classification of lymphoid neoplasms, nasal obstruction, bloody rhinorrhea and B symptoms are the most common symptoms at the time of diagnosis of N-NKTL [7]. The inflammatory component makes the swelling of cheek or orbit, sore throat, and hoarseness also major symptoms of N-NKTL, classically with good response to systemic steroids. In addition, systemic symptoms such as prolonged fever and weight loss are commonly seen. On the other hand, the PTCL-NOS have usually a systemic unspecific clinical presentation, with more or less generalized lymphadenopathy, which can be associated with bone marrow, liver and spleen invasion, but the classical B symptoms are common too and can have typical skin patches.

Although some compatible findings with N-NKTL in the present case, the most distinctive feature was the insidious presentation as a clinical picture of chronic relapsing remitting rhinosinusitis with associated orbital cellulitis, without the typical epistaxis, the midline destructive component or the systemic B symptoms. The overall good response to steroids in the first episodes delayed the diagnosis but the recurrences and the poor response to antibiotics in the absence of corticotherapy raised the suspicion of secondary cause to the recurrent orbital cellulitis, leading to a prompt biopsy indication, despite non-suspect blood counts. Additionally, the extraocular muscles affection described for the N-NKTL was present in this case as a painless ophthalmoparesis [9].

On the histopathologic exam, the N-NKTL tumor is typically composed by small to medium cells CD56+, with occasional large and anaplastic forms and may be mixed with a polymorphic infiltrate of nonneoplastic inflammatory cells. In the late 20th century, EBV has been recognized to play an etiological role in NNKTL, and plasma EBV DNA has been applied as a clinical progression/recurrence marker [5,6]. Actually, the WHO classification requires both EBV positivity and expression of cytotoxic granules or CD59

positivity for the diagnosis of N-NKTL [7]. This is a report of a challenging case: besides typical immunophenotype reported by the flow cytometry exam - classically described as positive for CD2, CD56, and cytoplasmic CD3 epsilon (ε), negative for surface CD3, CD7 and CD16 and with expression of the cytotoxic granule associated proteins granzyme B, TIA-1 and perforin [9]. – histopathologic evaluation of orbital tissue didn't found either EBV or CD56 membrane marker and the polyp´s biopsy showed no signs compatible with lymphoma and classified it as a PTCL-NOS. Additionally, EBV was negative in the peripheric blood but positive in the cerebrospinal fluid.

The challenges in this diagnosis continue. The N-NKTL develops usually in the fifth decade of live, predominantly in men [9]. However, this patient was older and a woman. On the other hand, the diagnosis was made in an early stage, as is described for the majority of patients [9]. Differently from the extra-nasal-NKTL, whose common primary sites involved include the skin, gastrointestinal tract, salivary glands, spleen, and testis and in which distant dissemination occurs early, in the N-NKTL the bone marrow involvement occurs in only less than 10% of patients and distant metastasis are unusual. Regarding the PTCL-NOS, patients often present in an advanced stage, with spread disease and associated skin affection as red patches. Our patient did not show any of these features.

In general, lymphomas are fluorodeoxyglucose-avid and PET-CT have usually high accuracy to define the disease extension by distinguishing lymphoma involvement from inflammatory masses [10]. The present case showed PET-scan alterations compatible with distant metastization in the lungs but with non-confirmed disease phenotype T-lymphocytes after a bronchofibroscopic biopsy.

Both entities have poor prognosis. The PTCL-NOS has in general, an overall 5-year overall survival of 20-30% and anthracycline-based combination chemotherapy remains the most frequently used frontline strategy, with overall response rates of 50-60%, and complete response rates of 20-30% [11]. For the N-NKTL, first -line treatment in localized nasal disease is radiotherapy, with a reported overall response ranged from 60% to 80% with a complete remission rate of 40% 80% and a 5-year overall survival of 40 to 59% [12]. However, despite the excellent initial response to radiotherapy alone, a high relapse rate of around 50% is reported, mostly associated with a radiotherapy dose of less than 45 to 50Gy and radiotherapy planning not assisted by imaging. Local relapses beyond 2 years are uncommon although late relapses have been reported [13,14]. Although the pathology exam did not confirm the flow cytometry proposed diagnosis, the patient was assumed and treated as a local N-NKTL and systemic chemotherapy was postponed. Due to the its rarity, neither a selective prognostic model or a treatment regimen had been consistently studied. Beyond the classic International Prognostic Index (age, stage, serum LDH, performance status and number of extranodal involved sites) developed to predict the prognosis of non-Hodgkin lymphoma, the level of circulating plasma EBV DNA at presentation has been shown to significantly affect disease-free survival in the N-NKTL [15]. The present case was staged as early (stage I/II) and low activity disease and the patient underwent local curative Radiotherapy (cumulative 40Gy dosis) assisted by image in the left periorbital region accompanied by monitorization of the pulmonary changes with a PET-CT. Systemic relapses occur in 25% to 30% of cases, more than half of which is not associated with local recurrences. In light of the high relapse rate with radiotherapy alone, combination of chemotherapy (CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone) and radiotherapy can be done [16].

After 3 years, no signs of local or distant recurrence were observed in the present case. However, Radiation Retinopathy was diagnosed as a side effect, with the need for laser photocoagulation and intravitreal anti-VEGF injections. As aforementioned, the option was not to perform systemic treatment, with proper clinical and PET-CT monitorization. Despite not confirmed, a suspect focus in the lung (PET-CT-scan) was reported after 3 years and is under study.

Conclusion

The PTCL-NOS and the NKTL are the most common orbital T-cell lymphomas. The N-NKTL is a very rare but locally aggressive entity with very unique characteristics. In the present case, besides a non-confirmed diagnosis by the histopathologic exam, the disease was managed as a N-NKTL. A good response was observed to local radiotherapy and the patient is locally disease-free after 3 years, with radiation retinopathy as sequel.

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