Aggressive Nasal Type Extranodal Natural killer/T-cell Lymphoma Presenting as Refractory Granulomatosis with Polyangiitis (Wegener’s Granulomatosis)

Andreea-Alexandra Aldea1, Anca Bojan2, Laura Muntean3, Simona Rednic3

Abstract

Background: Extranodal NK/T-cell lymphoma, nasal type is a locally invasive tumour, including ulcerative and necrotic lesions, preferentially originating in the nasal cavities and sinuses. It can be frequently confused with a localized form of granulomatosis with polyangiitis (GPA, formerly known as Wegener’s granulomatosis), which affects the upper respiratory tract through the same kind of destructive lesions. Case presentation: A 39-year-old man with bilateral nasal obstruction, purulent rhinorrhea, oro-pharyngeal pain, anosmia, halitosis, severe upper dysphagia, and nasal dysmorphism was referred for rheumatologic reevaluation. Over 2 years of evolution, multiple nasal biopsies were performed showing chronic granulomatosus inflammation and necrosis, with no malignant cells. Although antineutrophil cytoplasmic antibodies test was negative, the patient was diagnosed with GPA and treated with corticosteroids and immunosuppressors. The disease worsened progressively, leading to destructive lesions of the naso-sinusal region. A new biopsy revealed this time atypical lymphoid cells. Upon immunohistochemical characterization, the atypical cells showed CD3+ and granzyme B+ phenotype. In addition, Epstein-Barr virus was identified. Thereafter, nasal type of extranodal NK/T-cell lymphoma was confirmed. The patient underwent chemotherapy regimen with favourable outcome.

Conclusion: When evaluating a patient with destructive midline lesions, clinical suspicion for extranodal NK/T-cell lymphoma, nasal type is necessary. Multiple, large enough biopsies and immunohistochemistry studies are helpful for diagnosis.

Keywords: extranodal NK/T-cell lymphoma, granulomatosis with Poliangiitis (GPA), Epstein-Barr virus(EBV), immunohistochemistry
be ANCA negative and sometimes lead to destructive midline lesions\(^1\). Extranodal NK/T-cell lymphoma, nasal type is a serious and in most cases fatal disease, more typical for Asian (China, Japan, Korea, Southeast Asia) and South American (Mexico, Peru, Argentina) populations and very rare between Caucasian patients\(^2\). The rarity of this kind of lymphoma has now been more clearly elucidated as a result of progress in immunohistochemistry (IHC) and molecular biology\(^3\).

### CASE PRESENTATION

A 39-year-old man with bilateral nasal obstruction, f\(\text{e}\)-tid purulent rhinorrhea, oro-pharyngeal pain, oro-nasal regurgitation of liquids, anosmia, halitosis, severe upper dysphagia, and nasal dismorfolism was referred for rheumatologic reevaluation, in July 2017 to the Department of Rheumatology, Cluj-Napoca.
Two years before the admission in our department, in October 2015, at the time of the first symptoms, the patient was referred to the Ear-Nose-Throat Department with progressive nasal obstruction and inflammatory syndrome. The physical and endoscopic examination revealed complete obstruction of the nasal fossa with nasal dysmorphism and degenerated mucosa but no obstruction of the rhinopharynx. The first tissue biopsy was taken with a specimen consisting of left nasal cavity mucosa. The result of the histopathological examination was unclear, which only revealed profuse inflammatory reaction. A diagnosis of chronic sinusitis...
The following three biopsies performed from October 2015 until January 2016 presented solely aspects of reactive lymphoid hyperplasia. However, in March 2016, a new biopsy was taken for a histopathological analysis; the three biopsy specimens consisted of mucosa of each nasal cavity and from the rhinopharynx.

was established and the patient underwent antibiotic and anti-inflammatory therapy, together with nasal decongestants. Head computed tomography scans showed a homogenous soft tissue mass with obliteration of the left nasal cavity and maxillary sinuses and osteolytic lesions of the midline bones.

Figure 4. IHC - Ki67 proliferation marker.

Figure 5. In situ hybridization - Epstein Barr Virus (EBV)-encoded RNA (EBER)
The result in hematoxylin-eosin (H-E) and periodic acid-Schiff (PAS) staining showed, this time, an intense granulocytic infiltrate with the tendency to form granulomas and extensive areas of necrosis, with no malignant cells. The first differential diagnoses taken into account were the following: nasal inflammatory polyp, eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome) and GPA.

The paraclinical investigations showed leukocytosis, anaemia, important inflammatory syndrome (CRP=6.7 mg/dl, ESR=60 mm/h); the bacteriological examination was negative and the blood level of procalcitonin was low. Although ANCA was negative, the histopathologic examination suggested GPA. The patient was treated with oral corticosteroids - Methylprednisolone and immunosuppressors – Azathioprine.

Unfortunately, the disease worsened progressively a few months later. Despite the administration of antibiotics, corticosteroids, addition of Methotrexate and endoscopic aspiration of nasal secretions, rapid destruction of the naso-sinusal region, purulent rhinorrhoea, halitosis, inappetence, fever of 40°C and dehydration occurred. Careful examination revealed granulomatous lesions of the lateral pharyngeal walls with narrowing of the oropharyngeal isthmus. The endoscopic debridement of the invading tissue was unsuccessful.

A group of doctors, consisting of a rheumatologist, otorhinolaryngologist, hematologist and a pathologist cooperated to establish the possibility of a midline localization of the necrotic lesions with nasal soft tissue and bone invasion appear both in GPA and in extranodal NK/T-cell lymphoma, nasal type.

Another similar case report, published in The American Journal of the Medical Sciences, presented the case of a patient with recalcitrant periodontitis, who underwent multiple histopathological examinations which suggested GPA. Eventually, the final biopsy together with the phenotypic markers pointed toward a diagnosis of extranodal, nasal type NK/T-cell lymphoma. Another study compared the clinical course of patients diagnosed with sinonasal T-cell lymphoma with other recently treated patients with GPA in the upper airways and asserts that clinically, it may be almost impossible in the early stages of the disease to differentiate between T-cell lymphoma, GPA and non-specific chronic inflammation. One third of the T-cell lymphoma patients had a history of persistent „chronic rhinitis” for several years before the disease evolved into an ulcerative stage. What led to further diagnostic dilemma in our case was the missing ANCA, which is usually a characteristic marker for GPA, but still not detectable in a quarter of patients with limited GPA.
Ki67 is a proliferation marker, firmly associated with tumor cell proliferation and growth and is correlated with tumor aggressiveness. The expression of Ki67 was found in our case and was a diagnostic and prognostic marker.

Third, what indicates a diagnosis other than GPA, is the non-response to Azathioprine and the rapidly, progressively deterioration of the patient’s clinical course. The medical literature presents a large spectrum of differential diagnoses for destructive midline lesions. GPA, Churg Strauss syndrome, sarcoidosis, systemic lupus erythematosus, Sjögren's syndrome, syphilis, as well as cocaine abuse are just a few of them. Despite diagnostic advances and improved understanding of the disease, an etiology is often not identified. Therefore, a multidisciplinary collaboration between rheumatologists, otorhinolaryngologists, hematologists and experienced pathologists is required.

Take home messages
- A nasal obstruction with purulent rhinorrhea and destructive midline lesions may be the initial signs of the extranodal, nasal type, NK/T-cell lymphoma under the mask of a GPA.
- Multiple, large enough biopsies, immunohistochemistry studies and appropriate serological tests are the key in finding the correct diagnosis.
- The finding of EBV in the tumoral cells is an essential part in the diagnosis of NK/T-cell lymphoma.

Acknowledgements:
The authors want to thank Dr. Bogdan Fetica from Oncologic Institute „Prof. Dr. Ion Chiricuța”, Cluj-Napoca, Department of Pathological Anatomy for providing the biopsy and immunohistochemistry images from Figure 1-5.

Compliance with ethics requirements:
The authors declare no conflict of interest regarding this article.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.
References
