

Extranodal T-Cell Lymphoma of the Sinonasal Tract Presenting as Severe Rhinitis: Case Series

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ABSTRACT

Objectives: Systemic diseases such as Wegener granulomatosis, Churg-Strauss syndrome, and sarcoidosis can present initially as severe rhinitis alone. One clinical entity that mimics severe rhinitis and thus poses a particular challenge in this regard is extranodal T-cell lymphoma of the sinonasal tract. Sinonasal lymphoma has a vague initial presentation that masquerades as more common, benign causes of rhinitis but progresses as a "midfacial progressive destructive lesion" and is uniformly fatal if untreated. In the absence of systemic involvement, the precise etiology frequently defies diagnosis. We present a series of illustrative cases to raise awareness of this rare yet lethal disease to help reduce the therapeutic delays that are currently encountered clinically.

Methods: A retrospective case series of four patients was reviewed. Each patient presented initially with severe rhinitis but was later diagnosed with extranodal natural killer/T-cell non-Hodgkin lymphoma of the sinonasal tract.

Results: The predominant presenting symptoms were unilateral nasal obstruction (four patients), rhinitis (three patients), and facial pain (two patients). Only one patient reported systemic B symptoms. Initial management of all four patients included repeated biopsies revealing nonspecific inflammation, which resulted in extensive therapeutic delays (mean time until diagnosis 21.5 months). The primary outcomes were two deaths and two complete remissions.

Conclusion: The challenge in making an early diagnosis of T-cell lymphoma of the sinonasal tract has been reaffirmed in our case series. We emphasize that diagnosis requires a high index of clinical suspicion in combination with multiple deep and appropriately processed biopsies that are submitted for immunohistochemistry and molecular studies.

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Objectifs: Les maladies systémiques tel la granulomatose de Wegener, la maladie de Churg-Strauss, et la sarcoïdose peuvent présenter dans une forme limitée au vois nasosinusiennes. Une entité clinique qui mimique également la rhinite sévère et qui pose ainsi un défi diagnostique particulier est le lymphome a cellule T en situation extra nodale. La présentation clinique initiale du lymphome nasosinusal se caractérise par une symptomatologie non-spécifique qui se confond initialement avec d'autres formes plus bénignes de rhinite mais qui progresse ensuite a une forme plus sévère, 'la lésion destructive du tiers moyen du visage, qui est usuellement fatale si non traité. Nous présentons une série de cas a titre d'exemple afin de rehausser les re connaissance de cette entité rare mais létal afin de réduire les délais thérapeutiques qui surviennent usuellement en pratique.

Méthode: Révision rétrospective d'une série de quatre cas. . Chaque patient a présenté initialement avec une rhinite sévère pour ensuite avoir un diagnostique tardif de lymphome non-Hodgkinien a cellule T des voies nasosinusiennes.

Résultats: Le mode de présentation était l'obstruction nasale (quatre patients), une rhinite (trois patients) et de la douleur faciale chez deux patients. Un seul patient rapportait des symptômes de type B. Les biopsies multiples réalisées lors de la prise en charge des quatre patients n'ont démontré qu'une inflammation non-spécifique, ce qui a occasionné un délai moyen de 21.5 mois avant l'établissement du diagnostique approprié. Deux patients sont décédés et deux sont en rémission complète.

Conclusion: Nous réaffirmons le défi d'obtenir un diagnostique précoce de lymphome a cellule t des voies nasosinusiennes. L'établissement du diagnostique approprié nécessite un degré de suspicion clinique élevé en combinaison avec des biopsies profondes qui sont évalués par immunohistochimie et études moléculaires appropriées pour l'évaluation du lymphome.

Key words: extranodal non-Hodgkin lymphoma, severe rhinitis, sinonasal tract

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Severe inflammation of the sinonasal mucosa can be a vastly challenging entity for otolaryngologists, and the precise etiology frequently defies accurate diagnosis. Although it is well recognized that various systemic diseases, such as Wegener granulomatosis, Churg-Strauss syndrome, and sarcoidosis, can present locally as severe rhinosinusitis alone, the diagnosis of these conditions is particularly difficult in the absence of systemic involvement, even when the appropriate diagnostic modalities are applied.

The recognition of extranodal non-Hodgkin lymphoma of the sinonasal tract is especially challenging in this regard. This disease typically presents focally in a vague manner and masquerades as more common, benign causes of rhinosinusitis until much later in its progression.^{1,2} As a result, an early diagnosis is both elusive and unusual.³ Furthermore, its indistinct presentation often leads to repeated inadequate biopsies and inappropriate ablative procedures. Therapeutic delays ultimately ensue, permitting the neoplasm to progress to a fatal end-stage disease in the majority of patients who suffer from it.⁴

In this article, we present a case series of four patients who were each referred initially to Otolaryngology for severe rhinitis but who were ultimately diagnosed with extranodal lymphoma. Our primary objective is to raise the clinical awareness of extranodal natural killer cell or T-cell (NK/T) lymphomas of the sinonasal tract through an illustration of our institutions' recent experience with this disease. In addition, we offer strategies to facilitate and expedite the diagnosis of this rare yet lethal condition to help abolish the therapeutic delays that are currently being encountered clinically.

Materials and Methods

A retrospective review was conducted. Patients with a diagnosis of primary sinonasal lymphoma were included if they met the following criteria: initial and predominant symptoms related to the sinonasal area; diagnostic tissue obtained from the nasal cavity, sinuses, or a site of regional dissemination; and no prior history of lymphoma. Demographic data, initial signs and symptoms, clinical management, time from presentation until diagnosis, stage, and outcome were determined for each of the four patients. Patients were staged according to the Ann Arbor Classification system for malignant lymphomas.

Results

Four patients were diagnosed with extranodal NK/T-cell non-Hodgkin lymphoma of the sinonasal tract between

2002 and 2006. The clinical information of all patients is presented in Table 1. Our case series consisted of two males and two females who ranged in age from 36 to 56 years (mean 47.8 years). The predominant presenting symptoms were unilateral nasal obstruction (four patients), rhinitis (three patients), and facial pain (two patients). Other documented symptoms were epistaxis (one patient), rhinorrhea (one patient), and dysphagia or hoarseness (one patient). Only one patient reported systemic B symptoms defined as more than 10% weight loss, greater than 38.5°C fever, and the presence of night sweats. No patient demonstrated involvement of the central nervous system.

On examination, the gross appearance of the primary lesion and surrounding diseased tissue was consistently described as a crusted lesion with a friable and erythematous base. Facial and periorbital edema were identified in one patient. The primary extranodal site of the lymphoma was found to be the nasal septum (two patients), the lateral wall and inferior or middle turbinates (one patient), or the nasopharynx and larynx (one patient). None of the cases of primary non-Hodgkin lymphoma were found within the paranasal sinuses.

Initial management included cultures of the diseased nasal mucosa and multiple superficial biopsies yielding nonspecific inflammation in each of the four cases. Endoscopic sinus surgery was performed on three patients, in combination with either septoplasty (one patient) or endoscopic débridement (one patient). The remaining patient was not offered surgical therapy. The mean time until diagnosis was found to be 21.5 months and ranged from 18 to 24 months from the time of initial presentation to an otolaryngologist.

According to the Ann Arbor Classification of non-Hodgkin lymphoma and after thorough evaluation, two patients were staged as IE, one patient as stage IIIES, and one patient as stage IVE. The treatment of all patients involved a multidisciplinary team approach consisting of otolaryngologists, pathologists, and both medical and radiation oncologists. The treatment protocol in this series involved radiotherapy and anthracycline-based chemotherapy (CHOP; cyclophosphamide, doxorubicin hydrochloride, Oncovin [vincristine], prednisolone) with or without the addition of methotrexate.

The primary outcomes were two complete remissions (follow-up period of 4 months and 54 months) and two deaths related to intercurrent disease (neutropenic sepsis and pneumonia) within 5 months of diagnosis.

Table 1. Characteristics of patients with lymphoma of the nasal cavity and paranasal sinuses

Patient ID	Age (yr) and Gender	Signs and Symptoms	Management	Histology	Primary Site	Time until Diagnosis (mo)	Stage	Treatment	Course
1	36 F	L nasal obstruction	Biopsy × 2	NK/T-cell lymphoma	Nasal septum	20	IE	CHOP XRT	Complete remission × 4.5 yr
2	49 M	L nasal obstruction, polypoid, dysphagia, hoarseness, B symptoms Friable mucosa with crusting	Cultures Biopsy × 3 FESS	NK/T-cell lymphoma	Nasopharynx L + R TVC	18	IIIES	CHOP/MTX XRT	Died of disease 5 mo after diagnosis
3	56 M	L nasal obstruction, rhinorrhea, epistaxis, facial pain Crusted lesion, erythematous base	Cultures Biopsy × 2 FESS Septoplasty	NK/T-cell lymphoma	L middle turbinate	24	IE	CHOP XRT	Complete remission × 4 mo
4	50 F	R nasal obstruction, sinusitis, facial pain + abscess/edema R parotid adenopathy	Cultures Amphotericin IV Biopsy × 6 FESS × 6 Débridement × 3	NK/T-cell lymphoma (EBV positive)	Nasal septum	24	IVE	CHOP XRT	Died of disease 2 mo after diagnosis

CHOP = cyclophosphamide, doxorubicin hydrochloride, Oncovin [vincristine], prednisolone; EBV = Epstein-Barr virus; FESS = functional endoscopic sinus surgery; MTX = methotrexate; NK = natural killer; TVC = true vocal cords; XRT = chemotherapy.

Discussion

Lymphoma is defined as a malignant neoplasm of lymphoreticular origin.⁵ Non-Hodgkin lymphomas comprise 60% of all lymphomas of which there are B-cell and T-cell subtypes.⁵⁻⁷ Sinonasal non-Hodgkin lymphoma is a rare form of extranodal lymphoma in the Western population, representing less than 0.5% of all cases.⁸ This contrasts with the endemic prevalence in Asian countries, where the sinonasal tract is the second most common site of extranodal lymphoma.^{9,10} Epstein-Barr virus is believed to be primarily responsible for this higher prevalence, although the specific role of this virus remains unclear. The nasal cavity is the most common primary site of T-cell sinonasal lymphomas, whereas the paranasal sinuses contain the majority of the B-cell neoplasms.¹¹

Because non-Hodgkin lymphoma of the sinonasal tract develops gradually within a confined anatomic space, the initial signs and symptoms of this disease are known to be subtle and seemingly benign, mimicking those of non-specific rhinitis or sinusitis.^{1,2} The earliest chief complaint of patients has been demonstrated to be either unilateral nasal obstruction (76% of cases) or epistaxis (20%).¹⁰ It is only once the neoplasm reaches a considerable size and degree of involvement of the adjacent anatomic structures that a more alarming and revealing clinical picture evolves. This spectrum often includes periorbital or facial swelling, pain, and visual disturbances. Systemic B symptoms are relatively rare throughout the progression of the disease, implicated in only 4% of all cases.¹⁰

On examination of the patient, the primary lesion is typically grey-yellow in colour and classically appears as a crusted lesion on a friable, granular surface that is extensively necrosed. Nasal septal perforation is also reported as a common finding, but the general condition of the patient usually remains surprisingly good.⁸ It is because of this obscure and indistinct presentation that the diagnosis of NK/T-cell lymphoma of the sinonasal tract is so intangible. An early diagnosis is said to be highly unusual.³

The progression of NK/T-cell non-Hodgkin lymphoma emulates that of a "midfacial progressive destructive lesion" or of a "lethal midline granuloma."^{3,8} These are old umbrella terms that encompass a broad spectrum of neoplastic and non-neoplastic entities that evolve as progressive (and frequently fatal) ulceration of the midface and upper airway region, often in the absence of systemic involvement. The differential diagnosis of this syndrome includes Wegener granulomatosis, malignant lymphoma, Churg-Strauss syndrome, microscopic polyangiitis, and

drug abuse. NK/T-cell lymphoma can be differentiated from these other conditions only through a series of adequately taken and processed biopsies that are evaluated with specific immunohistochemical and molecular studies.

A recent retrospective review has demonstrated the importance of these techniques in the diagnosis of sinonasal lymphoma. This study included seven patients who were previously assigned a "wastebasket" diagnosis of "idiopathic midline destructive disease" lacking a discernible etiology and characterized by the pathologic hallmark of nonspecific inflammation and necrosis in the absence of identifiable malignant cells. When the previously acquired tissue specimens were reviewed using newly available immunohistochemical markers, all of the seven cases were unified into two distinct pathologic groups: Wegener granulomatosis and non-Hodgkin T-cell lymphoma.⁸

Generally, biopsies obtained in cases of sinonasal T-cell lymphoma are repeatedly inadequate because the involved mucosal tissue is so largely necrotic and inflammatory lymphocytes are so readily interspersed with atypical lymphoma cells that the recognizable malignant cells become highly scarce and difficult to identify through biopsy alone (Figure 1).¹² Thus, to accurately make the diagnosis, multiple (three or more) deep biopsies are required. The samples should be submitted fresh and unfixed, and immunohistochemistry (markers CD45 and CD45RO)¹³ with or without in situ hybridization (to

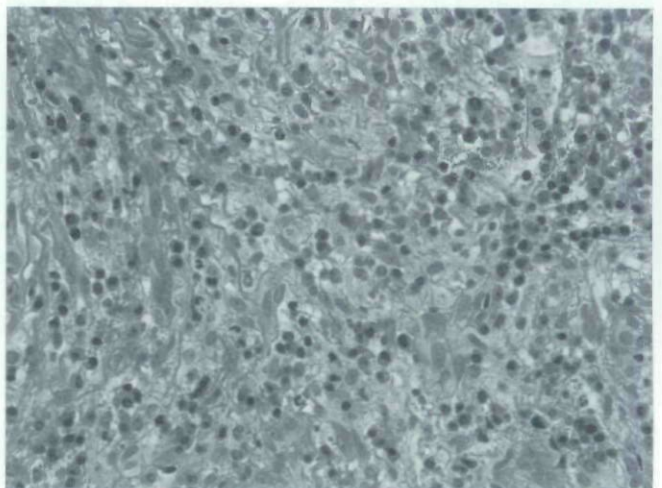


Figure 1. Microphotograph of a biopsy specimen of non-Hodgkin's lymphoma from this series. Note the abundant lymphocytic cell infiltrate characteristic of these lesions (hematoxylin-eosin stain, $\times 40$ original magnification).

demonstrate Epstein-Barr virus within the cell genome) is necessary for pathologic diagnosis.

Imaging is nonspecific for the diagnosis of sinonasal non-Hodgkin lymphoma, despite its classic appearance as a bulky tumour with bony and cartilaginous erosion of the sinus walls, nasal septum, and hard palate (Figure 2), in addition to sinus opacification and mucosal thickening.³ Because other potential diagnoses appear in an analogous manner, computed tomography and magnetic resonance imaging are primarily used for staging of the lymphoma and for monitoring its progression either locally (intraorbital or intracranial extension) or systemically. Imaging should not be relied on for diagnostic purposes.

Conclusions

Extranodal non-Hodgkin T-cell lymphoma of the sinonasal tract is a rare disease in North America, yet the challenge in making an early diagnosis of this lethal

neoplasm is well recognized and has been reaffirmed in this small case series. As we have demonstrated in this study, sinonasal lymphoma has an indistinguishable early presentation that mimics that of other causes of severe rhinitis and ultimately leads to extensive delays in its diagnosis and in the initiation of appropriate therapy.

The majority of undiagnosed, progressive destructive midfacial lesions prove to be either Wegener granulomatosis or non-Hodgkin T-cell lymphoma. The differentiation of these conditions can be made only with a high degree of clinical intuition in combination with multiple deep and adequately processed biopsies. The biopsies should be submitted fresh and unfixed, and the treating physician must insist on the application of immunohistochemistry with or without in situ hybridization to accurately make the diagnosis. Sinonasal non-Hodgkin NK/T-cell lymphoma has an aggressive clinical course and is uniformly fatal when untreated.⁴ But if a treatment regimen of chemotherapy and local radiation is initiated prior to malignant dissemination, a 45% 5-year survival rate can be achieved.¹⁴

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Figure 2.

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