Extranodal NK/T-cell lymphoma, nasal type: Report of 15 cases

Lymphome T/NK nasal. À propos de 15 cas


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KEYWORDS
Malignant lymphoma; Extranodal NK/T-cell lymphoma; Nasal lymphoma; Radiotherapy; Chemotherapy

Summary
Objectives: To define the epidemiological and clinical features and complementary investigation findings of extranodal NK/T-cell lymphoma, nasal type and to discuss the diagnostic difficulties and the various treatment options.

Patients and methods: This retrospective study was based on 15 patients with extranodal NK/T-cell lymphoma, nasal type, managed between 1990 and 2009.

Results: This series comprised 13 men and two women (sex ratio = 6.5) with a mean age of 52 years (range: 35–81 years). The mean time to first consultation was 6 months. The most common symptoms were nasal obstruction (87%) and purulent nasal discharge (73%), followed by epistaxis (60%). Physical examination demonstrated the presence of a tumour of the nasal cavity in 11 patients. The diagnosis was confirmed by histological examination of a biopsy completed by immunohistochemistry. CT scan of the facial bones was performed in all patients of this series. The site of extranodal NK/T-cell lymphoma was essentially nasal (12 cases). Orbital extension was observed in four cases, associated with intracranial extension in two cases and osteolysis was observed in 11 patients. Lymphomas were classified as stage IE in 74% of cases and stage IIE in 26% of cases. Only one patient was lost to follow-up during treatment. Three patients died before any treatment. Treatment therefore concerned 12 patients. Stage IE lymphomas were treated by radiotherapy and/or chemotherapy. All stage IIE lymphomas were treated by chemotherapy alone. Stage IE patients had a better prognosis.

Conclusion: Extranodal NK/T-cell lymphoma, nasal type, is an aggressive form of non-Hodgkin’s lymphoma comprising specific clinicopathological characteristics. The addition of chemotherapy for advanced stages does not appear to improve survival compared radiotherapy alone, which remains the treatment of choice especially for localized stages.

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Introduction

Previously known as lethal midline granuloma, extranodal NK/T-cell lymphoma, nasal type (ENKL) is a serious and
generally fatal disease. Extranodal NK/T-cell lymphoma, nasal type, is a clinical entity causing necrosis, preferentially starting in the nasal cavities and progressively invading mid-facial bones, causing centrifugal destruction of the facial bones with no tendency to healing.

Extranodal NK/T-cell lymphoma, nasal type is a rare disease [1], which has now been more clearly elucidated as a result of progress in immunohistochemistry and molecular biology.

The pathogenesis of this disease is unknown, but it is related to Epstein-Barr virus (EBV) infection, which is associated with a poor prognosis [1].

A retrospective review of 15 patients with extranodal NK/T-cell lymphoma, nasal type, was conducted in order to define the epidemiological and clinical features and complementary investigation findings of extranodal NK/T-cell lymphoma, nasal type, and to discuss the diagnostic difficulties and the various treatment options.

Patients and methods

This retrospective study was based on 15 patients with extranodal NK/T-cell lymphoma, nasal type, managed in the department of Otolaryngology-Head and Neck Surgery of Rabta hospital in Tunis over a 20-year period (January 1990–December 2009).

All patients in whom the diagnosis of extranodal NK/T-cell lymphoma, nasal type, was confirmed on histology and immunohistochemistry were included in this study and all histological slides labelled as midline granuloma were systematically reviewed.

All information available in medical files, including epidemiological and clinical data results of complementary investigations and treatment modalities, was collected and analysed.

The mean follow-up of this series was 13.6 months (range: 2–62 months).

Results

This series comprised 15 patients, most of whom (11 patients, i.e. 73% of the series) were diagnosed between 1999 and 2006, i.e. a mean of one case per year. A marked male predominance was observed, with a sex ratio of 6.5 (13 M/2 F). The mean age of patients in this series was 52 years (range: 35–81 years) and the mean time to first consultation was 6 months.

The presenting complaint in the majority of cases (13 patients) was nasal obstruction associated with purulent nasal discharge (11 patients) and epistaxis (nine patients). Two patients presented decreased visual acuity, while one patient presented with blindness. Upper dysphagia with a history of aspiration was reported by two patients due to tumour extension into the oropharynx. Five patients presented marked alteration of performance status with fluctuating fever in two cases.

Inspection of the face revealed the presence of a malar swelling in two patients and a mandibular swelling in only one patient. Hemifacial oedema was observed in two patients and deformity of the nasal pyramid was observed in four patients. Exophthalmos was noted in three patients, associated with chemosis in two patients (Fig. 1a).

Nasal endoscopy, performed in all patients, demonstrated an ulcerative and necrotic, friable and haemorrhagic tumour filling the nasal cavities in 11 patients, while no abnormality was detected in the other patients. The tumour was responsible for deviation of the nasal septum in three cases.

Examination of the oral cavity and oropharynx demonstrated necrotic ulceration of the mucosa of the hard palate in three cases, resulting in an oronasal communication in one case (Fig. 1b).

Cervical lymphadenopathy was demonstrated in three patients. A cranial nerve lesion was observed in four patients, comprising concomitant lesions of the 2nd, 3rd, 4th and 5th cranial nerves in one patient.

Biopsies were performed in all patients and histological examination completed by immunohistochemical study confirmed the diagnosis of extranodal NK/T-cell lymphoma, nasal type, in every case.

Histological examination demonstrated lymphomatous invasion of the lamina propria composed of sheets

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Figure 1

a: left exophthalmos with chemosis; b: necrotic ulceration of the mucosa of the hard palate.
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Figure 2  A. Great lymphomatous cells with clear cytoplasm (HE × 10). B. Tumour cells destroying the vessel walls (HE × 25).

of medium-sized to large cells with clear cytoplasm (Fig. 2a). Tumour cells were sometimes arranged in “angiocentric” perivascular cuffs destroying the vessel wall (“angiodestructive”) with haemorrhagic suffusions and tumour necrosis (Fig. 2b).

Immunohistochemical examination demonstrated, in every case, intense and diffuse positive cytoplasmic staining of tumour cells by anti-CD3 antibody and negative staining for anti-CD20 antibody and cytokeratin. CD56 staining was positive for all patients, while CD30 (performed in nine cases) was positive in only six patients (Fig. 3).

Computed tomography (CT) of the facial bones was performed in all patients, completed by magnetic resonance imaging (MRI) in four patients. The NK/T-cell lymphoma was essentially located in the nasal cavity (12 patients). Sinus involvement concerned the ethmoid sinus in seven patients, the maxillary sinus in six patients, the frontal sinus in three patients and the sphenoid sinus in only one patient.

Orbital extension was observed in four patients, associated with intracranial extension in two patients (Fig. 4). Extension to the nasopharynx was present in three patients, associated with extension to the oropharynx in two patients. Osteolysis was demonstrated in 11 patients. Soft tissue invasion was demonstrated in five patients, involving the malar mucosa in two patients, premandibular soft tissues in one patient (Fig. 5) and frontal subcutaneous soft tissues in one patient.

Patients were staged according to the Ann Arbor classification (Table 1) as stage IE in 11 cases (73%) and stage IIE in four cases (26%). Three patients died before initiation of treatment in a context of septic shock.

Radiotherapy alone was performed for four patients with stage IE disease. Combined treatment (radiotherapy and chemotherapy) was administered to four patients with diffuse stage IE, while cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy alone was administered in four patients: three stage IIE patients and one patient with diffuse stage IE disease.

Most patients had a poor outcome and nine patients died: two during radiotherapy, one during chemoradiotherapy and three during chemotherapy. Only four patients are in clinical remission with a mean follow-up of 46 months.

Follow-up head and neck CT scan was performed in seven patients, demonstrating complete radiological eradication of the lesions in four cases. Progressive disease was
observed in only one patient in this series. This patient had received radiotherapy for a very large space-occupying naso-ethmoido-frontal lesion with orbital and intracranial extension, followed by intensive chemotherapy. This patient currently presents stable disease after the 4th cycle of chemotherapy.

The mean follow-up of this series was 13.6 months (range: 2–62 months).

Discussion

Extranodal NK/T-cell lymphoma, nasal type, is a clinical entity 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%), the oral cavity (14%), larynx, hypopharynx (10%) and even in the mandible or cheek [2].

The incidence of extranodal NK/T-cell lymphoma, nasal type, varies considerably in different parts of the world, but it remains a rare disease since the first description in 1933. However, the number of new cases per year is on the increase due to a better knowledge of this disease. Extranodal NK/T-cell lymphoma, nasal type, represents 45% of all primary nasal lymphomas, while T-cell lymphoma represents only 21% of all primary nasal lymphomas [3].

Extranodal NK/T-cell lymphoma, nasal type, can occur at any age, but essentially affects subjects during the fourth and fifth decades [1]. The mean age of the patients in our series was 52 years (range: 35–81 years).

Extranodal NK/T-cell lymphoma, nasal type, is more frequent in men and the sex ratio varies between 2 and 4.5 in the literature [4, 5] with a sex ratio of 6.5 in our series.

The pathogenesis of extranodal NK/T-cell lymphoma, nasal type, is unknown. However, it is strongly associated with Epstein-Barr virus (EBV) infection [1]. EBV infection is associated with a poor prognosis with a high local recurrence rate, possible extension to other extranodal areas and development of macrophage activation syndrome [5], the most dreaded complication that occurs in 8 to 12% of cases due to secretion of cytokines by tumour cells, frequently inducing systemic symptoms such as fever and weight loss [5].

Some studies have attributed these lymphomas to overexpression of protein p53, possibly associated with a p53 gene mutation, often induced by the presence of EBV [6].

Extranodal NK/T-cell lymphoma, nasal type, is a rare disease characterized by polymorphic clinical features that can account for the diagnostic difficulties and the frequently delayed management, as the clinical presentation of this disease is non-specific and can often be misleading, resulting in an incorrect diagnosis. This misleading appearance was observed by Kyrmizakis et al. [7] in their series of three
cases, in which extranodal NK/T-cell lymphoma, nasal type, was initially mistaken for chronic sinusitis.

Most patients present a localized lesion with nasal obstruction caused by an aggressive tumour invading the sinuses, palate and nasal cavities [8]. Symptoms consist of non-specific nasal symptoms (epistaxis, nasal obstruction, nasal discharge), dysphagia, hemifacial pain or facial oedema [4]. Twenty to 40% of cases present a disseminated form consisting of generalized granulomatosis with cutaneous, subcutaneous, ocular, gastrointestinal, lung and nerve involvement [5,9,10].

It is now generally accepted that a large number of biopsies must be performed to confirm the diagnosis of extranodal NK/T-cell lymphoma, nasal type [11]. The histological features of NK/T-cell lymphoma are similar regardless of the site of the lesion [5,10], consisting of sheets of atypical small, medium-sized, large or giant Sternberg-like cells.

The characteristic feature of extranodal NK/T-cell lymphoma, nasal type, is the presence of vascular lesions with tumour cells arranged in perivascular (angiocentric) cuffs, with occasional penetration of these cells across the vessel wall and proliferation in the lumen, causing vascular thrombi (angiodestructive lesions). Areas of necrosis and fibrosis are observed, with marginal pseudoeplitheliomatous hyperplasia of the nasal mucosa [12].

Immunophenotyping reveals expression of T lymphocyte as well as NK lymphocyte cell markers, hence the term: extranodal NK/T-cell lymphoma [13]. The most typical immunophenotype of extranodal NK/T-cell lymphoma, nasal type, is: CD2+, CD56+, which is the specific marker of NK, cells with intracytoplasmic expression of anti-CD3 antibody and negative expression of CD3 on the cell surface [14].

EBV can be detected in tumour cells in the great majority of cases, as confirmed by several immunolabelling and molecular biology studies [15].

Cytogenetic studies have concluded on the presence of a variety of cytogenetic aberrations, such as mutation of the Fas and p53 tumour suppressor genes [16]. However, the most common cytogenetic abnormality is a deletion in the q21 q25 region or the p10 region of chromosome 6.

Computed tomography is the essential examination for investigation of extranodal NK/T-cell lymphoma, nasal type. It allows precise staging of the lesions by defining the tumour site, the presence of osteolysis and possible extension to adjacent structures [17]. It is also essential for pretreatment evaluation, assessment of the response to treatment and follow-up.

MRI more reliably demonstrates soft tissue invasion, as it is able to distinguish inflammation and soft tissue oedema from tumour invasion. MRI shows a lesion with a homogeneous low to intermediate intensity signal, which is isointense to muscles on T1-weighted sequences and moderately hyperintense to muscle on T2-weighted sequences and hypointense to mucus. Gadolinium enhancement is also moderate and heterogeneous and is useful to evaluate the anatomical relations of the tumour with intracranial structures [1].

The laboratory work-up is non-specific and of little value for the positive diagnosis of this disease [18].

When the diagnosis of extranodal NK/T-cell lymphoma, nasal type, has been confirmed, a staging assessment must be performed prior to any treatment, comprising physical examination looking for superficial lymph nodes, hepatomegaly or splenomegaly, chest x-ray, abdominal ultrasound, chest and abdomen CT, bone marrow biopsy, gastrointestinal endoscopy and possibly lumbar puncture in the presence of a lesion of the skull base [18].

Despite progress in immunohistochemistry and molecular biology, extranodal NK/T-cell lymphoma, nasal type, still remains a diagnosis of exclusion due to the absence of any specific clinical and histological features. Many diseases can present in the form of nasal and mid-facial ulceration and destruction, similar to that caused by extranodal NK/T-cell lymphoma [19], such as Wegener's granulomatosis, syphilis, tuberculosis, other malignant tumours and cocaine abuse.

Table 1  Ann Arbor staging.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region</td>
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<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site, hilar lymph nodes are each counted as a site)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of several lymph node regions on both sides of the diaphragm</td>
</tr>
<tr>
<td>E designation, when applicable, to stages I, II or III</td>
<td>Extranodal disease contiguous to lymph node involvement that can be encompassed within an irradiation field; different from the disseminated nature of stage IV disease</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement</td>
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<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>No symptoms</td>
</tr>
<tr>
<td>B</td>
<td>At least one of the following symptoms</td>
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<tr>
<td></td>
<td>Unexplained weight loss of &gt;10% of body weight during the 6 months before staging investigation</td>
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<td></td>
<td>Unexplained fever with temperatures &gt;38 °C for at least 7 days</td>
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<td>Drenching night sweats</td>
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The treatment of extranodal NK/T-cell lymphoma, nasal type, is difficult and complex. Some authors consider that surgery is ineffective and may even cause deterioration of the lesions by inducing rapid progression of the disease. Surgical resection of the lesions has been proposed, essentially for diagnostic purposes, but also to promote drainage of necrotic cavities.

External beam radiotherapy with a minimum dose of about 52 Gy delivered according to classical fractionation is recommended for localized stages (stages I and II) [5]. It achieves complete remission in 40 to 80% of cases with a 5-year overall survival of between 40 and 59% [20]. Aggressive chemotherapy is the only available treatment option for advanced forms (stage III and IV), inducing a complete response in less than 15% of cases [21]. According to the study by Hatta et al. [22], CHOP chemotherapy in combination with radiotherapy is ineffective for advanced extranodal NK/T-cell lymphoma, nasal type, beyond stage IIE and stage B NK/T-cell lymphoma. This combination could also significantly improve survival in stage IE and IIE NK/T-cell lymphoma [21].

Other so-called "salvage" chemotherapy protocols are sometimes used in the absence of response to first-line chemotherapy or in the case of early relapse, consisting of intensive chemotherapy (2nd or 3rd generation combination chemotherapy) (ranimustine, etoposide, carboplatin and cyclophosphamide), possibly followed by autologous bone marrow transplantation [5]. According to Mikhaeels and Spittle [23], intensive chemotherapy is necessary even for localized stages due to the highly aggressive nature of this lymphoma. Chemotherapy is now increasingly replaced by haematopoietic stem cell transplantation or addition of growth factors. Interferon therapy has not been shown to be effective.

This tumour has a poor prognosis, with a 5-year overall survival ranging between 10 and 45% depending on the series [24,25].

Conclusion

Extranodal NK/T-cell lymphoma, nasal type, is a rare disease, but the number of new cases reported each year has been continually increasing over recent years due to a better knowledge of this disease. This disease has been more clearly elucidated as a result of progress in immunohistochemistry and molecular biology.

Extranodal NK/T-cell lymphoma, nasal type, is characterized by its polymorphic clinical features, responsible for diagnostic difficulties and frequently delayed management. Histological examination of biopsy samples completed by immunohistochemistry is essential to establish the positive diagnosis.

The pathogenesis of extranodal NK/T-cell lymphoma, nasal type, is unknown, but it is strongly associated with Epstein-Barr virus infection. These EBV-associated lymphomas have a poor prognosis with a high local recurrence rate and the presence of macrophage activation syndrome in the majority of cases.

Optimal management of extranodal NK/T-cell lymphoma, nasal type, must be based on multidisciplinary collaboration between otorhinolaryngologists, radiotherapists, medical oncologists and nutritionists in order to improve the prognosis of this disease.

EBV immunotherapy, monoclonal antibodies and gene therapy have been proposed as possible treatments for the future, as the EBV virus could become a major therapeutic target in combination with conventional combination chemotherapy. Research into p53 expression is currently underway to elucidate the carcinogenesis of extranodal NK/T-cell lymphoma and probably also as an approach to the treatment and prognosis of these aggressive lymphomas.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

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