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Extranodal lymphoma of the head and neck: A 67-case series

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ABSTRACT

The present study sought to describe clinical presentation in extranodal lymphoma of the head and neck (ELHN), with the aim of improving diagnostic management.

Material and methods: A single-center retrospective observational study was conducted over the period 2001–13. Age, gender, histologic type, location, type of clinical presentation, time interval between symptom onset and histologic diagnosis and presence of specific symptoms were recorded, as were the specialty of the physician initially consulted and of the physician taking the diagnostic sample.

Results: Sixty-seven cases of ELHN were diagnosed: 39 male and 28 female patients, with a median age of 68 years. B-cell lymphoma (84%) was more frequent than plasmacytoma (7%) or T-cell lymphoma (6%). Location was mainly palatine tonsil (28%), nasal fossa and sinus (19%), nasopharynx (14%) or parotid (13%). Revelation often involved a mass (33%), and only rarely any specific symptoms (9%). Time interval from symptom onset to diagnosis was short in aggressive lymphoma and longer in low-grade lymphoma (mean 4 and 10 months respectively). The physician initially consulted was an ENT specialist in 67% of cases, and an ENT specialist performed diagnostic sampling in 97% of cases.

Conclusion: ELHN is a rare pathology (5 cases per year in our department) of highly variable clinical presentation depending on location and histologic type. The ENT physician should be prepared for diagnosis regardless of anatomic location, so as to optimize diagnostic management.

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1. Introduction

Hodgkin and non-Hodgkin lymphoma is the third most frequent malignant tumor of the head and neck region (12%), following squamous cell carcinoma (46%) and thyroid carcinoma (33%) [1]. Incidence has been rising for several decades. There are some 10,000 new cases of non-Hodgkin lymphoma of whatever location per year in France, slightly more than half occurring in male subjects. Twenty-three percent of non-Hodgkin and 4% of Hodgkin lymphomas of the head and neck are extranodal [2]. These lymphoid tumors mainly involve 4 sites: Waldeyer's ring, the nasal sinuses and fossae, the oral cavity and the salivary glands.

Extranodal lymphoma comprises a heterogeneous group of tumors of various histologic types and highly varied clinical presentation. Diagnosis may fail to be suspected when the clinical and/or radiological tumoral syndrome mimics epithelial tumor or infection, but needs to be considered as treatment is specific.

The present study sought to describe the characteristics of patients with extranodal lymphoma of the head and neck (ELHN), highlighting the polymorphic clinical presentation and the role of the ENT physician in the optimization of management.

2. Materials and methods

Files of all patients presenting with ELHN between January 1st, 2001 and December 31st, 2013 were analyzed retrospectively, excluding intra- and juxta-parotid nodal locations.

Definitive diagnosis was histologic. Pathology exams were analyzed according to their code on the ADICAP classification (Association pour le Développement de l'Informatique en Cytologie et en Anatomie Pathologique: Association for the Development of Informatics in Cytology and Anatomom-Pathology), enabling all extranodal locations (excluding code SG: [node]) of the head and neck to be selected: codes AA (amygdala), XF (face), AC (nasopharynx), XC (cervical region), AF (nasal fossae), AS (facial sinus), OE (eye), BX (oral cavity), AL (larynx), BL (tongue) and BP (parotid).

The WHO 2009 classification was used for characterizing histologic type: B-cell, T-cell or lymphocytic (LCL) lymphoma or plasmacytoma. B-cell lymphoma was classified as: MALT
Table 1
Frequency of histologic types of ELHN.

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>Number</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell lymphoma, n = 56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
<td>36</td>
<td>54</td>
</tr>
<tr>
<td>MALT B-cell lymphoma</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Lymphoctic lymphoma (LCL)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Brain B-cell lymphoma</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Burkitt’s B-cell lymphoma</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>Centroblastic B-cell lymphoma</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Low-grade B-cell lymphoma</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>T/NK nasal lymphoma</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>Plasmacytoma</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Undetermined</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

(mucosa-associated lymphoid tissue) lymphoma, small-cell cerebral lymphoma, Burkitt’s lymphoma, CD20+ diffuse large B-cell lymphoma (DLBCL), centroblastic B-cell lymphoma or other low-grade B-cell lymphomas T-cell lymphoma was classified as angioimmunoblastic T-cell lymphoma or angiocentric T/NK-cell nasal lymphoma.

Lymphomas were further classified as aggressive or indolent.

DLBCL, Burkitt’s and T/NK-cell lymphomas are highly malignant and aggressive. Lymphoma associated with HIV is generally highly malignant. Follicular, low-grade B-cell, brain cell, LCL, MALT lymphomas and plasmacytoma are of low malignancy or indolent.

Age at diagnosis, gender, histologic type, location, type of clinical presentation, time interval between symptom onset and histologic diagnosis and known risk factors (HIV-positive status and history of immune disorder) were recorded.

The presenting symptom leading to diagnosis was recorded and counted as the clinical presentation. B symptoms and cervical adenopathies were recorded; B symptoms comprise general symptoms: fever, night sweats and weight-loss, associated with both Hodgkin and non-Hodgkin lymphoma.

The specialization (ENT or other) of the physician seen for the presenting symptom leading to diagnosis and of the physician taking the diagnostic sample was recorded in each case. The type of sample enabling histologic diagnosis was classified as surgical specimen (total or partial organ resection) or surgical biopsy. Fine-needle aspiration ahead of diagnostic biopsy was also recorded.

All patients underwent local and remote imaging. Fig. 1A and B shows two examples (CT and MRI) of a temporal plasmacytoma and a thyroid lymphoma. The images are not pathology-specific and contrasted with the respective clinical presentations.

3. Results

Sixty-seven ELHNs were diagnosed in the department between January 1st, 2001 and December 31st, 2013: 39 male and 28 female patients (M/F sex ratio, 1.4), with a mean age of 65 years (range, 17–97 years). Fig. 2A shows incidence according to age.

B-cell lymphoma (n = 56, 84%) was more frequent than plasmacytoma (n = 5, 7%) or T-cell lymphoma (n = 4, 6%). Table 1 shows frequency according to histologic type.

The most frequent histologic type was DLBCL, a high-grade B-cell lymphoma (n = 36). MALT B-cell lymphoma was systematically parotid (n = 6) and LCL systematically tonsillar (n = 4). There were no cases of Hodgkin lymphoma.

T-cell lymphoma comprised T/NK nasal lymphoma (n = 3) and angioimmunoblastic T-cell lymphoma (n = 1). T/NK lymphoma was systematically EBV-positive, with sinonasal location; the angioimmunoblastic T-cell lymphoma was nasopharyngeal.

The most frequent ELHN locations were: palatine tonsil (n = 19, 27%), nasal fossa and sinus (n = 13, 19%), nasopharynx (n = 10, 14%) and parotid gland (n = 9, 13%). Other locations comprised tongue, soft palate, face, orbit, thyroid, lingual tonsil, temporal bone and larynx. Four patients had 2 extranodal locations of simultaneous or consecutive onset: 1 hypophyseal LCL with concomitant tonsillar LCL; 1 basilingual DLBCL 9 years after rhinopharyngeal DLBCL; 1 left parotid MALT lymphoma 6 years after right parotid MALT lymphoma; and 1 tonsillar DLBCL 4 years after sinonasal DLBCL. ELHN locations are shown in Fig. 2B.
Presenting symptoms comprised a mass or locally increased volume (n = 22, 33%), pain (n = 4, 6%), and B symptoms (n = 6, 9%), without visible or palpable mass, presenting symptoms were related to tumor location in 52% of cases: nasal obstruction, odynophagia, pharyngeal discomfort, dysphagia, dysphonia, etc. Clinical presentations are shown in Table 2.

Mean interval time between symptom onset and definitive histologic diagnosis was 6 months (median, 3 months; range, 7 days to 5 years).

Involvement was strictly extranodal head and neck in 37 cases (55%); 24 (36%) had associated cervical lymph-node involvement, and 10 (15%) associated involvement outside the head and neck region. Two patients were HIV-positive.

Aggressive lymphoma (n = 43) was associated with cervical lymph nodes in 40% of cases (n = 17) and with involvement beyond the head and neck region in 16% (n = 7). Mean time between symptom onset and diagnosis of aggressive lymphoma was 3.9 months. Fine-needle aspiration was associated in 18.6% of cases.

Indolent lymphoma (n = 23) was associated with cervical adenopathies in 39% of cases (n = 9) and with involvement outside the head and neck region in 13% (n = 3). Mean interval time between symptom onset and diagnosis was 10.3 months. Fine-needle aspiration was associated in 43.5% of cases.

Eight of the 67 patients (12%) had been treated in the hematology department for lymphoproliferative disorder before diagnosis of head and neck lesion.

Sixty-seven percent of patients initially consulted an ENT physician; 21% had consulted an internal medicine/hematology specialist, and 7% another specialist (2 ophthalmologists, 1 endocrinologist, 1 stomatologist and 1 emergency physician); the specialty of the physician initially consulted was unknown in 3 cases.

Diagnosis was systematically confirmed on histology: partial or total organ specimen in 54% of cases (n = 36) and surgical biopsy in 46% (n = 31). Pre-sampling fine-needle aspiration was feasible in only 46% of cases and actually performed in 24%; cytology found lymphoma in 31% of cases was uncertain in 44% and non-contributive in 25.

### 4. Discussion

Extranodal lymphoma of the head and neck is rare: our ENT department receives 12,000 patients per year, and over the last 13 years only 67 ELHNs have been diagnosed (i.e., 5 per year). This incidence matches those of single-center retrospective studies published since 1986: 1.9 to 11.4 cases per year [2–13].

This type of lymphoma affects patients with a median age of 68 years, with peak incidence in the 6th and 7th decades, although all ages may be concerned. Patients are more often male (M/F sex ratio 1.4 in the present series).

There were no cases of Hodgkin lymphoma in the present series. Hodgkin ELHN is extremely rare, at less than 0.9% of Hodgkin lymphomas [14].

The most frequent location in the present series was the palatine tonsils (27%). Other studies reported rates of 22–54% [3–5,8,11,13]. Waldayer’s ring, a lymphoid structure, is reported to be a frequent ELHN site (41% of cases).

The most frequent histologic type was large B-cell lymphoma (54%), as in Western and Japanese reports (34–72%) [8,11–13]. T/NK-cell nasal lymphoma is more common in Asia and Latin America, and is the most frequent histologic type in China [10,15].

Clinical presentation is non-specific. ELHN shows as a mass or in symptoms related to the location of the mass (in 85% of cases in the present series). Clinical presentation is very heterogeneous, varying with location [4,4,8], and may be explosive or insidious according to histologic type.

Symptomatology is patient in aggressive lymphomas such as DLBCL or Burkitt’s lymphoma, and may require intensive care. Tumor mass increases rapidly, doubling in 24–48 hours in some cases [16]. The interval between onset and histologic diagnosis is very short (1–3 months on average).

In contrast, indolent lymphomas (plasmacytoma, cerebral lymphoma of the brain and MALT lymphoma) show an insidious presentation. Symptomatology becomes chronic and onset-to-diagnosis interval is much longer (a mean 9, 13 and 17 months respectively in the present series).
T/NK-cell nasal lymphoma is a special case. It is aggressive, with poor prognosis (overall 5-year survival, 42% [17]); the sinonasal clinical presentation is relatively silent: nasal obstruction, sinusitis, rhinorrhea, epistaxis, etc. In the literature as in the present series, B symptoms are absent, there is little or no pain, and onset-to-diagnosis time is long (11 months in the present series, and up to 14 months elsewhere [18]). Few studies, however, have focused on clinical presentation in these cases, and a larger patient base would be needed to support any conclusions.

Unlike nodal forms, ELHN is rarely revealed by general signs. B symptoms do not dominate clinical presentation, constituting the presenting symptom in only 7% of the present series and 1.6% in Sheffield’s report [8], which was limited to “localized” forms, with no associated involvement beyond the head and neck region (versus 15% in the present series), which may account for the lower rate of B symptoms.

T/NK-cell nasal ELHN is rare in European populations; the present series included 3 cases. Males are more often affected: all 3 of the present cases, and two-thirds in the literature [15]. Location is predominantly sinonasal (2 nasal fossa locations in the present 3 cases interval). There may be contiguous extension to adjacent structures, as in 1 of the present 3 cases. Rare nasopharyngeal, oropharyngeal, laryngeal, and even non-head and -neck (skin, digestive tract, etc.) locations have been reported [18]. Etiology remains unclear, but there is a definite link with EBV: a literature review reported 90–100% of T/NK-cell nasal lymphomas were EBV-positive [15] (100% in the present series).

Only 1.2% of Burkitt’s lymphomas are ELHN [16] (3 in the present series). They occur in younger patients (mean 27 years in the present series, and a median 46 years, taking all locations together, in the literature [16]).

Extradural head and neck plasmacytoma is rare; there are few studies, with small series. It is an indolent hemopathy, of slow evolution and relatively silent clinical presentation. Onset-to-histology time is long: 7.5 months in a retrospective study of 46 cases [19], and about 9 months in the present series. There is male predominance: 1.5 in the present series and 1.7–4 in the literature [19–21]. There were no sinonasal location in the present series, compared to 40–43% in the literature [19–21]. Other locations are those previously mentioned: nasopharynx (18–20%), oropharynx (18%) and larynx (6–18%) [19–21]. Exceptional temporal bone location has been reported.

Thyroid lymphoma is revealed by goiter, with few if any B symptoms [22]. The two main histologic types are MALT lymphoma and DLBCL [22]. The present series included 2 cases of thyroid lymphoma. Presentation was highly patent, with inspiratory dyspnea and compressive goiter with or without recurrent nerve palsy requiring intensive care. Mean onset-to-histology time was short: 1.5 months. The literature reports female predominance (1.83 to 7.6 [23]), especially in case of history of Hashimoto’s thyroiditis (relative risk, 67 [24]); the present cases were 1 man and 1 woman, without history of immune disorder or thyroiditis.

These differences were probably due to the present 2 cases being DLBCL. In thyroid lymphoma, DLBCL shows a clinical presentation highly distinct from MALT lymphoma. It is less rare in males (2 males to 11 females, versus 0 males to 6 females for MALT lymphoma), the goiter is larger, B symptoms are more common and history of thyroiditis is rarer [23]. Hashimoto’s thyroiditis would seem to predispose toward MALT lymphoma rather than other histologic types: 92% of MALT lymphomas involved history of Hashimoto’s thyroiditis, versus only 40% for other histologic types [22].

Parotid lymphoma is usually of MALT form: 27.9% in the literature [8,25], and 66% in the present series. There is female predominance: 1.5 in the present series, and 1.4 in a study of 2140 parotid lymphomas [25]. Revelation is by a progressively enlarging parotid mass (8 of the present 9 cases, the other being serendipitously discovered on imaging). It causes paresis or facial palsy in 4–15% of cases [25], although there were no such cases in the present series. Clinical presentation is usually an aspect of benign parotid tumor. In the present series, one-third of the patients (1 male, 2 females) had history of Sjögren’s disease. In parotid lymphoma, history of immune disorder such as Sjögren’s syndrome is more frequent than in the general population and may induce lymphoproliferative disorder, in turn inducing parotid lymphoma [25].

In the present series, aggressive lymphomas showed rapid evolution, were frequently disseminated (head and neck lymph nodes and non-head and -neck locations), with patent symptomatology and short onset-to-diagnosis times (mean, 4 months). Emergency treatment was required in some cases. Fine-needle aspiration was performed in at least 20% of cases. Rapid diagnosis was mandatory to initiate treatment. In indolent lymphomas, onset-to-diagnosis time was longer (mean, 10 months). The symptomatology of a chronically evolving mass without impaired general health status does not incite early consultation. Fine-needle aspiration was performed in almost half of the cases (43.5%).

In the present series, 85% of NLHN patients had symptoms inciting ENT consultation: indolent head and neck mass (33% of cases) or ENT symptomatology related to the location of the mass (52%), usually without impaired general health status. An ENT physician was consulted initially in 67% of cases, and an ENT physician took the diagnostic sample in 97%. More than half of the lesions were inaccessible to fine-needle aspiration, especially when there were no associated cervical adenopathies. In 22% of cases, fine-needle aspiration was not performed despite being feasible, due to easy access for tissue biopsy, context (e.g., history of lymphoproliferative disorder) or diagnostic urgency. In 25% of cases, it was non-contributive and of uncertain interpretation in almost half the cases (44%); one-third of cytology findings suggested lymphoma.

Suggested diagnosis of lymphoma by an ENT specialist in case of a non-specific aspect of tumor or positive fine-needle aspiration cytology optimizes management of ELHN, orienting the report to the patient, scheduling flow cytometry of the histology specimen, tumor biopsy in sufficient quantity to detect the various tumor markers, and osteomedullary biopsy under general anesthesia in the same step as the tumor biopsy.

5. Conclusion

Extranodal lymphoma of the head and neck is rare. Clinical presentation varies greatly according to location and histologic type.

ENT physicians should be able to make this diagnosis, whatever the anatomic location, so as to optimize diagnostic management.

Disclosure of interest

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

References


