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HEAD AND NECK

Clinical findings of extranodal SNT lymphoid malignancies in a four-decade single-centre series

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Abstract Sinonasally located lymphoid malignancies are rare lesions with first symptoms similar to other obstructive conditions. Additionally, they often coexist with nasal inflammation and mucosal necrosis. Therefore, time from the first symptoms to diagnosis tends to be long. Awareness and early diagnosis of this disease entity could improve treatment outcome. Altogether, 142 patients with sinonasal or nasopharyngeal (i.e. sinonasal tract, SNT) lymphoid malignancies, diagnosed and treated at the Helsinki University Hospital, during a 39-year period from 1975 to 2013, were retrospectively reviewed. There were 90 males (63 %) and 52 females (37 %) with a median age of 64 years (range 26–92). Eighty-four percent of the patients had primary diseases and 16 % had relapses of lymphoid malignancies primarily diagnosed at other locations. The mean duration of symptoms prior to diagnosis was 4.8 months (range 0.5–24). The most common histological entity was diffuse large B-cell lymphoma (43 %), followed by plasmacytoma (18 %). The most common location was nasopharynx (58 %) followed by nasal cavity (44 %) and paranasal sinuses (35 %). Sixty-nine percent of the lesions were at a single anatomic location of the sinonasal tract. Fifty-two percent of the cases were of Ann Arbor Stage I. Lymphoid malignancies form an important and diverse group in the differential diagnosis of SNT tumours. They most often present with general obstructive nasal symptoms due to tumour location. Most of them are primary lesions, highlighting the importance of an accurate diagnosis as early as possible.

Keywords Diffuse large B-cell lymphoma · Lymphoid malignancies · Incidence · Ann Arbor classification · Sinonasal lymphoma · Extranodal lymphoma · Tumour

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Introduction

Sinonasal and nasopharyngeal, i.e. sinonasal tract (SNT) lymphoid malignancies represent less than 0.5 % of all extranodal lymphoid malignancies in the Western population [1–3], whereas in Asian populations they are more common [4–7]. In previous studies, the incidence of sinonasal diffuse large B-cell lymphoma (DLBCL) was 0.06–0.1 per 100,000 in USA [8, 9]. Sinonasal lymphomas in Western population have been reported to be mainly of B cell origin [6, 10–12] whereas NK/T- and T-cell lymphomas are predominant in Asian populations [3, 13, 14].

SNT lymphoid malignancies typically present with local nasal complaints [15–17]. These symptoms are often unspecific and the diagnostic delay tends to be long [3, 18, 19]. This delay may be further prolonged by factors related to the quality and representativeness of the biopsy and histopathological studies. Repeated biopsies are often needed as sinonasal lymphoid malignancies regularly coexist with rhinosinusitis and the tumour may change the

sinonasal anatomy making it difficult to obtain a representative tissue sample [3]. Therefore, recognition and correct early diagnosis of these lesions by the otorhinolaryngological community is crucial for their adequate management.

The primary aim of this study was to review our institutional series of SNT lymphoid malignancies to delineate their main clinical characteristics. The secondary aim was to investigate the incidence of this disease entity in Southern Finland. More importantly, we want to remind clinicians of SNT lymphoid malignancies as a potential differential diagnostic possibility when treating patients with persistent nasal complaints, especially when a sinonasal or nasopharyngeal mass is encountered.

Patients and methods

A retrospective review was performed of all patients diagnosed with and treated for SNT lymphoid malignancies at the Departments of Otorhinolaryngology-Head and Neck Surgery and Oncology, Helsinki University Hospital (HUH), Helsinki, Finland between 1975 and 2013. The patients with a verified disease in the nasopharynx, nasal cavity or paranasal sinuses were identified from the files of the Department of Pathology, University of Helsinki. In addition, all SNT lymphoid malignancies from the same hospital district area reported in the nationwide Finnish Cancer Registry and were searched and collected (Malila 2015, personal communication). As all lymphoma diagnostics and treatment in Finland are centralized to University Hospitals and new cancer diagnoses are registered to the Finnish Cancer Registry, our study can be considered to cover the population (1.6 M) of the Hospital District of Helsinki and Uusimaa. The annual population data for the corresponding hospital referral area were obtained from the Finnish public authority, Statistics Finland. These were used for incidence calculations and a mean annual incidence for each decade was determined.

Diagnosis was considered to be of primary SNT lymphoma, if the SNT area was affected at the time of primary diagnosis. Tonsillar primary diseases were excluded. Staging and location were recorded from the patient files, and thus reflect the available imaging techniques at each time point. The determination for the extent and location of the disease for patients diagnosed in earlier decades was based on clinical findings, and later also on CT findings. Current diagnostic methods include MRI and PET/CT. All original lymphoma diagnoses were reviewed and confirmed by an experienced hematopathologist (M.-L.K.-L.). The study group consisted of 142 patients with adequate clinical and histopathological data available. Ninety patients were male (63 %) and 52 female (37 %). Mean age at diagnosis was 62 years and median 64 years (range 26–92).

All but two patients were of European origin and the remaining two patients were from Asia and South America. Data on patient characteristics, and clinical and histological details were recorded. Categorization of presenting symptoms is shown in Table 1. An institutional research approval was granted for the study design. Due to the nature of this study (retrospective chart review), no approval by the institutional Research Ethics Board or informed consent from the patients was required according to the Finnish law. Permission to access Finnish Cancer Registry data was granted by the National Institute of Health and Welfare.

Results

The incidence varied between 0.11 and 0.36/100,000 inhabitants during the examined 10-year periods for SNT lymphomas, and between 0.08 and 0.17 for SNT DLBCL, respectively (Figs. 1, 2). DLBCL accounted for over 70 % of the lymphomas during the first 10-year period, but during the succeeding decades the proportion was 36–47 %.

Table 1 Description of symptom classifications for data recording

Symptom type	Description
Nasal symptoms	Rhinorrhea, epistaxis, bloody discharge, congestion
Pharyngeal and laryngeal symptoms	Pharyngalgia and other laryngopharyngeal sensations and symptoms
Ear symptoms	Hypacusis, various sensations in the ear
Eye symptoms	Problems with vision, eye movement impairment
Neurological symptoms	Paraesthesia or facial paralysis
General symptoms	Sweating, fever or sense of fever if not measured, mass at different sites (outside the above mentioned areas)

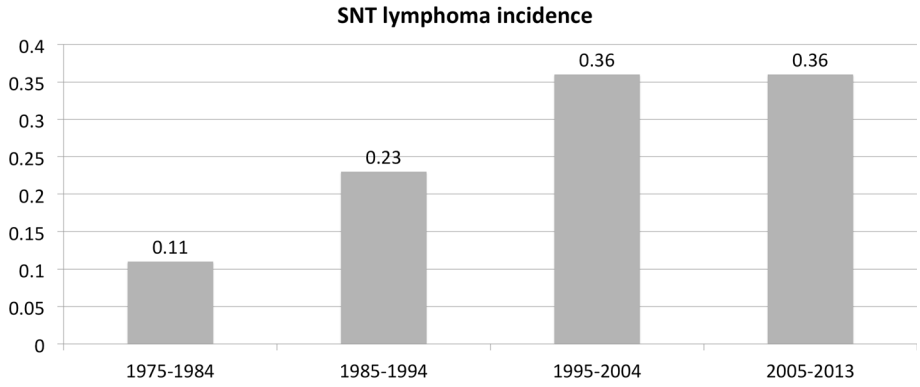

Fig. 1 Annual incidence of lymphoid malignancies in the sinonasal tract per 100,000 inhabitants in 10-year periods during the years 1975–2013 (population data derived from Statistics Finland 2014)

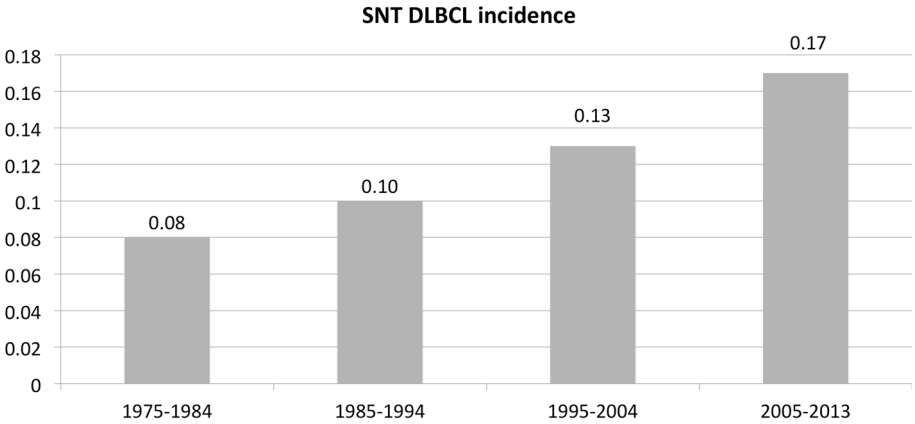

Fig. 2 Annual incidence of DLBCL in the sinonasal tract per 100,000 inhabitants in 10-year periods during the years 1975–2013 (population data derived from Statistics Finland 2014)

The presenting symptoms are shown in Table 2. Many patients had several symptoms and their duration prior to diagnosis was available for 124 patients with a mean of 4.8 months (range 0.5–24). In addition, in some of the remaining cases the symptoms were reported to have continued long without any accurate account on their duration. Nasal complaints (rhinorrhea, epistaxis or bloody discharge or congestion) were the most common presenting symptoms with 85 cases (60 %), and 26 (31 %) of them also had bloody discharge. Laryngopharyngeal symptoms occurred in 48 (34 %) of the patients. Ear symptoms occurred in 25 patients (18 %) and eye problems in 22 patients (15 %). Sixty-three patients (44 %) had general symptoms (for description see Table 1).

Table 2 Distribution of symptoms

Presenting symptoms	*N*	%
Nasal symptoms	85	60
Pharyngeal and laryngeal symptoms	48	34
Ear symptoms	25	18
Eye symptoms	22	15
Neurological symptoms	18	13
General symptoms	63	44
Data missing	1	1

A patient may have symptoms in many areas and will, therefore, be classified into several groups

In 119 cases (84 %), the nasal lymphoid malignancy was the primary disease, whereas in 23 (16 %) it was a disease relapse or a secondary lesion. The anatomic locations and Ann Arbor classifications of the diseases are shown in Table 3. In 82 patients (58 %) the disease occurred in the nasopharynx. Nasopharynx was the only sinonasal tract location in 55 patients (39 %). Nasal cavity was affected in 62 patients (44 %) and this was the only involved SNT location in 27 patients (19 %). Paranasal sinuses were involved in 50 patients (35 %) and in 16 patients (11 %) this was the only SNT site involved. The patient with missing data regarding tumour location was diagnosed with severe breathing difficulties, which led to tracheostomy. The local extent of the disease for this patient could not be determined but it most likely occurred in more than one of the regions recorded for this study. In 43 patients (30 %), the tumour occurred at two or three of the listed SNT regions at the time of diagnosis whereas in 98 patients (69 %) the tumour occurred at a single SNT location. In 74 patients (52 %) the Ann Arbor classification was Stage I, whereas 19 patients (13 %) had Stage II disease. Fourteen patients (10 %) had Stage III and 31 patients

Table 3 Tumour SNT location and Ann Arbor classification

Findings	*N*	%
Location		
Nasopharynx only	55	39
Nasal cavity only	27	19
Paranasal sinuses only	16	11
Nasopharynx and nasal cavity	9	6
Nasopharynx and paranasal sinuses	8	6
Nasal cavity and paranasal sinuses	16	11
Nasopharynx, nasal cavity and paranasal sinuses	10	7
Data missing	1	1
Ann Arbor classification		
Stage I	74	52
Stage II	19	13
Stage III	14	10
Stage IV	31	22
Data missing	4	3

(22 %) had Stage IV disease. The stage could not be determined retrospectively for four patients (3 %) because of refusal of all treatment and investigation modalities in one patient and inadequate patient documentation in three patients. In these three cases, the tumour was large in diameter and, therefore, they were more likely higher than lower stage. For patients with primary tumour in SNT area ($N = 119$) the stage distribution was as follows: Stage I 68 patients (57 %), Stage II 16 patients (13 %), Stage III 11 patients (9 %) and Stage IV 20 patients (17 %), with data missing on four patients (3 %) as mentioned above.

DLBCL was the most common histological entity ($n = 61$, 43 %). Twenty-five (18 %) of the patients had plasmacytoma. Peripheral T-cell lymphoma (8 %) and Mantle-cell lymphoma (8 %) were equally common. In all but one of the six chronic lymphocytic leukaemia patients and in both Richter transformation patients, the SNT occurrence was a relapse or a secondary disease lesion. Different entities are presented in Table 4.

Routine HIV testing has been performed only during the recent years at our institution. Three patients were tested positive for HIV and 49 patients were tested negative for HIV in this series.

Discussion

We present a single-institution review of 142 patients with SNT lymphoid malignancies during almost four decades. Our aim was to review the symptoms and clinical findings (including growth pattern) that are typical for this patient population and would thus guide the clinician in the primary diagnostic phase. Primary disease in the nasopharyngeal area was the most common presentation in our series. Nasal cavity had higher distribution than paranasal sinuses. The presenting symptoms were most often similar to common cold or other obstructive conditions and only 18 % had bloody discharge or epistaxis. DLBCL was the most common (43 %) histological entity.

This is a large population-based analysis that includes practically all patients diagnosed with SNT tract lymphoid malignancies in our referral area of 1.6 million inhabitants covering almost one-third of the Finnish population. It comprises one of the largest clinical series of patients with SNT lymphoid malignancies. To ensure all patients were included, we also received data from the nationwide Finnish Cancer Registry, which has been functioning over six

Table 4 Presentation of various histology types as primary, secondary or relapsed disease

Histology	*N* (%)	SNT as primary location (proportion of all primary tumours, %)	Relapse or SNT as secondary location (proportion of all secondary location or relapse tumours, %)
Diffuse large B-cell lymphoma	61 (43)	55 (46)	6 (26)
Plasmacytoma	25 (18)	22 (18)	3 (13)
Mantle-cell lymphoma	12 (8)	8 (7)	4 (17)
Peripheral T-cell lymphoma	12 (8)	10 (8)	2 (9)
Follicular B-cell lymphoma	8 (6)	8 (7)	0 (0)
Chronic lymphocytic leukaemia	6 (4)	1 (1)	5 (22)
Nasal NK/T-cell lymphoma	5 (4)	4 (3)	1 (4)
Marginal-zone lymphoma	5 (4)	5 (4)	0 (0)
Burkitt's lymphoma	4 (3)	4 (3)	0 (0)
Hodgkin's disease	2 (1)	2 (2)	0 (0)
Chronic lymphocytic leukaemia Richter transformation	2 (1)	0 (0)	2 (9)

decades and has a complete coverage of the cancer cases in Finland.

This study has the limitations of a retrospective study. Symptoms and growth patterns of the tumours were recorded from patient files. Some data on certain parameters were not available for all patients. Imaging techniques have developed significantly during the past decades and have increased the information on the extent of the disease but were not available for the first cases in this series.

Patient characteristics in the existing reports showing equal gender proportions or slight male dominance are similar to our findings [8, 9, 12, 17, 20, 21]. Also the mean age (62 years) in the present series was similar to what has been reported [8, 9, 12, 17, 20, 21].

In previous studies in USA, the incidence of sinonasal DLBCL has been 0.06–0.1/100,000 [8, 9]. In our study the annual incidence was 0.11–0.36/100,000 during the examined 10-year periods (Fig. 1). The incidence for DLBCL was 0.08–0.17/100,000 (Fig. 2) during the examined 10-year periods. There seemed to be an increasing trend in the number of patients across the study period, even when the increase in the referral area population was taken into account. This increasing trend may be explained by the normal variation of incidence of a rather uncommon disease. Further, the number of patients is too small for definitive conclusions but a slightly increasing trend for sinonasal DLBCL has been reported earlier as well [8]. This finding is in line with the increased incidence of non-Hodgkin lymphomas in general [22, 23]. The current improved diagnostics and longer life expectancy for the general population may be considered as possible reasons for increasing incidence of SNT lymphoid malignancies. The incidence of HIV is rather low in Finland. In the data retrieved from the National Institute for Health and Welfare in Finland, the incidence was 5.8/100,000 for the year 2013 in the Hospital District of Helsinki and Uusimaa. As only three of the tested patients were positive for HIV, HIV-induced diseases could not explain the increasing trend in our series. The effect of HIV on the incidence of SNT lymphoid malignancies remains unclear.

According to previous reports in the Western populations and to the present findings, nasal symptoms that could refer to common cold or its complications have been the presenting symptoms in approximately half of the patients (60 % in the present study) [15–17]. Patients in a series including tumours of the orbit had understandably less nasal symptoms and more eye symptoms [21]. Peng et al. described, in their series from USA ($N = 17$), the occurrence of diplopia to be 18 % [15] whereas Cuadra-Garcia et al. ($N = 58$) described eye symptoms in 33 % of their patients. In the present series, the occurrence of eye symptoms was 16 %. It is noteworthy that bloody discharge was among the first symptoms in only 18 % of the patients. Various symptoms in other neighbouring organs and tissues should also be an indication for a general practitioner to perform rhinoscopy or to send the patient for consultation to an ear, nose and throat specialist. Among these are neural symptoms (numbness, facial pain, facial paralysis), eye symptoms (visual impairment, limitation of eye movement), or throat symptoms (problems with swallowing, voice problems, sore throat) and these may also occur without nasal symptoms.

The mean duration of symptoms prior to diagnosis in the present series was almost 5 months, which is less than in previous studies. Sands et al. reported a mean diagnostic delay of 21.5 months in their report from Canada, whereas Fajardo-Dolci et al. reported a patient delay of 3–24 months (median 10.5 months) in Mexicans and Yen et al. a patient delay of 1 week–4 years (average 8.9 months) in the Taiwanese population [3, 18, 19]. The present retrospective study setting may, however, have caused inaccuracies in this matter.

In our study, tumours occurred more often in nasal cavity than in paranasal sinuses. Previous studies in Western populations have reported a higher occurrence in paranasal sinuses compared with nasal cavity [6, 8, 20] whereas in a large study in USA ($N = 120$) nasal cavity was affected in 63 % of the patients and paranasal sinuses in 43 % and both sites were affected in 10 % of all patients [12]. The reason for this discrepancy could be the differences in reporting the results; Logsdon et al. reported only the primary site, and similarly, Kanumuri et al. described only one location for each patient whereas Abbondanzo and Wenig described all involved sites [6, 8, 12]. Cuadra-Garcia et al. also reported all involved sites in their study on 58 American patients and had involvement of paranasal sinuses in 46 patients (79 %) and nasal cavity involvement in 33 patients (57 %), 21 of which (36 % of total patient count) had involvement of both sites. In our study, 50 patients (35 %) had involvement of paranasal sinuses and 62 (44 %) had involvement of the nasal cavity, 26 (18 %) having involvement of both sites. If only nasal cavity and paranasal sinus patients of our study are taken into account ($n = 87$), the share for paranasal sinuses is 57 % and for nasal cavity 71 %. Thirty percent of the 87 patients had involvement of both areas, thus results in the present study are close to findings by Abbondanzo and Wenig [12]. Cuadra-Garcia et al. reported higher proportion of paranasal involvement compared to nasal cavity, but involvement of both areas was similar to the current study [20]. Most often it is difficult to interpret which area has been the primary site and, therefore, we would encourage authors to report all affected areas.

In the present study, Stages III and IV were more widely presented than in most previous studies. In a study from USA by Logsdon et al. ($N = 70$), a higher proportion of

patients had Ann Arbor Stages I or II tumour and only 20 % had Stage III or IV disease whereas in our series 31 % (26 % in primary tumours) had Stage III or IV disease [6]. Stage III and IV lymphoid malignancies accounted only for 17 % of the cases in a series from UK ($N = 24$) [16] and from USA ($N = 58$) [20]. Both Cuadra-Garcia and Logsdon et al. reported Stage I diseases in 60 % of the cases whereas in the present series 52 % (57 % in primary diseases) had Stage I [6, 16]. In a Taiwanese series of 24 patients, the portion of Stage I disease was even higher (75 %) and only 13 % had Stage IV diseases (no patients with Stage III) [3]. The difference in Ann Arbor classification could be explained by faster diagnosis in the recent years as Yen et al. had searched for patients treated between 1990 and 2010. However, Cuadra-Garcia et al. had searched for patients treated between 1960 and 1998 and Logsdon et al. between 1947 and 1993 and still patients with lower stage were more widely represented compared with the present study [3, 6, 20]. On the other hand, patients from earlier decades might have been more often falsely classified with lower stage as tools to determine distribution were limited. None of the studies reported the amount of patients per each year, so there could be a difference in the amount of patients treated during the recent years as opposed to patients treated in earlier decades. In a small series of eight DLBCL patients, Shohat et al. had only one patient with Stage I disease and almost half of the patients had Stage III or IV disease [17].

Forty-three percent of the patients in our study had DLBCL, whereas in another European series consisting of 36 patients with primary extranodal and sinonasal lymphoid malignancy this proportion was 30 % [21]. The spectrum of other subtypes was similar, even though Sandner et al. included also orbital tumours in their study [21]. In small studies including only paranasal sinuses and nasal cavity, DLBCL typically has represented more than half of lymphoma subtypes [15, 17, 20]. It is noteworthy that DLBCL represents an even higher proportion of lymphoid malignancies in oral cavity compared with nasal cavity [24–27].

Conclusions

SNT lymphoid malignancies most often present with symptoms similar to those caused by obstructive or inflammatory conditions in these locations. This may increase the diagnostic delay. More importantly, almost half of the patients in our study had general symptoms and not all patients had symptoms in the SNT area. SNT has a more diverse distribution of lymphoid malignancy subtypes than oral cavity, but DLBCL still is the most common lymphoma subtype in both of these locations. However, our conclusion can be considered to apply only for Caucasian patients.

Compliance with ethical standards

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Conflict of interest None.

Ethical standards This article does not contain any studies with human participants performed by any of the authors. No informed consent from the patients or approval by the Research Ethics Board is needed for a retrospective chart review.

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