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**Small-cell predominant extranodal NK/T-cell lymphoma, nasal type:
Clinicopathologic analysis of a series of cases diagnosed in a Western
population**

Running Title: Small-cell extranodal NK/T-cell lymphoma

Penelope A. McKelvie^{1,2}, Fina Climent³, Gregor Krings⁴,
Robert P. Hasserjian¹, Jeremy S. Abramson⁵, Ben Z. Pilch¹, Nancy Lee Harris¹,
Judith A. Ferry¹, Lawrence R. Zukerberg¹, Aliyah R. Sohani¹

¹The James Homer Wright Pathology Laboratories of the Massachusetts General Hospital and Department of Pathology, Harvard Medical School, Boston, MA; ²Department of Anatomical Pathology, St. Vincent's Hospital, Melbourne, Australia; ³Department of Pathology, University Hospital of Bellvitge-IDIBELL, Barcelona, Spain; ⁴Department of Pathology, University of California San Francisco School of Medicine, San Francisco, CA; ⁵Center for Lymphoma, Massachusetts General Hospital Cancer Center and Department of Medicine, Harvard Medical School, Boston, MA

Correspondence:

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Aliyah R. Sohani, MD
Department of Pathology,
Massachusetts General Hospital,
55 Fruit Street, WRN 219
Boston, MA 02114
Phone: (617) 726-3187
Fax: (617) 726-7474
E-mail: arsohani@mgh.harvard.edu

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Word Count: 3000 **ABSTRACT**

Aims: Extranodal NK/T-cell lymphoma, nasal type (ENKTCL) is usually composed of medium-sized to large lymphoid cells showing prominent angiotropism and tumor cell necrosis. We report 13 cases composed predominantly of small lymphocytes diagnosed in the United States and Western Europe.

Methods and Results: Patients included seven females and six males, aged 17-75 years. Ten presented with sinonasal and three with buccal disease. Nine had stage IE/IIIE and four had stage IV disease. In 5 of 7 patients with multiple biopsies at different time intervals, the lymphoma was misinterpreted as representing chronic inflammation on an earlier biopsy. Morphology in all cases showed a dense infiltrate of small lymphoid cells with minimal cytological atypia. Necrosis, angioinvasion and angiodestruction were each seen in 17%, 22% and 17% of biopsies. Median Ki67 was 5%. Four patients died of lymphoma 4-16 months after diagnosis, including 3 of 4 patients with stage IV disease; seven (54%) are alive with no evidence of disease at a median of 39 months ; one patient with stage IV disease is alive at 10 months; and one recurred at 17 months.

Conclusions: In sinonasal biopsies with predominantly small lymphocytic infiltrates with admixed chronic inflammation, focal hypercellularity, focal surface ulceration or microscopic bone invasion by small lymphoid cells should alert pathologists to the possibility of small-cell

predominant ENKTCL. Awareness of the full histological spectrum of ENKTCL, particularly in non-endemic areas, is important in avoiding a delay in diagnosis and ensuring timely initiation of therapy, in order to positively impact patient outcome.

KEY WORDS: Extranodal NK/T-cell lymphoma, nasal type; Epstein-Barr virus; chronic rhinosinusitis; EBER *in situ* hybridization; chronic active EBV infection.

INTRODUCTION

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL) is an aggressive, predominantly extranodal lymphoma associated with Epstein-Barr virus (EBV) that most commonly presents in the upper aerodigestive tract, particularly the nasal cavity. The classic histological features include a proliferation of pleomorphic medium-sized to large cells with prominent angioinvasion and angiodestruction, and large areas of tumor cell necrosis. Cases composed mostly of small cells have been described, mainly in endemic areas with higher prevalence such as East Asia, Mexico, and Central and South America.¹⁻⁵ Diagnosis of such cases in non-endemic regions may be challenging due to the lower prevalence and subtle histology.^{6, 7} We have encountered sinonasal cases in which the diagnosis of ENKTCL was delayed for more than a year due to the bland, uniform cytology, absence of characteristic angioinvasion and angiodestruction, minimal necrosis and prominent admixture of inflammatory cells, mimicking a reactive process. We describe the clinicopathological

features of 13 cases of small-cell predominant ENKTCL occurring in patients in the United States (US) and Western Europe, with the goal of identifying characteristics to aid in the timely recognition of such cases in non-endemic regions.

MATERIALS AND METHODS

The study was approved by the Partners HealthCare Institutional Review Board prior to its initiation (protocol # 2007P001458, last approval date 1/25/2016). A total of 13 cases of small-cell predominant ENKTCL were identified from various sources, as detailed in the online Supporting Information, of which eight were previously presented at national or international meetings and one was previously published.^{6, 8, 9} The diagnosis of ENKTCL was made in all cases according to criteria specified in the 2008 World Health Organization (WHO) classification.⁵ Small-cell predominance was defined as ENKTCL in which over 90% of the neoplastic cells had nuclei that were the same size or slightly larger than those of small lymphocytes, but clearly smaller than histiocytic nuclei. Cases with predominantly medium or large nuclear size (similar to or exceeding the size of histiocytic nuclei) were excluded. Based on these criteria, cases with small-cell predominance represented 12% of all ENKTCL diagnosed at a single institution in the US over a ten-year interval.

All cases were positive for EBV-encoded small RNA (EBER) by *in situ* hybridization and exhibited either a typical NK-cell immunophenotype (CD2+, surface CD3-, CD56+) or were CD56- but positive for cytotoxic granule proteins. Haematoxylin and eosin (H&E) and immunohistochemical-stained slides were examined in all cases, and subsets of cases were analyzed by additional immunohistochemistry, flow cytometry, and/or molecular genetic analysis using methods described previously and as outlined in further detail in the online Supporting Information.¹⁰⁻¹³

Clinical follow-up was obtained from medical records or by contacting outside pathologists or other physicians involved in the patient's care. Differences in continuous and categorical variables between groups were compared using the Mann-Whitney and Fisher's exact tests, respectively. Overall survival (OS) was defined as the time from diagnosis to death from any cause, and was analyzed using the Kaplan-Meier method with the log-rank test used to

compare differences in survival between various disease subgroups. Patients who were alive or lost to follow-up were censored at the time last seen alive. Statistical analyses were performed using GraphPad Prism software version 5 (La Jolla, CA).

RESULTS

Clinical features

Clinical features are summarized in Table 1. The 13 patients included six males and seven females (M:F ratio 0.85) with a median age at diagnosis of 48 years (range 17-75). Patients were of diverse ethnic backgrounds, including six Caucasians (46%), five Hispanics (38%), and one each of Native American (7.5%) and South-East Asian (7.5%) origin. Caucasians were significantly older than non-Caucasians (median ages 68.5 vs. 30 years, $p=0.002$).

Ten patients (77%) had involvement of nasal cavity or paranasal sinuses, with bilateral involvement in eight, and three patients (23%) had disease in the buccal cavity or mouth. Patient 4 who presented initially with buccal disease developed contemporaneous disease in the endomyocardium and pericardium and subsequently had sinonasal involvement eight months later. This patient had a history of acute EBV infection involving a cervical lymph node one year prior to diagnosis and chronic dacryoadenitis with lymphocytic infiltration of the lacrimal gland seven months before diagnosis for which she was treated with intermittent high dose prednisone over the course of a year. These clinical findings, in conjunction with markedly elevated antibody titers to EBV-associated antigens, were consistent with chronic active EBV (CAEBV) infection.¹⁴⁻¹⁸

Patients with sinonasal disease presented with symptoms of chronic rhinosinusitis and nasal obstruction and congestion, with or without deviated nasal septum. In one patient, the tumor was diagnosed from a biopsy of tissue taken during surgery for septal repair. Only two of 10 patients with sinonasal disease presented with a clinically evident mass or polyp, although additional abnormalities were detectable by imaging (see below). The three patients with buccal involvement presented with visible mucosal lesions, with associated numbness in two and a two-year history of gradual facial swelling in one.

Information from computed tomography (CT) imaging studies was available in seven patients. Five patients with sinonasal disease had variable mucosal thickening in the nasal cavity and sinuses consistent with chronic rhinosinusitis, and in four patients, imaging identified a polypoid soft tissue mass in the nasal cavity, measuring up to 5 cm in maximum dimension. No bone invasion was detected by CT scan in any of the cases.

Nine patients (69%) had localized disease (stage IE or IIE) confined to the upper aerodigestive tract. Four had stage IV disease, one each with involvement of bone marrow, heart, skin, and parotid gland and associated cheek soft tissue. Bone marrow examination was performed in three patients, two for staging (both negative) and one for investigation of pancytopenia, which revealed subtle marrow involvement by ENKTCL with associated haemophagocytic lymphohistiocytosis.

Morphology

A total of 23 biopsies from the 13 cases were examined, with seven patients (five with sinonasal and two with extranasal disease) having multiple biopsies at different time intervals. All cases, including the initial biopsies in patients with multiple biopsies, showed dense infiltrates of uniformly small or slightly enlarged lymphocytes with condensed chromatin, round to slightly irregular nuclei and absent nucleoli, in a background of non-neoplastic inflammatory cells, including small lymphocytes, plasma cells (often numerous), histiocytes and eosinophils (Fig. 1A-C). In some biopsies, the cells had clearing of the cytoplasm and monocytoid features similar to those seen in marginal zone lymphoma (Fig. 1D). In two sinonasal cases, the infiltrates were multinodular rather than diffuse, with focal areas of hypercellularity. Unlike typical cases of ENKTCL, mucosal glands were generally intact, without replacement or destruction by the lymphoma cells (Fig. 1E-F); this feature was present in all but one biopsy, which showed only focal lymphocytic infiltration into ducts and acini. In the sinonasal cases, a minor degree of surface ulceration and necrosis was seen in four biopsies from two patients, while one case had prominent pseudoepitheliomatous hyperplasia of the surface epithelium (Fig. 2A-B). Zonal tumor cell necrosis was seen in four cases (three sinonasal, one buccal), and overall in only 4/23

biopsies (17%) (Fig. 2C). Five cases (22% of biopsies) had angioinvasion with infiltration of vessel walls by neoplastic lymphoid cells, but only four showed angiodestruction with vascular injury and associated thrombosis or fibrinoid necrosis (17% of biopsies) (Fig. 2C-D). Four sinonasal cases (5/16 biopsies, 31%) had focal microscopic bone invasion, one with associated bone destruction (Fig. 2E-F). In one of three buccal cases, there was invasion of skeletal muscle. Among the 13 cases, 11 lacked mitotic figures, but small numbers (up to two per 10 high power fields) were seen in two cases. No reactive lymphoid follicles with germinal centers were seen, but two cases contained small nodules of B cells.

Immunophenotype and molecular diagnostic studies

Immunophenotypic features, as assessed by immunohistochemistry and/or flow cytometry, and molecular diagnostic studies are summarized in Table 2. All 13 cases showed dense, diffuse or nodular positivity for EBV by EBER *in situ* hybridization in virtually all tumor cells (Fig. 3). Eight cases (62%) were of NK lineage with CD56 positivity in all but one, which showed cytotoxic granule expression of perforin and TIA-1. Five cases (38%) showed features consistent with T-cell lineage, which was significantly associated with Caucasian ethnicity ($p=0.005$). CD30 was negative in all eight cases tested. Ki67 stain was performed in 14 biopsies from nine patients, and showed a median proliferation index of 5% (range <5% to 70%); only three biopsies had a proliferation index of $\geq 30\%$.

A monoclonal *TCR* gene rearrangement was detected by PCR in three patients with T-lineage tumors in whom this study was performed. In case 13, biopsies of lymphoma involving the skin, nasal cavity and ethmoidal sinus showed identical clones. *TCR* gene rearrangement studies were performed in one NK-lineage case and were negative. In case 4 with CAEBV infection, clonal EBV and *TCR* β segment deletion were detected by Southern blot in the lymphoma specimens. The prior lymph node and lacrimal gland showed clonal EBV of the same band size as the lymphoma.

Evolution of pathological features in patients with multiple biopsies

In 5/13 patients (38%), the diagnosis of ENKTCL was missed on an earlier biopsy and the morphological features were initially thought to represent a reactive process, usually chronic rhinosinusitis. One patient (case 1) had undergone two biopsies of sinonasal mucosa before the diagnosis of ENKTCL was made. In two patients (cases 9 and 13) with time intervals between biopsies of 14 and 34 months, respectively, there was significant progression from bland cytology and <5% Ki67 proliferation index to more typical features of ENKTCL and a higher Ki67 proliferation index of 50-70% (Figs. 3-4). In other patients with multiple biopsies, more subtle changes over time were seen, including the development of slightly more atypical cytology, small foci of necrosis, and a mild increase in mitotic activity.

Treatment and clinical outcome

Clinical follow-up was available in all 13 patients (Table 1). Four patients (three sinonasal, one buccal) received localized radiotherapy only; seven patients (six sinonasal, one buccal) received localized radiotherapy with chemotherapy, one of whom subsequently underwent autologous stem cell transplant; one patient with stage IV disease (case 13) received chemotherapy only; and the patient with buccal disease and bone marrow involvement (case 10) received supportive care only. Four patients (31%) died of disease at 4-16 months (median 12 months) after diagnosis, including 3/4 patients (75%) with stage IV disease. All three patients who presented with buccal disease died, with rapid disease progression in two and development of haemophagocytic lymphohistiocytosis in the other. The fourth patient who died (case 13) was initially diagnosed with ENKTCL on a biopsy of a skin nodule and was subsequently found to have nasal involvement by lymphoma on retrospective review of a sinonasal biopsy from three years prior. Although she achieved remission after initial chemotherapy, she relapsed with cutaneous, nodal and central nervous system disease 12 months after diagnosis, then developed leukemic dissemination while undergoing salvage treatment and died at 16 months. Seven patients are alive with no evidence of disease at a median follow-up of 39 months (range 7-70 months). One patient is alive with stage IV disease at 10 months and one developed recurrent tumor at 17 months with no further follow-up available.

The median OS of all 13 patients was not reached after a median follow-up time of 38.5 months for living patients (Fig. 5A). Patients with primary buccal disease had a significantly shorter OS vs. those with sinonasal disease (10 months vs. not reached, $p=0.0003$, Fig. 5B), as did patients who presented with stage IV vs. localized disease (10 months vs. not reached, $p=0.004$, Fig. 5C). Other clinical and pathological features were not associated with OS, including older age (>50 or >60 years), Caucasian vs. non-Caucasian ethnic background, and NK vs. T-cell lineage.

DISCUSSION

Small-cell predominant ENKTCL is generally well-recognized in endemic areas with a high prevalence of this EBV-related lymphoma, but in Western regions, the diagnosis may be overlooked in clinical specimens of sinonasal mucosa, particularly when there is no mass or clinical suspicion of malignancy.³⁻⁷ Our series included a number of sinonasal cases where the diagnosis was delayed for up to three years due to the bland, uniform cytology, low proliferation index and associated reactive inflammatory background, including small reactive lymphocytes, histiocytes, eosinophils, and often many plasma cells. Another feature leading to difficulty in distinguishing small-cell predominant ENKTCL from the more common diagnosis of chronic rhinosinusitis was only patchy hypercellularity and no loss of acinar architecture, features that contrast with the more typical histology of this entity. Tumor cell necrosis, angioinvasion and angiodestruction were uncommon in our series, occurring in 17-22% of biopsies examined. This is similar to a Taiwanese series of 22 ENKTCL that included five (23%) small-cell predominant cases, none of which had angiodestruction, thrombosis or necrosis, and only two of which showed angioinvasion.⁴ By contrast, a recent large US series of 73 cases of ENKTCL found angioinvasion and angiodestruction in 69% and necrosis in 92% of cases overall; this series included five cases (7%) with small-cell predominance, but the presence or absence of such features in these cases was not specifically reported.⁷ Clues to the diagnosis of small-cell predominant ENKTCL in sinonasal biopsies include focal hypercellularity, focal surface ulceration or necrosis, and microscopic bone invasion by small lymphoid cells. Some cases may also show some cytologic atypia, with slight cellular enlargement, slight nuclear irregularity, and more abundant cytoplasm than normal small

lymphocytes. Such features, which can be subtle, should alert the pathologist to the possibility of small-cell predominant ENKTCL and prompt screening with EBER *in situ* hybridization, followed by immunohistochemistry for NK- and T-cell markers, including cytotoxic granule proteins, to confirm the diagnosis.

In addition to these morphological differences, cases of small-cell predominant ENKTCL also showed immunophenotypic differences from tumors with more typical histology.

Proliferation index by Ki67 was overall low in our series, ranging from <5 to 10% in most initial biopsies, with a single case showing a moderate proliferation index of 30% on initial biopsy. By contrast, the median Ki67 proliferation index in the recent large US study was 50% overall, with only 15 cases (21%) having a proliferation index <30%.⁷ CD30 was negative in all cases tested in our series. This contrasts with the findings of other authors who have demonstrated CD30 reactivity, indicative of an activated phenotype, in 43-75% of ENKTCL.^{7,}

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Several cases in our series with multiple biopsies taken at intervals ranging from 12 to 35 months showed evidence of histological progression, including development of more typical features of ENKTCL with medium-sized to large cells showing increased cellular pleomorphism, necrosis and proliferation index. This suggests that small-cell predominant tumors may represent an early manifestation of ENKTCL, particularly when the clinical symptoms closely mimic benign sinonasal disease with nasal congestion and obstruction and no mass lesion is identifiable by clinical exam or imaging. Few studies have reported clinical differences among histological subtypes of ENKTCL. Kuo *et al* reported a younger median age at diagnosis in patients whose tumors contained mostly small or medium-sized cells (43 years, similar to 48 years in our series) compared to those with large or pleomorphic cells (60-72 years), but their study did not show any correlation between histology and survival.⁴ While Pongpruttipan *et al* showed a trend towards better OS in patients whose tumors had a small-cell component, defined as at least 25% of neoplastic cells, vs. those whose tumors lacked a small-cell component, only three patients in their series had small-cell predominant tumors (>90% neoplastic cells), precluding a meaningful survival analysis in this specific subgroup.¹⁹ Interestingly, we noted an apparent association in our series between Caucasian ethnicity, older age at diagnosis and T-lineage disease, a

finding that has not been previously reported to our knowledge. Due to the small number of cases in our series, this finding requires confirmation in larger studies.

Given that survival in ENKTCL is strongly correlated with stage and presence of extranasal disease,^{7, 19-22} early detection is optimal and would likely contribute to improved prognosis. Three of four patients with fatal outcome in our cohort had stage IV disease at diagnosis, and three had extranasal primary tumors involving buccal mucosa, suggesting that these risk factors apply similarly to cases with small-cell predominance and that the bland histology in such cases does not portend a better outcome. The significantly worse OS in the three patients with primary buccal disease relates not only to their extranasal location, but also to disease stage and/or limited initial therapy. Two of these patients presented with stage IV disease and the third, with longstanding facial swelling before development of a mass lesion, was treated only with localized radiotherapy prior to disease progression. While radiotherapy has been the mainstay of treatment for patients with localized nasal disease, two Japanese studies have shown improved survival in patients with localized nasal ENKTCL who received combined-modality chemoradiotherapy compared to radiotherapy alone.^{21, 23} Progress has also been made in the treatment of stage IV ENKTCL, although outcome for these patients remains significantly inferior to those with localized disease treated with radiation with or without chemotherapy. For sufficiently fit stage IV patients, SMILE (steroid [dexamethasone], methotrexate, ifosfamide, L-asparaginase, and etoposide) produces a one-year survival of 55%, which is improved compared to historical series.²⁴ These studies and the poorer outcomes noted in our patients with advanced-stage and extranasal disease underscore the importance of early recognition of the diagnosis and initiation of appropriate therapy prior to tumor dissemination.

In conclusion, we report 13 patients with small-cell predominant ENKTCL diagnosed in the West, nearly half of whom were Caucasian. In several patients with multiple biopsies, the diagnosis was delayed for up to three years due to the deceptively bland cytomorphology and admixed inflammatory cell background. The findings of even focal dense hypercellularity, focal surface ulceration or microscopic bone invasion should alert the pathologist to the possibility of small-cell predominant ENKTCL in routine sinonasal biopsies, even when there is no clinical suspicion or identifiable mass lesion. Screening of such cases

by EBER *in situ* hybridization followed by confirmatory immunohistochemistry to further characterize the lymphoma should prevent a misdiagnosis, leading to earlier institution of therapy and possible improvement in patient outcome.

AUTHOR CONTRIBUTIONS

PAM designed the research, collected and analyzed the data, and wrote the manuscript. FC, GK, BZP, NLH, JAF and LRZ collected data and edited the manuscript. RPH and JSA analyzed the data and edited the manuscript. ARS designed the research, collected and analyzed the data, and edited the manuscript.

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LIST OF ONLINE SUPPORTING INFORMATION

- Further details related to materials and methods.

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FIGURE LEGENDS

Figure 1. Cytomorphological features of small-cell predominant extranodal NK/T-cell lymphoma. Nasal biopsy from patient 3 showing dense, diffuse infiltrates of small, bland-appearing lymphocytes with slight nuclear irregularities (A, H&E). Initial nasal cavity biopsy from patient 1, thought to represent benign chronic rhinosinusitis, showing uniform small cells (B, H&E). In many cases, there was an intimate admixture of chronic inflammatory cells, including histiocytes and plasma cells; the latter were often numerous as in this case from patient 2 (C, H&E). Nasal biopsy from patient 7 showing small lymphocytes with scant clear cytoplasm forming focal intraepithelial collections within glands mimicking extranodal marginal zone lymphoma (D, H&E). Buccal biopsy from patient 4 showing small lymphocytes with moderate clear cytoplasm and slight nuclear irregularities with focal involvement of overlying epithelium (E, H&E), but overall preservation of mucosal glands (F, H&E)

Figure 2. Epithelial, vascular and bone changes seen in cases of small-cell predominant extranodal NK/T-cell lymphoma. Examples of cases exhibiting surface ulceration with necrosis (A, H&E), pseudoepitheliomatous hyperplasia of surface epithelium (B, H&E), and angioinvasion by tumor cells (C, H&E) with associated zonal necrosis of tumor (arrow), both of which were focal. Higher-power view of angioinvasion with adjacent tumor cell necrosis and apoptosis below and viable small lymphoid cells above the affected blood vessel (D, H&E). Microscopic bone invasion, as seen in two different cases (E and F, H&E).

Figure 3. Low-power histological features of small-cell predominant extranodal NK/T-cell lymphoma and similarity to benign chronic rhinosinusitis in early lesions. Sinonasal fragments from a patient with benign chronic rhinosinusitis showing some nodular hypercellularity, but less than the density seen in early ENKTCL (A, H&E). Initial sinonasal biopsy, called negative, from patient 9 showing multiple areas of dense hypercellularity within the lamina propria but overall preservation of the glandular architecture (B, H&E). Initial sinonasal biopsy from patient 9 showing multiple areas of dense nodular reactivity for EBV-EBER in the lymphoma cells within the lamina propria (C and inset, EBER *in situ* hybridization). Sinonasal fragments from the second and diagnostic sinonasal biopsy from patient 9 taken 14 months after the first, showing uniform dense hypercellularity of the lamina propria, surface ulceration and loss of the normal glandular architecture (D, H&E).

Figure 4. Changes in cytological features and proliferation index over time in a patient with small-cell predominant extranodal NK/T-cell lymphoma (ENKTCL). The initial biopsy from patient 9 (same case as illustrated in Fig. 3B-C) shows areas of dense hypercellularity within the lamina propria (A, H&E) consisting of uniformly small lymphocytes with relatively bland cytology (B, H&E) and a low proliferation index of <5% (C, Ki67 immunohistochemistry). The subsequent biopsy from the same patient (same case as illustrated in Fig. 3D) shows more typical features of ENKTCL with a proliferation of pleomorphic medium-sized cells (D, H&E), occasional large cells and rare apoptotic debris (E, H&E), and a higher proliferation index of approximately 50% (F, Ki67 immunohistochemistry).

Figure 5. Kaplan-Meier curves showing overall survival (OS) for all 13 patients with small-cell predominant extranodal NK/T-cell lymphoma (A, median OS not reached). Patients with primary buccal disease had significantly shorter OS vs. those with sinonasal disease (B, median 10 months vs. not reached, $p=0.0003$), as did patients who presented with stage IV vs. localized disease (C, median 10 months vs not reached, $p=0.004$).

Table 1: Clinical Features of Small-Cell Predominant Extranodal NK/T-cell Lymphoma, Nasal Type

Case	Age	Sex	Race/ Ethnicity	Site(s) of disease*	Presenting symptoms	Radiology	Stage	Treatment	Follow-up**
1	30	F	Hispanic	A. Nasal cavity B. Nasal cavity and sinus contents, 2 months C. Nasal cavity and sinus contents, 12 months*	Nasal congestion and chronic sinusitis with granular, friable, bloody turbinate and deviated nasal septum.	Polypoid soft tissue in nasal cavity, intact but slightly deviated septum, opacification and mucosal thickening of sphenoid and maxillary sinuses.	IE	Localized XRT (60 Gy).	NED at 38 months.
2	23	M	Native American	A. Right buccal mucosa B. Right buccal mucosa, time interval not known*	Facial swelling, with gradual increase in size over 2 years.	NK	IE/IIIE	Localized XRT (initial), salvage with ICE, brain XRT.	Local recurrence, 11 months. CNS relapse, 13 months. DOD, 14 months
3	48	M	Caucasian	Left nasal mass*	Left nasal congestion, obstruction, and mass.	5 cm soft tissue mass in left nasal cavity with deviation of bone but no bone invasion.	IE/IIIE	Combined XRT (50.4 Gy) and chemotherapy (3 cycles DeVIC).	NED at 7 months.
4	17	F	Hispanic	A. Endomyocardium B. Buccal mucosa, 3 days* C. Pericardium, 1 week D. Nasopharynx and right osteomeatal complex, 8 months	Acute EBV infection with cervical adenopathy 2 years prior. Swelling and sores on buccal mucosa, with lower lip numbness. Pericardial effusion.	Positive gallium scan in lacrimal, submandibular and parotid glands following acute EBV infection.	IV	XRT, multiple cycles CHOP.	Progressive disease involving mediastinum, liver, parotid gland, pericardium and chest wall. DOD at 10 months
5	46	M	Hispanic	A. Ethmoid sinuses, bilateral turbinates* B. Right nasal cavity and ethmoid sinus, 4 months	Chronic sinusitis, nasal congestion.	NK	IE	XRT, unspecified chemotherapy.	NED at 70 months
6	29	M	Hispanic	A. Bilateral paranasal sinuses* B. Bilateral paranasal	Chronic sinusitis, nasal obstruction with deviated nasal septum.	Mucosal thickening in ethmoid, frontal, maxillary, and sphenoid sinuses bilaterally. Deviated nasal	IE	XRT.	Recurrent disease, 17 months.

				sinuses, 17 months		septum. Opacified ostiomeatal unit complexes.			
7	51	F	Hispanic	Right nose and turbinate*	Incidental finding at surgery for deviated septum and chronic sinusitis.	NK	IE	Combined XRT and chemotherapy (3 cycles DeVIC).	NED at 49 months.
8	32	F	South-East Asian	Bilateral maxillary ethmoid sinus*	Chronic rhinitis, hypertrophied turbinates.	Changes consistent with chronic sinusitis.	IE	Combined XRT and unspecified chemotherapy, autoSCT.	NED at 39 months.
9	66	M	Caucasian	A. Bilateral ethmoid and sphenoid sinuses B. Bilateral ethmoid and sphenoid sinuses, 14 months*	Chronic rhinosinusitis, nasal obstruction, recurrent sinus infections.	A. Opacified right maxillary antrum, mucosal thickening in ethmoid, consistent with chronic sinusitis. B: 4 cm soft tissue FDG-avid mass in left nasal cavity.	IE	Bilateral total ethmoid, sphenoid maxillary and frontal sinusotomies. XRT (60 Gy) followed by 3 cycles CHOEP.	NED at 61 months.

10	73	F	Caucasian	Right cheek muscle and mouth*	Spontaneous lesion within oral cavity extending to cheek muscle, associated with numbness and gross purulence.	Cheek mass with central necrosis, suggestive of abscess.	IV	Supportive care.	DOD at 4 months.
11	75	F	Caucasian	Bilateral nose and sinus contents*	Recurrent chronic sinusitis.	NK	IE	XRT.	NED at 12 months.
12	71	M	Caucasian	Bilateral sinus contents*	Nasal blockage, periorbital edema, extending to cheeks after surgery.	CT: Advanced pansinusitis. MRI: Bilateral paranasal sinus, maxillofacial, orbital, prenasal and glabellar superficial soft tissue disease.	IV	XRT + 2 cycles attenuated SMILE, HD IT MTX, leucovorin rescue and PEG-asparaginase	Alive with persistent disease at 10 months.
13	63	F	Caucasian	A. Ethmoidal sinus B. Forearm skin, 34 months*	Chronic sinusitis at time of ethmoidal biopsy. Development of skin lesion and nasal polyp subsequently.	Changes consistent with chronic sinusitis.	IV	CHOP x 6. Salvage regimens included SMILE and ESHAP.	Cutaneous, nodal and CNS recurrence at 12 months. Leukemic dissemination at 15

				C. Nasal polyp, 35 months D. Skin, 46 months E. Peripheral blood, 49 months													months. DOD at 16 months.
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*Patients with multiple specimens have these listed in chronological order, followed by time from first biopsy. Asterisk indicates the biopsy in which the diagnosis of ENKTCL was initially made.

**All follow-up intervals are from time of biopsy in which the diagnosis of ENKTCL was initially made (indicated by single asterisk in patients with multiple specimens).

Abbreviations: M – male; F – female; NK – not known; CT – computed tomography; FDG – fluorodeoxyglucose; XRT – radiotherapy; ICE – ifosfamide, carboplatin, etoposide; CHOP – cyclophosphamide, adriamycin, vincristine, prednisolone; CHOEP – cyclophosphamide, adriamycin, vincristine, etoposide, prednisolone; DeVIC - dexamethasone, etoposide, vincristine, ifosfamide, carboplatin; SMILE – steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide; ESHAP – etoposide, cytarabine, cisplatinum and methylprednisolone; HD IT MTX – high dose intrathecal methotrexate; autoSCT – autologous stem cell transplant; NED – no evidence of disease; DOD – died of disease; Gy – Gray.

Table 2: Immunophenotypic and Molecular Genetic Features of Small-Cell Predominant Extranodal NK/T-cell Lymphoma, Nasal Type*

Case	Biopsy (if multiple)	Lineage	CD2	Surface CD3**	Cyto CD3^	CD5	CD7	CD56	CD4	CD8	TCR [#]	Perforin	Granzyme B	TIA-1	CD30	Ki67 proliferation index	TCR gene rearrangement
1	A-C	NK	+	-	+w	-	+w	+	-	-	αβ-, γδ-	-	+	ND	-	<5% on earlier 2 biopsies; 5-15% on 3rd biopsy	Polyclonal TCRγ
2	A, B	NK	ND	ND	+	-	ND	+	-	-	ND	ND	ND	+	-	ND	ND
3	-	NK	+	ND	+w	-	+w	+	-	-	β F1-	+	+	ND	-	5-10%	ND
4	A-D	NK	+	-	+w	-	+	+	-	-	αβ-, γδ-	+	ND	+	-	<5%	No signal with TCRβ probe
5	-	NK	+	ND	+w	-	-	+	ND	ND	ND	ND	ND	ND	-	<5%	ND
6	A, B	NK	+	ND	+	ND	ND	-	-	-	ND	Scattered +	ND	+	ND	ND	ND
7	-	NK	+	-	+w	-	+w	+	-	-	αβ-, γδ-	+	Scattered +	ND	ND	30%	ND
8	-	NK	ND	ND	+	-	+	+	-	-	ND	ND	ND	ND	ND	ND	ND

9	A	T	ND	ND	+	+w	-	-	-	+	β F1+	ND	ND	ND	-	5%	ND
	B		+	+	+	+w	-	-	-	+	αβ+, γδ-	+	+	ND	ND	50%	ND
10	-	T	ND	ND	+	+	-	-	-	+	ND	-	+	ND	-	5-10%	Monoclonal TCRγ
11	-	T	ND	ND	+	+w	-	-	-	+	ND	-	+	ND	ND	10%	Monoclonal TCRγ
12	-	T	ND	ND	+	+	ND	+	-	+w	ND	ND	+	ND	ND	ND	ND
13	A	T	ND	ND	+	+	-	-	-	+	ND	ND	ND	ND	-	<5%	Monoclonal TCRβ
	B		+	ND	+	+	-	+	-	+	ND	ND	+	+	-	70%	Monoclonal TCRβ
	C		+	+	+	+	-	-	-	+	αβ+, γδ-	ND	ND	ND	-	15%	Monoclonal TCRβ

*All cases showed dense nodular or diffuse positivity for EBV by EBER *in situ* hybridization. EBV latent membrane protein (LMP) was performed by immunohistochemistry in cases 4 and 6, both of which were negative.

**Performed by flow cytometry.

^Performed by immunohistochemistry.

#Staining for αβ and γδ performed by flow cytometry and β F1 by immunohistochemistry.

Abbreviations: + – positive; +w – weakly positive; - – negative; Cyto – cytoplasmic; ND – not done; TCR – T-cell receptor.

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Author/s:

McKelvie, PA;Climent, F;Krings, G;Hasserjian, RP;Abramson, JS;Pilch, BZ;Harris, NL;Ferry, JA;Zukerberg, LR;Sohani, AR

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