Head and Neck Pathology (2019) 13:624–634
https://doi.org/10.1007/s12105-019-01027-z

ORIGINAL PAPER

Extranodal NK/T-Cell Lymphoma, Nasal Type in Guatemala: An 86-Case Series Emphasizing Clinical Presentation and Microscopic Characteristics

Celeste Sánchez-Romero[1] · Oslei Paes de Almeida[1] · Javier Rendón Henao[2] · Román Carlos[3]

Received: 24 January 2019 / Accepted: 4 March 2019 / Published online: 21 March 2019

Abstract

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL-NT) is a lymphoid malignancy that mainly affects the nasopharynx and is associated with the Epstein-Barr virus (EBV). Increased incidence is seen in some Latin American and Asian countries. In this study, we describe a case series of 86 Guatemalan patients with ENKTCL-NT from a single diagnostic head and neck center. We emphasize the distinctive clinical, microscopic, and immunohistochemical (IHC) features, as well as EBV positivity by in situ hybridization (ISH). Most of the patients (90.6%) were of Mayan descent and low socioeconomic status (SES). Males were more often affected than females, comprising 68.3% of cases. Patient age ranged from 8 to 71, with a mean of 34.7 years. All cases arose in the upper aerodigestive tract and mainly presented as a rapidly progressive, necrotizing midfacial process affecting the nasal, nasopharyngeal, sinonasal, palatal, and oropharyngeal structures. Microscopically, ENKTCL-NT showed a diffuse polymorphic and atypical lymphoid infiltrate. Angiocentric and angiodestructive growth patterns were present with associated necrosis. Peripheral hyaline necrosis of blood vessels was a histologic hallmark. The ISH and IHC profiles included positivity of EBV, LCA, CD3, CD45RO, CD30 (focal in 39.2%), granzyme-B, TIA-1, perforin (in 82.3%), and CD56 (in 83.7%). CD20 was negative, and the Ki-67 index ranged from 70 to 90%. In Guatemala, this lymphoma is strongly associated with people of low SES and indigenous ethnicity. When affected, the palatal mucosa provides the best site to obtain a representative biopsy. Since ENKTCL-NT is highly aggressive, it is extremely important to recognize the spectrum of clinical presentations and microscopic features in order to avoid misdiagnosis and treatment delay.

Keywords Extranodal NK-T-cell lymphoma · Nasal and nasal-type · Non-Hodgkin lymphoma · Herpesvirus 4 · Human · Guatemala

Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL-NT) is an aggressive malignancy of natural killer cell/T-cell lineage associated with the Epstein-Barr virus (EBV). Angiotropism, vascular destruction, and hyaline vascular necrosis are the prominent histologic features. It is commonly found in adult males, primarily in the nasopharynx. Non-nasal sites, such as skin or the gastrointestinal tract, are affected less frequently. The ENKTCL-NT is more prevalent in Southeast Asia and some Latin American countries. There is a notable predilection for the indigenous population of Mexico, Guatemala, and Peru [1–4].

Although there are several sizable studies of this malignancy from Asian and Latin American countries, detailed documentation of the clinical and microscopic presentations is limited [3–11]. The main purpose of this study is to

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12105-019-01027-z) contains supplementary material, which is available to authorized users.

✉ Celeste Sánchez-Romero
csr_90@hotmail.com

[1] Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Av. Limeira 901, P.O. Box. 52, Piracicaba, Sao Paulo 1314-903, Brazil

[2] Medical School, Universidad de Antioquia, Medellín, Colombia

[3] Centro Clínico de Cabeza y Cuello, Guatemala City, Guatemala

thoroughly describe these features as well as the immunohistochemical (IHC) and EBV in situ hybridization (ISH-EBV) profiles in a case series of 86 Guatemalan ENKTCL-NT patients.

Materials and Methods

Cases diagnosed as ENKTCL-NT from 1985 to 2018 were obtained from the files of the pathology laboratory at Centro Clínico de Cabeza y Cuello (Guatemala). Only nasal cases were included. The microscopic features in hematoxylin and eosin (H-E) stained sections were reviewed. All diagnoses were confirmed by ISH-EBV and an IHC panel including CD20, CD3, CD45RO, CD30, granzyme-B, perforin, CD56, and Ki-67. Clinical data were gathered from other providers, our own direct clinical examination, and/or review of the medical charts. All data were recorded and analyzed descriptively. This study was approved by the Piracicaba Dental School, University of Campinas (Piracicaba, Brazil) Ethical Committee (process no. 67128417.4.0000.5418).

Results

Demographics

Eighty-six cases of ENKTCL-NT were included in this study with a majority (68.3%) occurring in male patients. The mean age was 34.7 years and ranged from 8 to 71 years. Most of the patients (90.6%) were of Mayan origin and low socioeconomic status (SES).

Clinical and Radiographic Findings

The main presentation was a rapidly progressing, aggressive, necrotizing, midfacial process affecting the nasopharyngeal, sinonasal, palatal, and oropharyngeal structures. Most patients initially had serous or hemorrhagic nasal discharge, breathing difficulty, and/or nasal obstruction with resulting mouth breathing. These findings were commonly accompanied by palatal ulcers and, less frequently, anterior maxillary gingival ulcers with diffuse erythema. The gingival mucosa at times exhibited features similar to those described in Wegener's granulomatosis (Fig. S6 C, E).

Initial signs of edema affecting the nose, cheek, and upper lip rapidly progressed to severe midfacial edema, necrosis, and destruction of nasal structures (skin, mucosa, nasal septum, turbinates, and maxillary sinus). The palatal ulcers commonly led to perforations resulting in oroantral communication (Fig. 1).

The most common manifestation was obstruction of the upper airways. The second most frequent was midfacial edema, with increased local temperature and erythema. Oral ulceration was the third most common finding, affecting the hard palate, anterior maxillary gingiva, the upper vestibular sulcus, and, more rarely, the oropharynx (Table 1).

Other signs and symptoms included nasal discharge and painful ulcers with foul odor. Mobility of the maxillary anterior teeth was observed in cases with anterior palatal or gingival involvement. Systemic manifestations such as fever, weight loss, lymphadenopathy, or deteriorated general condition were uncommon. These findings were present in only nine patients (11.2%); three of whom also showed hemophagocytic syndrome (HPS) (Table 1).

Out of the 86 cases, 17 were pediatric/adolescent patients (younger than 18 years old). Most of the patients in the pediatric/adolescent age group presented with more mild nasal or facial manifestations. These mainly comprised partial obstruction and slight nasal asymmetry. Superficial to deep palatal ulcers were the most significant sign of disease. Only two pediatric patients progressed to severe midfacial edema and extensive necrosis (Fig. 2).

According to patient reporting, symptoms ranged from 0.5 to 12 months in duration, with a mean of 4.8 months. Sixteen patients received previous clinical misdiagnoses such as chronic sinusitis or infection, including rhinoscleroma or mycosis (primarily aspergillosis). This resulted in initial treatments of antibiotics or antimycotics (Fig. S3 F–I). Some of these cases showed a mild to moderate initial response since ENKTCL-NT is often secondarily infected.

Further confounding the clinical diagnosis was an observed lack of mass effect. Asymmetry or increased volume was caused exclusively by edema and inflammation secondary to the angiodestruction rather than a tumoral mass.

The main features identified by computed tomography (CT) scan were destruction of the nasal septum, turbinates, lateral walls of the maxillary sinus, and floor of the orbit. Infiltration/occupation of the maxillary, sphenoid, ethmoid and/or frontal sinuses was also noted. Advanced cases had bilateral involvement (Fig. 3).

While most patients did not present with signs of disseminated disease, it was not completely ruled out. Additional studies such as whole-body CT scan, positron emission tomography (PET) scan, bone marrow aspiration, or biopsy were not routinely performed due to the financial limitations of the patient group. Instead, immediate treatment was prioritized in light of the rapid progression of this disease.

Microscopic Findings

A higher proportion of palatal mucosa biopsies contained viable tissue than those from the nasal skin or mucosa. The nasal samples frequently comprised entirely necrotic tissue, inhibiting adequate microscopic analysis and diagnostic confirmation by IHC and ISH.

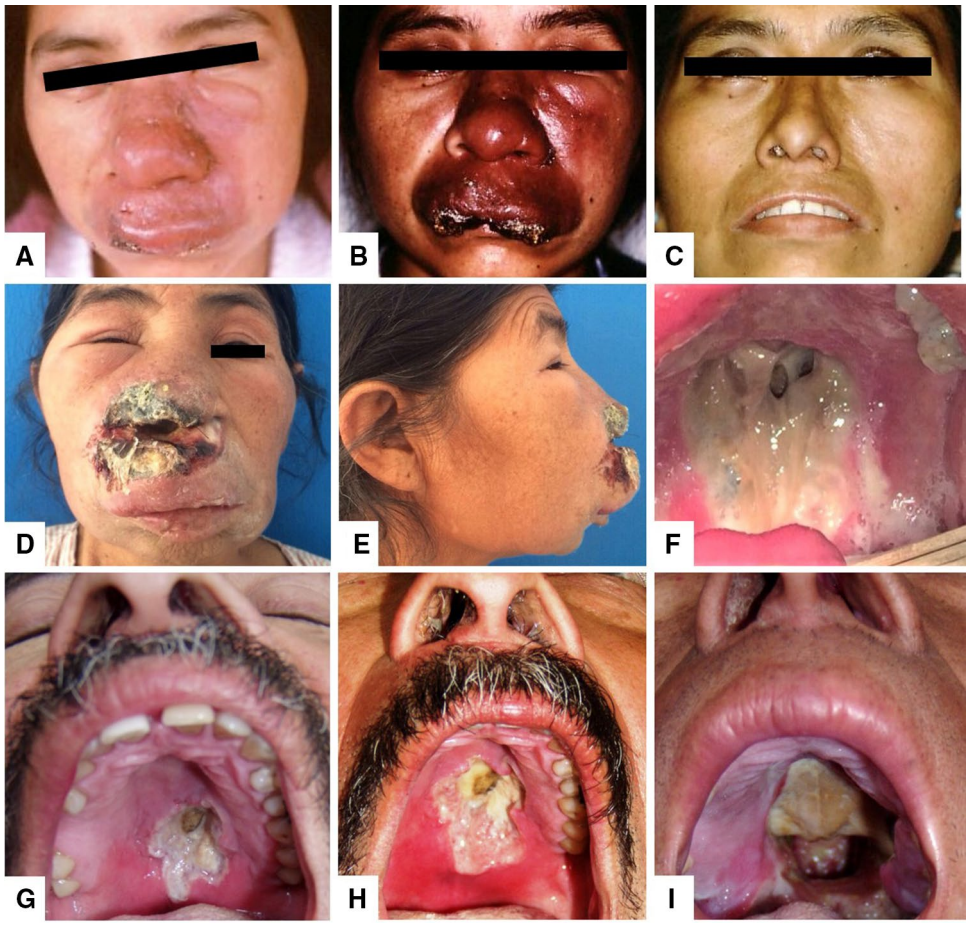

Fig. 1 Clinical features of ENKTCL-NT. **a–c** A 27-year-old female presented with initial midfacial edema, redness, and scabby and eroded areas (**a**). In 10 days, the disease progressed to a more severe presentation affecting upper lip, nose, and inferior eyelid (**b**). The same patient exhibiting complete remission seven years after concurrent chemoradiotherapy (RT-CHOP) (**c**). **d–f** A 60-year-old female presenting with a facial edematous, necrotizing, and destructive process with periorbital edema and a nasal epicenter (**d**, **e**). The upper lip, palate, and oropharynx were also affected (**f**). The time of evolution of the lesions was 2 months, and the patient died during treatment, three weeks after diagnosis. **g–i** A 54-year-old male showing a deep palatal ulcer without facial signs (**g**). After one week, the ulcer progressed in size with intense peripheral edema and redness (**h**). Nasal discharge was also observed. He exhibited extensive palatal destruction, perforation, and oroantral communication after two months duration of disease and beginning treatment (**i**). The patient died two weeks after this consult

Microscopically, all cases of ENKTCL-NT showed a diffuse polymorphic and atypical lymphocytic infiltrate. Angiocentric and angiodestructive growth patterns caused areas of geographic necrosis (Fig. 4a–c). Peripheral hyaline necrosis affected the walls of small to medium-sized blood vessels and was a histologic hallmark (Fig S8). Surface atrophy or ulceration with secondary superimposed subacute inflammation was present in most cases. Mitoses and clear cells were frequent.

We found 18 cases (20.9%) presenting with pseudoepitheliomatous hyperplasia (PEH). Most had minimal or no epithelial atypia, and the Ki-67 staining was restricted to the basal layer and lymphoid cells. Occasionally, focal areas of epithelial atypia were observed with an increase in Ki-67 staining. These features combined raised the potential for confusion with a squamous cell carcinoma (Fig S7).

The morphology of the neoplastic cells was variable. Cell sizes within the same tumor ranged between small, medium, and large. Most of the cases presented with small cells and admixed medium-sized cells, or medium cells mixed with large-sized cells. ENKTCL-NT with predominant small cells or predominant large cells (representing > 90% of tumor cells, according to the criteria of Mckelvie et al.) were less frequent (12.7 and 9.3% respectively) [12]. Medium and large cells showed higher pleomorphism than the small cells (Fig. S9). Depending on the cell size, the cytoplasm was scarce or more abundant. A variable number of cells had clear cytoplasm (Fig. S9).

Table 1 Clinical manifestations of extranodal NK/T-cell lymphoma, nasal type in Guatemalan patients

Type of manifestation	Present in (*n*)% of cases[a]
Nasal	*(61) 76.2%*
Breathing difficulty or nasal obstruction	(61) 76.2%
Necrosis affecting nasal skin, mucosa, septum	(33) 41.2%
Bloody discharge	(17) 21.2%
Snoring	(2) 2.5%
Oral	*(49) 61.3%*
Necrotic ulcers affecting: palate, vestibular sulcus, anterior upper gingiva, oropharynx	(42) 52.5%
Hard palate perforation (oroantral communication)	(8) 10%
Lip edema	(9) 11.2%
Tooth mobility	(2) 2.5%
Facial	*(45) 56.2%*
Midfacial edema, heat and erythema	(45) 56.2%
Skin erosion, ulceration and necrosis	(33) 41.2%
Inferior eyelid edema	(17) 21.2%
Periorbital edema	(9) 11.2%
Systemic	*(9) 11.2%*
Weight loss	(3) 3.7%
Hemophagocytic syndrome	(3) 3.7%
Lymphadenopathy	(2) 2.5%
Weakness and deteriorated general condition	(2) 2.5%
Headache	(1) 1.2%
Night fever	(1) 1.2%
Thrombocytopenia and neutropenia	(1) 1.2%
Others	*(34) 42.5%*
Ulcers with foul smell	(25) 31.2%
Painful lesions	(9) 11.2%

[a]Percentages were calculated based on 80 cases with detailed clinical description or documentation. Patients may present more than one specific manifestation form each group

The nuclear features were also variable. They were round or angulated and some had cerebriform morphology, irregular contours, or indentations. Nucleoli were mostly inconspicuous or small, but prominent nucleoli or macronucleoli were also identified, especially in large cells. In addition, granular or dense, coarse chromatin was commonly present.

Ancillary Studies

All cases were positive for ISH-EBV, fulfilling one of the most important diagnostic criteria. The IHC profile of the tumor cells included: CD3 cytoplasmic positivity; CD45RO positivity with membranous staining and higher intensity than CD3; strong granzyme-B positivity in all cases with a cytoplasmic dot-like and granular pattern; perforin positivity in most cases (82.3%), however, it was weaker than granzyme-B; CD56 positivity in most cases (83.7%) with membranous and sometimes focal expression; CD30 positivity in 39.2% of cases, most with membranous staining only in focal cells. Due to economic reasons, TIA-1 was performed in 18 cases, exhibiting positivity in all of them. The Ki-67 proliferation index ranged between 70 to 90% in tumor cells. CD20 and CD79a were negative in neoplastic cells but positive in the reactive B-cells present in most cases. The reactive B-cells comprised 5 to 20% of the total lymphoid infiltrate.

Additionally, IHC for CD34 and podoplanin (D2-40) was performed to assess blood vessel and lymphatic invasion/destruction (Fig. S8 D–F). We observed that blood vessels showing destruction or necrosis lost CD34 expression. Consequently, most of the blood vessels within the tumor showed weaker, discontinuous, or negative CD34 staining when compared to the well-preserved surface vessels. Immunostaining of podoplanin revealed the presence of lymphatic vessels subjacent to the surface epithelium (normally expected) but not in deeper portions of the tumor. Therefore, no evidence of lymphovascular destruction or invasion by H-E or IHC was identified.

Clinical Outcomes

The clinical follow-up data was available for 34 patients. Fifteen (44.1%) died and nineteen (55.9%) survived. Most patients who finished treatment showed complete remission of disease with no recurrences. Three cases, two pediatric and one adult, experienced relapse at 1, 2, and 10 years, respectively, after completing treatment. The mean follow-up time for those who completed the treatment was 6.6 years and ranged from 1 to 18 years.

We observed a marked difference in survival between adult and pediatric patients: 15 out 16 pediatric/adolescent patients (93.7%) survived with complete remission. The exception was an 8-year-old female who developed HPS (Fig. 2a, b). Available follow-up data from adult patients showed that 14 of 18 (77.7%) died shortly after diagnosis or during treatment, and only four (22.3%) survived with complete remission. Three of the four surviving adults were women. It is important to mention that periorbital edema in adults and HPS were both associated with 100% of mortality.

A 29-year-old male (Fig. S5 C, D) died due to hemorrhage subsequent to a contraindicated surgical process (partial maxillectomy, aiming to remove the necrotic bone). The patient was experiencing the side effects of chemotherapy and likely pancytopenic. A 14-year-old boy who also underwent debridement of the necrotic tissues survived and is in complete remission (Fig. 2c, d). These two patients were the only ones to undergo surgical procedures in the hospitals where they were treated.

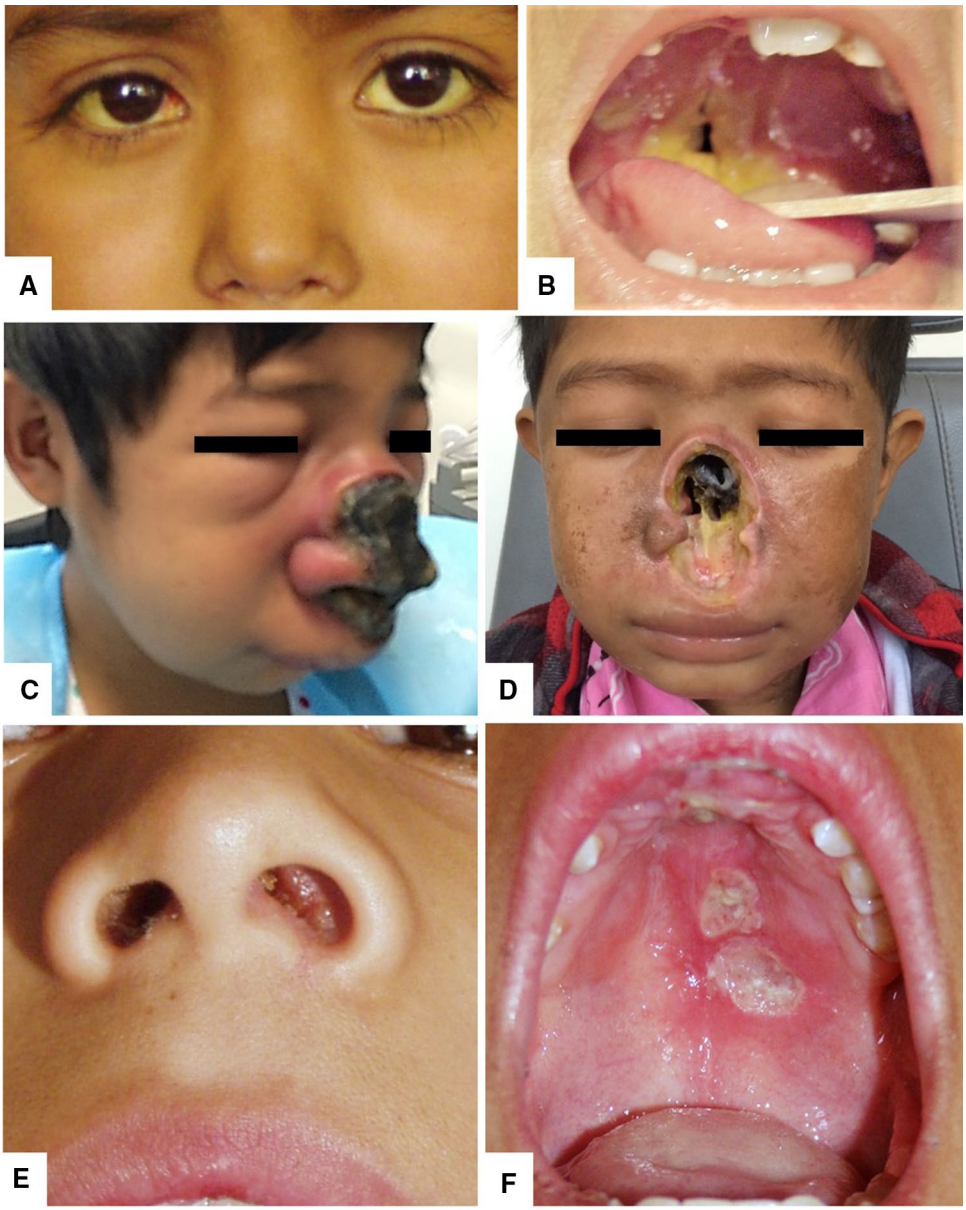

Fig. 2 Clinical features of ENKTCL-NT in pediatric patients. **a, b** An 8-year-old girl with hemophagocytic syndrome exhibiting jaundice including the sclera. Note the absence of facial edema or necrosis (**a**). A characteristic palatal ulcer with perforation, covered by yellowish fibrin, is present (**b**). This was the only pediatric patient with known fatal outcome. **c**, **d** A 14-year-old boy showing an unusual presentation in pediatric patients with extensive midfacial necrosis and edema, as well as bilateral periorbital and upper lip edema. After treatment, the patient is alive and under remission but with severe morbidity. **e**, **f** An 11-year-old boy showing the most common manifestations in pediatric patients with slight nasal asymmetry and mucosal edema of the left nasal fossa. Facial edema and necrosis are absent (**e**). Intraorally, superficial palatal ulcers with peripheral erythema were observed (**f**). The patient is alive and under remission after completion of treatment

One factor associated with higher mortality was error in initial diagnosis, which mostly occurred in cases interpreted as a nonspecific inflammatory process or necrotic tissue unsuitable for diagnosis. Misdiagnoses were the main factor for the delay of treatment (Fig S3 F, G). One patient developed drug-induced acute renal failure related to the use of IV Amphotericin-B (Fig S3 H, I).

Most patients were treated with concurrent radiation therapy and CHOP chemotherapy using cyclophosphamide, doxorubicin, vincristine, and prednisone (RT-CHOP). At the beginning of the present decade, this protocol was replaced by RT-2/3DeVIC (dexamethasone, VP16, ifosfamide, carboplatin) which increased the proportion of patients who showed remission compared to those who underwent RT-CHOP. Patients who experienced destructive midfacial or intraoral lesions survived with significant morbidity (Fig. 2c, d) (Fig. S1).

Discussion

This is one of the largest case series of ENKTCL-NT from a single diagnostic head and neck center in Latin America. This study confirms that ENKTCL-NT is an aggressive EBV-related lymphoma associated with indigenous ethnicities, low SES, and poor nutrition. This malignancy has distinctive clinical, microscopic, and immunohistochemical features; however, misdiagnoses may occur with necrotic or poorly representative samples. We emphasize the importance of intraoral examination since oral manifestations are

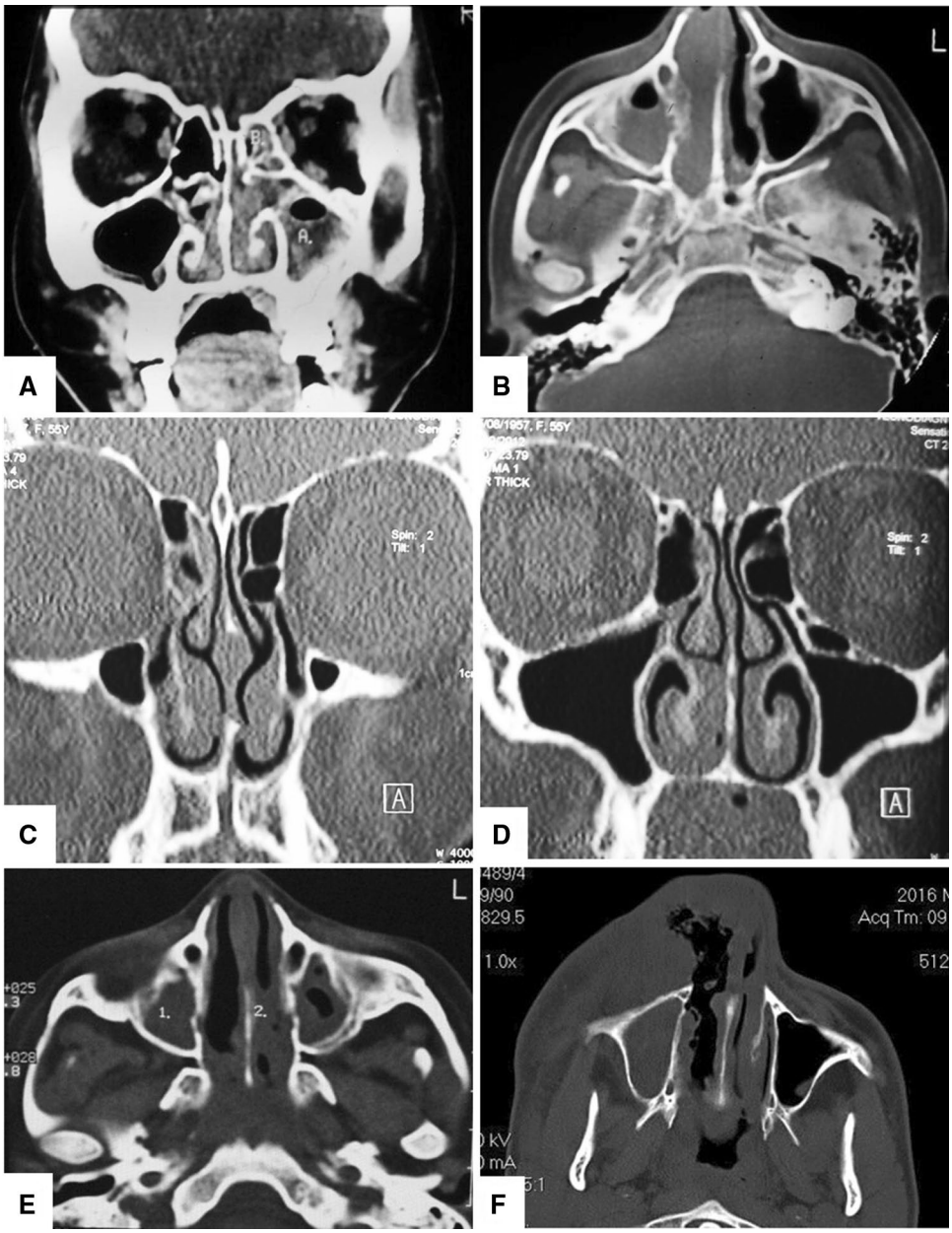

Fig. 3 Imaging of patients affected by ENKTCL-NT. **a**, **b** Computed tomography (CT) scan of an 11-year-old girl demonstrating involvement of the nasal cavity as well as the right maxillary and ethmoid sinuses (**a** coronal view, **b** axial view). **c**, **d** Coronal views of a CT scan of a 55-year-old female showing slight enlargement of the turbinates, and mild tumor occupation of the nasal cavity and left ethmoid sinus. The maxillary sinus is uninvolved. **e** Axial CT scan of an 8-year-old female (patient of Fig. 2 a, b) with involvement of the nasal cavity and both maxillary sinuses. **f** Axial CT of patient "A–C" from Figure "S3" showing opacification of the right maxillary sinus and nasal cavity, as well as markedly asymmetric facial contours

as frequent as facial or nasal signs. Oral mucosa biopsies, particularly from the hard palate, provide more representative and well-preserved tissue samples than those from nasal skin or mucosa.

Although ENKTCL-NT is the most common T-cell lymphoma in Guatemala, with significantly higher frequency than other countries in the Americas, it has been more extensively studied in Southeast Asian [2–11, 13]. The increased incidence in Guatemalan Mayans is theorized to be related to a shared ancestry with Asian people [14–16]. It is postulated that Amerindian Natives are descendants of people that migrated from Asia through the Bering Strait between 30,000 and 12,000 years B.C. Other theories, however, have been proposed [17].

In the United States (US), the incidence of ENKTCL-NT seems to be recently increasing. According to data from the National Cancer Data Base (NCDB) and Surveillance, Epidemiology, and End Results (SEER), the populations within the US principally affected are Asians and Native Americans compared to Caucasians or African Americans [18, 19]. This finding reinforces the association of this malignancy to ethnicity rather than geographic distribution. A study of 73 ENKTCL-NT cases at MD Anderson Cancer Center found most of the patients were white; but it must be considered that Latin American immigrants, particularly Mexicans, represent a high proportion of the Texas population [20, 21].

In accordance with the literature, most of the patients affected by ENKTCL-NT in our study were adult males.

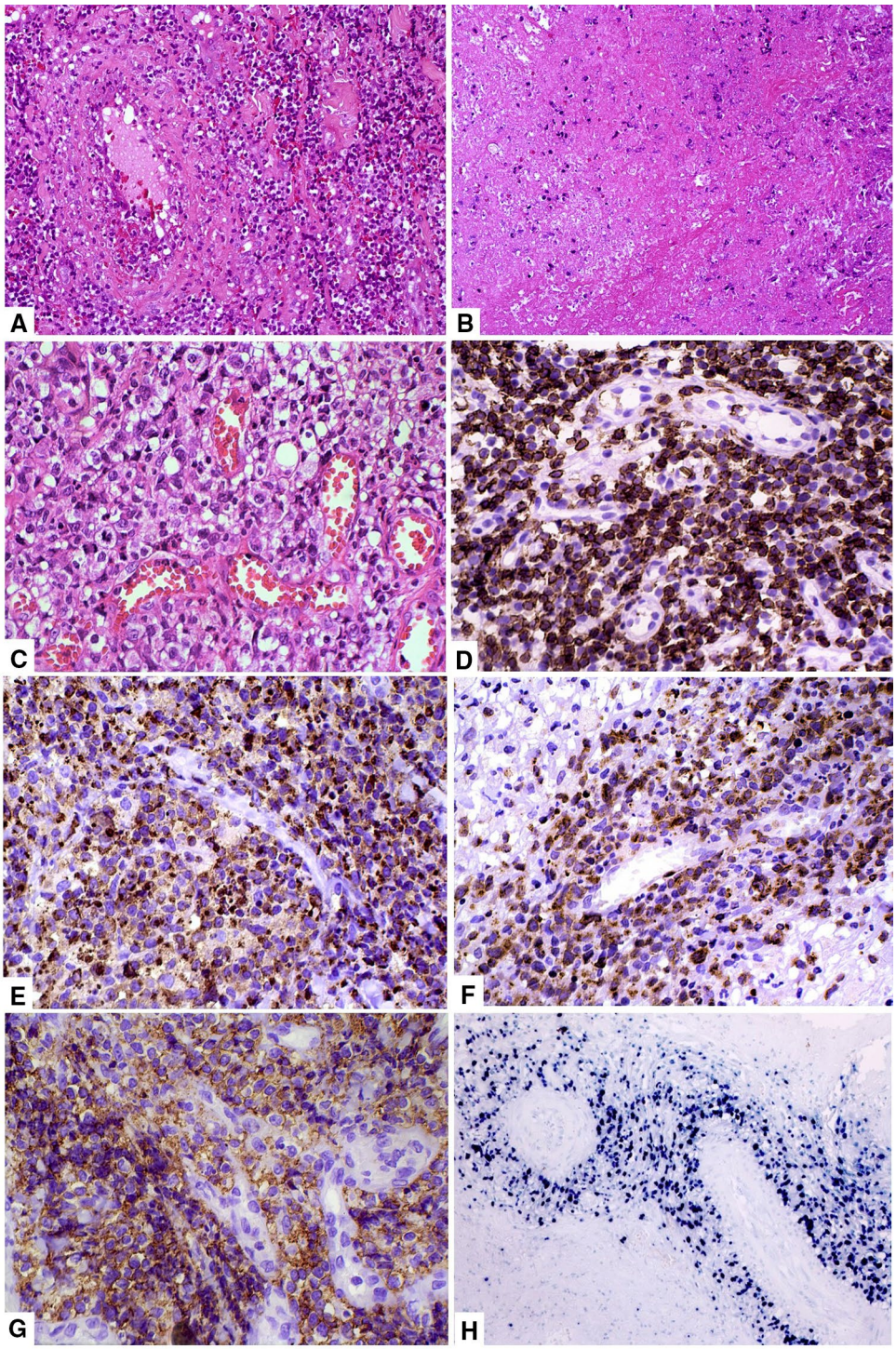

Fig. 4 Microscopic, immunohistochemical, and in situ hybridization features of ENKTCL-NT. **a** A lymphoid infiltrate of mixed small and medium-sized cells with an angiocentric and angiodestructive growth pattern. Perivascular hyaline necrosis is identified. **b** Geographic necrosis is common, especially in nasal biopsies. **c** A case with predominant large cells showing marked pleomorphism, mitotic figures with atypical forms, and irregular nuclear contours. Some cells have an eosinophilic, pale, granular cytoplasm while others have clear cytoplasm (H-E, a, b ×200; c ×400). The most useful immunohistochemical markers for confirm diagnosis are CD3 (**d**), granzyme-B (**e**), perforin (**f**) and CD56 (**g**). In a few cases, the latter may be negative. The angiocentric and angiodestructive patterns are highlighted by immunohistochemistry (IHC, **d**–**g**: ×400). **h** Positivity of Epstein Barr virus by in situ hybridization is necessary to confirm the diagnosis. Note the perivascular disposition of the positive cells (**h** ISH-EBV: ×200)

The mean age was lower (34.7 years old) when compared to previous studies (average age between 42 and 54 years) [4, 8, 11, 13, 20, 22]. This was likely due to 19.7% our cases occurring in pediatric/adolescent patients.

Geographic, racial, and sex predilections were previously described for ENKTCL-NT; however, few studies mention low SES as a factor associated with a higher incidence and more aggressive clinical presentation. In our study, 90.6% of patients were of low SES. Approximately 59.3% of Guatemalans live below the poverty line, particularly the indigenous population. This group represents more than 40% of the overall Guatemalan population. Chronic malnutrition is common and affects approximately one-half of children under the age of five [23–25]. Although the exact mechanism of the increased frequency among the Guatemalan Mayan population is unclear, variations in immunogenetic

background, undernutrition, environmental factors, and disparities in medical services received may be contributing factors [14, 15, 19, 26].

The potential link between socioeconomic factors and ENKTCL-NT necessitates further investigation in other impoverished populations. Cases of ENKTCL-NT with massive midfacial destruction have been described in patients from India, Senegal, and South Africa. In support of this association, some of these cases were also identified in patients of poor nutritional status and illiteracy [27–30]. Studies from septentrional and sub-Saharan Africa show different geographic and racial features than those classically described for ENKTCL-NT. This raises the possibility of an underestimated incidence in other underdeveloped countries [27, 30–34].

Lifestyle and environmental factors, principally associated with occupation, have also been suggested as potential risk factors for the disease. One report details Japanese father and son farmers who were affected within an interval of 26 months [35]. No genetic alterations were detected. The suspected risk factor was a constant exposure to pesticides [35]. Furthermore, a multicentric Asian study revealed a higher frequency of ENKTCL-NT in farmers, pesticide users, and chemical factory workers as compared to self-employed individuals and special workers [36].

The association between environmental factors and some EBV-related lymphomas and lymphoproliferative disorders is documented. Some examples include the role of malaria in endemic Burkitt lymphoma pathogenesis and the hypersensitivity to mosquito bites (HMB) in the development of cutaneous EBV-positive T-cell and NK-cell lymphomas. HMB affects mainly Asian and Latin American populations and is more common in childhood. Features overlap with hydroa vacciniforme-like lymphoproliferative disorder [37–40]. The etiologic potential of these environmental factors in NK/T-cell lymphoma should be further investigated in Guatemalan patients.

Careful clinical examination is important to avoid delay of treatment, especially in countries where the incidence is high and population is poor. Well-documented clinical descriptions of the disease are required in the literature. Clinical misdiagnoses such as infectious diseases or atrophic rhinosinusitis are common and delay proper management. Many patients experience several weeks or months of erroneous treatments before being biopsied [41–44]. To aid early clinical detection of this type of lymphoma, we present a detailed description and documentation of the spectrum of clinical findings. We also emphasize that intraoral examination and biopsy can be helpful for diagnosis. Oral signs are commonly present but underestimated since intraoral examination is not routine in some medical centers. Most case series do not mention the frequency of intraoral manifestations, but our findings, along with several previous studies, confirm that the incidence of oral involvement is high [3, 16, 41]. In fact, palatal ulcers were the most common presentation of disease among pediatric patients in this series.

Additionally, we found that tissue obtained from oral mucosa biopsies presented with less necrosis and superimposed subacute inflammation than those from nasal skin or sinonasal mucosa. These biopsies facilitated microscopic study and ISH-EBV and IHC analysis. This is supported by Miyake et al. (2014) who also recommended palatal biopsy over nasal to obtain more representative tissue [41]. The need for several biopsies to confirm diagnosis is frequently mentioned in the literature [45]. The first five patients in our series (diagnosed at the end of 1980s) needed two to four biopsies. However, once the spectrum of clinical manifestations of ENKTCL-NT was recognized and we discerned the palate was the best site for adequate biopsy, correct diagnosis was achieved in the first sample in almost all subsequent cases. The one exception was a case of recurrence in the larynx. The technical complexity and small endoscopic biopsy necessary in this location required three samples to confirm the diagnosis (Fig. S6 G, H).

Positivity for ISH-EBV in ENKTCL-NT is essential for diagnosis [1]. EBV is known to play a role in the pathogenesis of several lymphoproliferative diseases of NK/T-cell lineage, but the precise mechanism is still unclear. Initially, authors found common cytologic and cytogenetic features in EBV-positive NK cells in malignant and non-malignant lymphoproliferative conditions [46]. This suggested that EBV infection is not sufficient for malignant transformation of NK cells and additional genetic abnormalities may be involved [46]. Subsequent studies showed that cytokines, such as IL-2, IL-9 and IL-10, produced by EBV-infected NK cells and microenvironment cells promote proliferation and overexpression of the oncogenic protein LMP1 [47, 48]. Recently, it was discovered that EBV induces NF-κB activation thus contributing to the survival of infected NK/T-cells [49]. Also, it is suggested that EBV-infected NK cells proliferate as a chronic active EBV infection (CAEBV), and, during this process, they may acquire diverse genetic imbalances or aberrations that result in ENKTCL-NT [48]. Several molecular aberrations, principally in tumor suppressor genes such as p53 and dysregulations of the JAK/STAT and PDGF pathways, have been identified in ENKTCL-NT. These mechanisms can lead to proliferation and survival of malignant cells [48, 50–52].

Most, but not all, cases are CD56 positive, indicating a NK-cell lineage. Other NK-cell markers such as CD16 and CD57 are usually negative, however [1]. The proportion of CD56 positive cases reported in the literature is approximately 78–90% and similar to that reported in our study [8, 11, 20, 53]. Nevertheless, there are no clinical implications or prognostic differences between CD56+ and CD56− tumors or either ENKTCL-NT lineage [8,

54–56]. Additionally, previous studies found the frequency of CD30 positive cases ranges from 19 to 65%. It is more commonly positive in extranasal tumors with a focal staining pattern. Although there is controversy about the prognostic value of CD30, this marker was proposed as a potential therapeutic target using anti-CD30 antibody-based therapy (brentuximab vedotin) [11, 57].

In cases of ENKTCL-NT exhibiting PEH, squamous cell carcinoma may be included in the differential diagnosis [58]. Authors have reported this feature as occasional or uncommon, with a frequency of 3.8% [59]. We found PEH in 20.9% of the cases, that eventually exhibited epithelial atypia, architectural disorganization, and higher Ki-67 expression in focal areas. This finding may be a diagnostic pitfall for pathologists. The characteristic clinical and microscopic features of ENKTCL-NT should be carefully assessed to confirm diagnosis [10, 59, 60].

Historically, the prognosis of ENKTCL-NT has been poor, and some patients do not respond even with aggressive treatments [1]. Most case series report survival rates of 33–61%. The higher survival rates are in patients treated with a combination of chemotherapy and radiotherapy [3, 7, 8, 10, 11, 20]. If we consider all our patients with follow-up the findings are similar (55.9% survival). Importantly, we found a notably higher survival rate in pediatric/adolescent patients (93.7%) than adults (22.3%). Although there are scarce studies with data specific to age, it seems that treatment response is increased in young patients. The result is a higher survival rate (between 73–77%) when compared to adults [61, 62]. This finding is maintained even in patients in early stages of disease treated with radiotherapy alone [61, 62].

The standard treatment ENKTCL-NT is concurrent chemotherapy. Even in the initial stages of disease, treatment with radiotherapy alone has higher systemic failure rates [4, 63]. Chemotherapeutic regimens containing anthracycline (CHOP or CHOP-like) are now considered ineffective for ENKTCL-NT. This is explained by the presence of P-glycoprotein in the tumor cells which produces drug resistance [60, 64]. Non-anthracycline-containing regimens containing platinum and/or L-asparaginase (Such as DeVIC and GELOX) showed better results in the initial stages of disease. SMILE (steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) is indicated for advanced-stage or refractory disease [60, 64, 65]. This regimen is extremely toxic, however, and requires intensive supportive care, especially in older patients [10].

Surgical procedures are not effective in management of the disease, even with the aim of eliminating necrotic tissues. In fact, surgery is contraindicated especially when the patient is under the chemotherapy effects. Once neoplasia is controlled and the necrotic process stabilized, it is our recommendation to avoid or delay surgery for 12 to 18 months after treatment completion.

In our study 3 out of 86 patients (3.4%) developed HPS. This was characterized by high fever, jaundice, liver dysfunction, pancytopenia, and hyperferritinemia. All three patients presented with palatal ulcers and died 3 to 5 days after the onset of HPS (Fig. 2a, b) (Fig. S4 A, B, D). HPS is an uncommon complication in ENKTCL-NT. It can present at the time of diagnosis, during the clinical course, or as manifestation of relapse [5, 66]. In Asian patients, it is associated with early age and related to poor treatment response and low survival [6, 66].

Conclusion

In Guatemala, ENKTCL-NT represents an aggressive, EBV-related lymphoma associated with indigenous ethnicity and poverty. Since palatal ulcers are commonly found and represent the ideal site for biopsy, intraoral examination is essential. Awareness of its distinctive clinical, microscopic, and immunohistochemical features is important to avoid misdiagnosis and treatment delays.

Funding This work was supported by the São Paulo State Research Foundation (FAPESP), Grant/Award Number: 2017/14880-3, and by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Compliance with Ethical Standards

Conflict of interest The authors declared no conflict of interest with respect to this research, authorship, and/or publication of this article.

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