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Extranodal Nasal NK/T-Cell Lymphoma: A Rare Oral Presentation and FASN, CD44 and GLUT-1 Expression

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Extranodal natural killer (NK)/T-cell lymphoma is an aggressive malignant tumor with distinctive clinicopathological features, characterized by vascular invasion and destruction, prominent necrosis, cytotoxic lymphocyte phenotype and a strong association with Epstein-Barr virus. Here is reported an extranodal nasal NK/T-cell lymphoma case, involving the maxillary sinus, floor of the orbit, and interestingly extending to the oral cavity through the alveolar bone and buccal mucosa, preserving the palate, leading to a primary misdiagnosis of aggressive periodontal disease. Moreover, this work investigated for the first time the immunohistochemical expression of fatty acid synthase (FASN) and glucose transporter 1 (GLUT-1) proteins in this neoplasia. FASN showed strong cytoplasmatic expression in the neoplastic cells, whereas GLUT-1 and CD44 were negative. These findings suggest that the expression of FASN and the loss of CD44 might be involved in the pathogenesis of the extranodal nasal NK/T-cell lymphoma, and that GLUT-1 may not participate in the survival adaptation of the tumor cells to the hypoxic environment. Further studies with larger series are required to confirm these initial results.

Key Words: CD44, fatty acid synthase, glucose transporter 1, lymphoma.

Introduction

Extranodal natural killer (NK)/T-cell lymphoma is a very aggressive malignant neoplasia that presents a poor prognosis and limited survival rates (1,2). It is characterized by vascular damage and destruction, prominent necrosis, cytotoxic phenotype and association with Epstein-Barr virus (EBV) (3). The nasal cavity is the most commonly involved site, usually presenting extension to the oral cavity through destruction of the palate midline. These lymphomas are rare in Western populations, with higher prevalence in some Asian and Latin American countries (2-4).

Fatty acid synthase (FASN) is a key lipogenic enzyme responsible for the endogenous synthesis of fatty acids, catalyzing its biosynthesis from acetyl coenzyme A and malonyl coenzyme A (5,6). FASN is over-expressed in a variety of human malignancies and it is correlated with tumor progression and aggressiveness. Nevertheless, the involvement of this protein in the pathogenesis of extranodal nasal NK/T-cell lymphoma has not been evaluated. The increased expression of the glucose transporter-1 (GLUT-1) protein in aggressive, dedifferentiated and fast-growing malignant neoplasms, exemplify the adaptative property of metabolic switching from oxidative phosphorylation to glycolysis as the predominant energy production pathway of cancer cells (5,7). Therefore, GLUT-1 would be expected to be overexpressed in extranodal NK/T-cell lymphoma, especially due to the angiocentric and angiodestructive features, typically observed in this lymphoma. CD44 represents a polymorphic group of transmenbrane glycoproteins that is expressed in many types of tumors and it has long been linked to pro-oncogenic functions (8). However, a tumor suppressor role has also been attributed to these proteins both in solid and hematologic neoplasias, suggesting that CD44 structure-function must be separately analyzed in each tumor (9,10). CD44 has been extensively evaluated in different lymphoma subtypes; however, its role in the extranodal NK/T-cell lymphoma remains to be fully investigated.

Here is reported a case of extranodal nasal NK/T-cell lymphoma that extended to the oral cavity preserving the palate midline. Moreover, the immunohistochemical expression of FASN, GLUT-1 and CD44 proteins and their possible significance in the pathogenesis of extranodal NK/T-cell lymphoma were investigated and discussed.

Case Report

A 41-year-old female patient was referred to the Service of Oral Pathology of the João de Barros Barreto University Hospital, Brazil, complaining of a painful and extensive destructive lesion involving the buccal mucosa and upper gingiva, treated by her private dentist as a necrotizing ulcerative periodontitis. The extraoral examination showed

an erithematous asymmetry on the left side of her face with elevation of the nasal wing and inferior eyelid (Fig. 1A). The patient also presented nasal obstruction, mild fever and weight loss, but there was no cervical lymph node involvement. Intraoral examination revealed a large ulceration affecting the gingiva and buccal mucosa extending from the maxillary left second molar to the right first premolar, causing a significant alveolar bone loss and exposing the roots of several teeth (Fig. 1B). The palate mucosa was not involved by the lesion and no perforation could be observed clinically. Magnetic resonance image (MRI) revealed the presence of a lesion infiltrating the nasal cavity, extending to the maxillary sinus, floor of the orbit and vestibular alveolar bone, but preserving the palate (Fig. 1C,D). Oral manifestation of a leukemic condition or a lymphoma affecting the nasal and oral cavities were considered as differential diagnoses at this time. Systemic examination, hemogram and blood chemistries were normal and the ELISA **test** for HIV detection was negative.

Histopathological analysis showed the presence of a diffuse lymphoid infiltrate composed of small to medium-sized neoplastic cells with irregular nuclei, inconspicuous nucleoli and moderate pale cytoplasm, with scattered mitotic figures. A prominent amount of reactive plasma cells was found throughout the specimen. Significant areas of necrosis and an angiocentric and angiodestructive growth pattern could be easily identified (Fig. 2). An immunohistochemical analysis was carried out (Table 1) and positivity for LCA, CD3, CD3ε, CD30, CD43, CD45RO, CD56 and granzyme B (Figs. 3 and 4) was observed. Ki-67 labeling index was 49%. EBV *in situ* hybridization using an EBV-encoded small nuclear RNA (EBER)-1/2 probe was strongly positive (Fig. 3). The diagnosis of extranodal nasal NK/T-cell lymphoma was confirmed. The possible role of FASN, GLUT-1, and CD44 in the pathogenesis of this lymphoma was evaluated by immunohistochemistry. FASN was strongly positive in the cytoplasm of neoplastic cells, whereas GLUT-1 and CD44 were negative (Fig. 4). The patient was then referred for oncological treatment; unfortunately, she died three months after start of chemotherapy.

Discussion

Extranodal nasal NK/T-cell lymphoma is an aggressive malignant tumor consistently associated with EBV infection

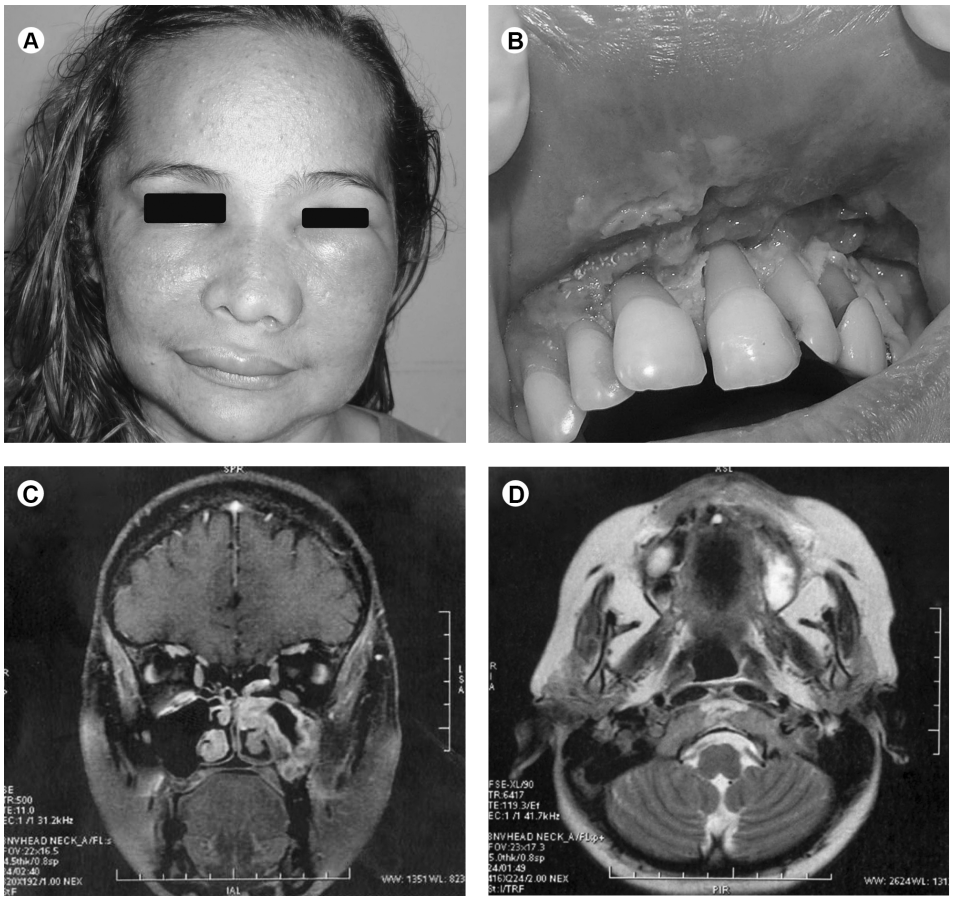

Figure 1. A: Erythematous facial asymmetry with elevation of the nasal wing and inferior eyelid. B: Large ulceration in the upper gingiva and buccal mucosa. C: Coronal and D: axial magnetic resonance image showing the involvement of the nasal cavity, nasal sinus and the preservation of the palate.

(3,11,12). Male adults are commonly affected and nasal cavity is the most frequently involved site causing nasal obstruction, nasal discharge, epistaxis and midfacial destructive and ulcerative lesions (4). Moreover, oral cavity is usually secondarily involved following palate midline destruction (1,2). Diagnosis of NK/T-cell lymphomas can be challenging, particularly in cases of unusual clinical presentation. The here reported case involved the oral cavity by destruction of the vestibular alveolar bone and buccal mucosa instead of the more common palate perforation of non-Asian patients. This led the patient's dentist to consider an initial diagnosis of necrotizing ulcerative periodontitis, delaying the prompt correct treatment of the patient. However, because of other clinical manifestations including facial swelling with elevation of the nasal wing and inferior eyelid regions and nasal cavity involvement, a more aggressive condition was considered, including an oral manifestation of leukemia and lymphoma. Since no systemic hematological alterations were found, a provisional diagnosis of lymphoma was raised.

Although EBV is strongly associated with extranodal nasal NK/T-cell lymphoma, little is known about the etiology of this aggressive lymphoma (13). Therefore, besides the usual antibodies used for diagnosis, in the current study was investigated the immunoexpression of FASN, GLUT-1 and CD44. FASN is a multifunctional

Table 1. Antibodies used for immunohistochemical analysis in the current case of extranodal nasal NK/T cell lymphoma.

Antibody	Source/clone	Dilution	Result
LCA	DAKO/2B11+PD7-26	1:200	Negative
CD20	DAKO/L26	1:10.000	Negative
CD79a	DAKO/JCB117	1:1.000	Negative
Plasma Cell	DAKO/VS38c	1:400	Negative
CD138	DAKO/MY15	1:100	Negative
EMA	DAKO/E29	1:400	Negative
CD3	DAKO/Polyclonal	1:300	Positive
CD3ε	DAKO/F7.2.38	1:200	Positive
CD43	DAKO/DF-T1	1:50	Positive
CD45RO	DAKO/UCHL1	1:200	Positive
CD56	Novocastra/CD56-1B6	1:50	Positive
Granzyme B	DAKO/GRB7	1:50	Positive
CD30	DAKO/BR-H2	1:40	Positive
CD57	DAKO/NK1	1:800	Negative
Ki-67	DAKO/MIB-1	1:100	49%
FASN	BD Bioscience/23	1:200	Positive
GLUT-1	Biosystems/Polyclonal	1:100	Negative
CD44	DAKO/DF1485	1:100	Negative

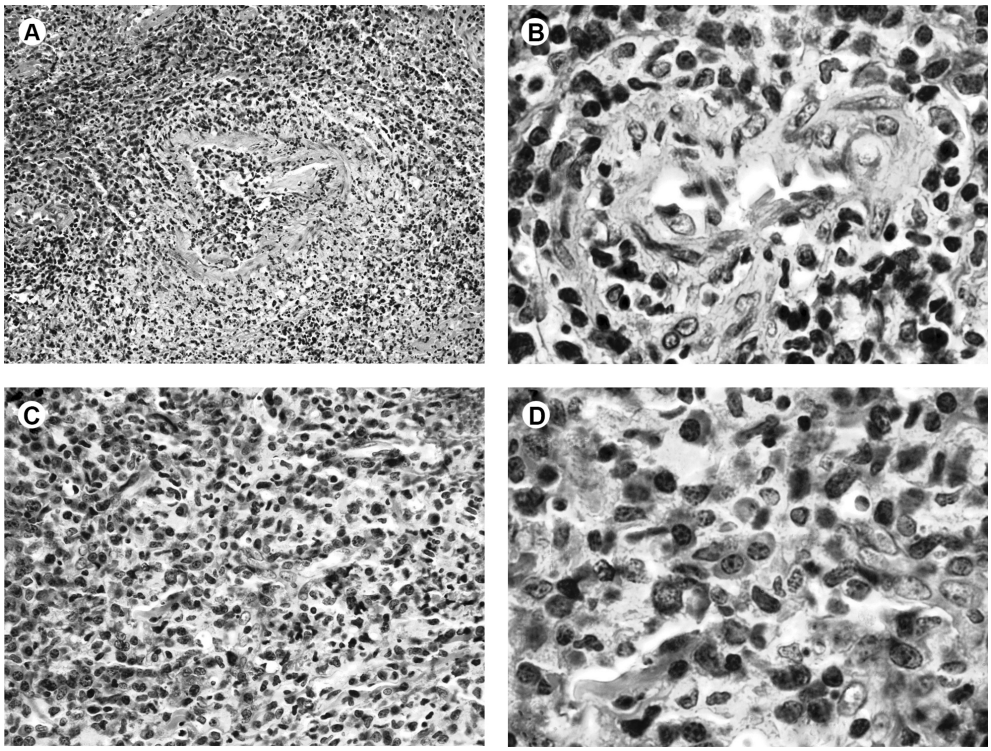

Figure 2. Histopathological features. A and B: Presence of a diffuse lymphoid infiltrate with an evident angiocentric and angiodestructive growth pattern (HE, A-100× and B-400×). C: Small to medium-sized cells with irregular nuclei and moderate pale cytoplasm (HE, 200×). D: Prominent amount of reactive plasma cells (HE, 400×).

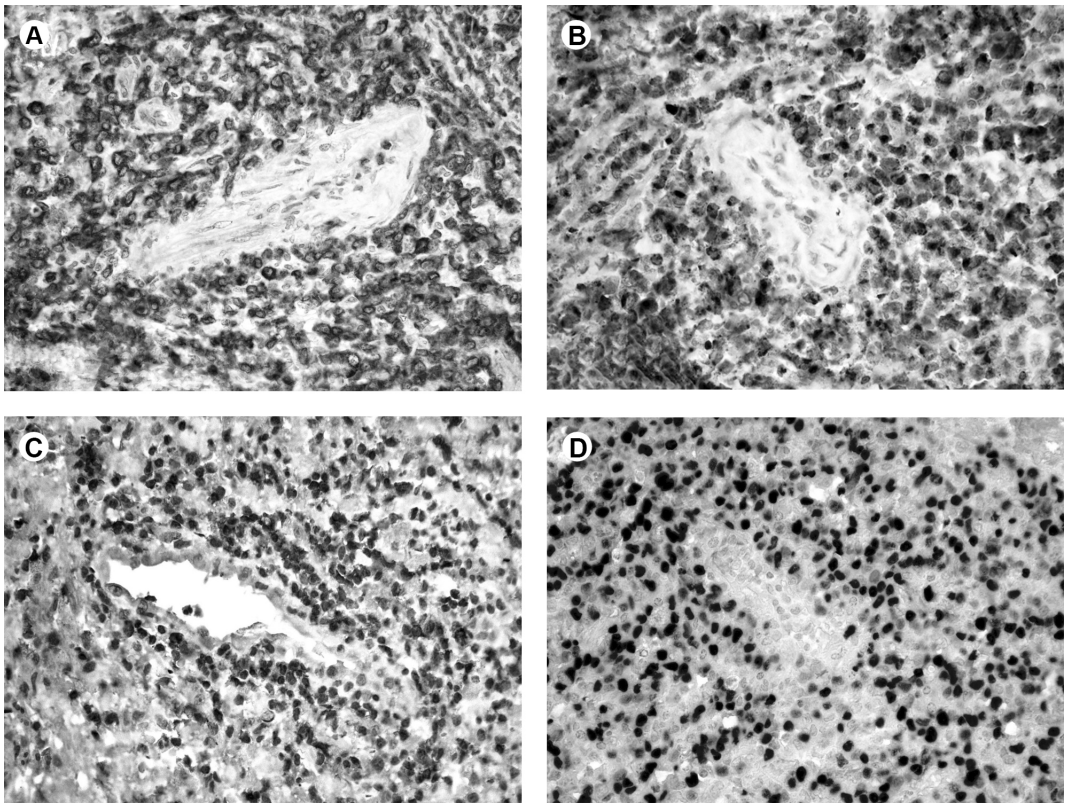

Figure 3. Immunohistochemical and *in situ* hybridization reactions. The neoplastic cells showed immunopositivity for CD3 (400×) (A), Granzyme B (400×) (B) and CD45RO (400×) (C). D: Positive nuclear labeling for *in situ* hybridization for EBV (EBER, 400×).

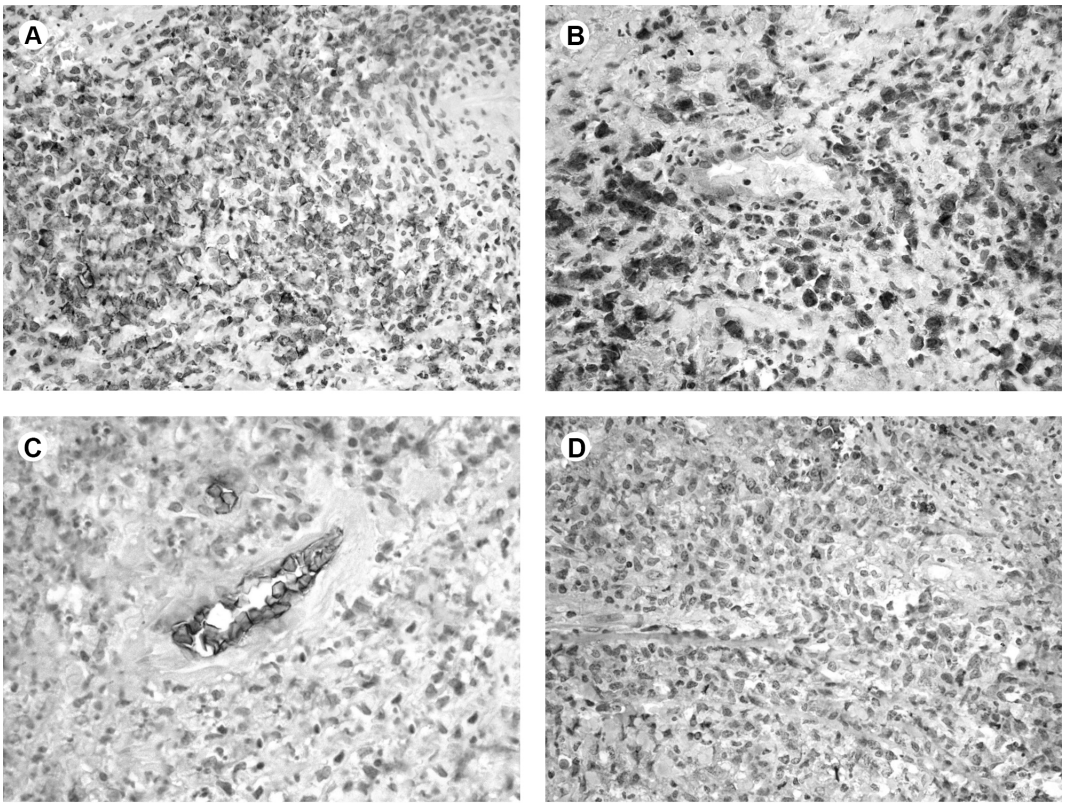

Figure 4. Positive immunohistochemical reactions for A) CD56 (400×) and B: FASN (400×) and negative immunohistochemical reactions for GLUT-1 (400×) (C) and CD44 (400×) (D).

enzyme that catalyzes the biosynthesis of long chain fatty acids as palmitate from acetyl coenzyme A and malonyl coenzyme A (5). Normal cells express relatively low levels of FASN, but it is overexpressed in various human neoplasias including hematological neoplasms, such as multiple myeloma, leukemia and diffuse large B cell lymphoma (6,14). Neoplastic cells in the present case showed a significant moderate to strong cytoplasmatic positivity, suggesting that this molecular biomarker might be involved in the pathogenesis of extranodal nasal NK/T-cell lymphoma, as also suggested for other hematological neoplasms. However, it would be interesting to confirm this observation in a larger series of NK/T cell lymphomas.

GLUT-1 is a glucose transporter that favors the glycolysis process, the predominant energy production pathway in cancer cells. Overexpression of GLUT-1 has been associated with tumor aggressiveness and poor patient survival rates in many human cancers (5,15). Expression of GLUT-1 was negative in the present case, suggesting that other glucose transporters may be involved in NK/T-cell lymphoma. CD44 represents the cell surface glycoproteins important for lymphocyte migration, homing, hemopoiesis, apoptosis and metastasis (8). It was recently shown that CD44 might behave as a tumor suppressor gene in several solid and hematopoietic neoplasias (10,16). As shown previously in nasal-nasopharyngeal NK/T-cell lymphomas (17), the present case was negative for CD44, indicating that this tumor suppressor gene might be epigenetically silenced in extranodal nasal NK/T cell lymphoma, favoring its development.

Extranodal nasal NK/T cell lymphoma presents a poor prognosis despite chemotherapy and radiotherapy treatments, as also shown in the present case (4,12). The search for new treatment modalities, including high dose chemotherapy followed by stem cell transplantation and the identification of new molecular markers that can be used as therapeutic targets, such as FASN and CD44, may improve the survival rate of patients affected by extranodal nasal NK/T cell lymphoma.

Resumo

O linfoma de células natural killers (NK)/T extranodal é um tumor maligno agressivo com características clinicopatológicas distintas, caracterizadas por invasão e destruição vasculares, necrose proeminente, fenótipo linfocítico citotóxico e uma forte associação com o vírus Epstein-Barr. Relatamos aqui um caso de linfoma de células NK/T nasal extranodal, envolvendo o seio maxilar, assoalho de órbita, e interessantemente estendendo-se para a cavidade oral através do osso alveolar e mucosa vestibular, preservando o palato, levando a um diagnóstico inicial equivocado de doença periodontal agressiva. Ainda, nós investigamos pela primeira vez a expressão imunoistoquímica das proteínas Fatty acid sinthase (FASN) e glucose transporter 1 (GLUT-1) nesta neoplasia. FASN revelou uma forte expressão citoplasmática nas células neoplásicas, enquanto GLUT-1 e CD44 foram negativas. Estes achados sugerem que a expressão de FASN e a perda de CD44 podem estar envolvidas na patogênese do linfoma de células NK/T nasal extranodal, e que GLUT-1 não deve participar da adaptação das células tumorais ao ambiente de hipóxia. Estudos adicionais com séries maiores são necessários para confirmar nossos resultados iniciais.

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