CD56$^-$ extranodal natural killer (NK)/T-cell lymphoma, nasal type presenting as skin ulcers in a white man

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INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL) rarely presents in the skin, with a relative frequency of less than 1% among primary cutaneous lymphomas.[1] It is most prevalent among Asian and South American natives.[2] Plaques or tumors located on the trunk are the most common presentation.[3] The prognosis is grave with a median survival time of 15 months from the time of diagnosis.[4] We present a case of CD56$^-$ ENKTL manifesting as 2 ulcers on the extremities of a white man.

Abbreviations used:

EBER:	Epstein-Barr virus–encoded small RNAs
EBV:	Epstein-Barr virus
ENKTL:	extranodal natural killer/T-cell lymphoma
NK:	natural killer
PET/CT:	positron emission tomography/computed tomography
R-CHOP:	cyclophosphamide, Adriamycin, vincristine, prednisone, plus rituximab
R-ICE:	ifosfamide, carboplatin, and etoposide plus rituximab
SMILE:	L-asparaginase, ifosfamide, methotrexate, etoposide, and dexamethasone
TCR:	T-cell receptor

CASE REPORT

A 61-year-old white man presented with rapidly enlarging 7- 8-cm tender dome-shaped nodules with central ulceration and necrosis on the left posterior calf (Fig 1) and left forearm (not shown). The patient complained of fatigue and night sweats over the prior week. The further examination was unremarkable with no other skin findings or palpable lymphadenopathy.

Skin biopsy of the left forearm showed a diffuse and nodular lymphohistiocytic and granulomatous infiltrate in the superficial and the reticular dermis centered around skin appendages and blood vessels (angiocentricity) extending in subcutaneous adipose tissue (Fig 2, *A* and *B*). Repeat biopsy 1 month later found a thinned epidermis with impending ulcer with extensive area of necrosis, lymphocyte exocytosis, basal vacuolization, and Civatte bodies (Fig 2, *C*). The dermis showed diffuse sheets of monotonous medium-sized cells with hyperchromatic nuclei that extended into the epidermis and included numerous (about 25%) large atypical lymphocytes (Fig 2, *D*). The infiltrate consisted of predominantly T cells and some CD20$^+$ B cells (Fig 3). Epstein-Barr virus (EBV)-encoded small RNAs (EBER) were positive in approximately 75% of the infiltrate. The atypical lymphocytes stained positively with CD2 and CD3 and exhibited loss of CD7 expression. Although there were many CD4 (about 75%) and fewer CD8 (about 25%) cells, the precise phenotype of the neoplastic cells was difficult to ascertain because of the numerous admixed reactive T cells. BF-1 was positive in about 75% of cells. LCA, TIA-1, and granzyme were positive in 50% of cells. CD5 highlighted background T cells. Ki-67 stained about 50% of the infiltrate. CD30 stained about 30% of the cells. FOXP3 and CD123 stained about 10% of cells. CD56 and CD34 were negative and CD57 stained rare cells. Southern blot did not detect T-cell receptor

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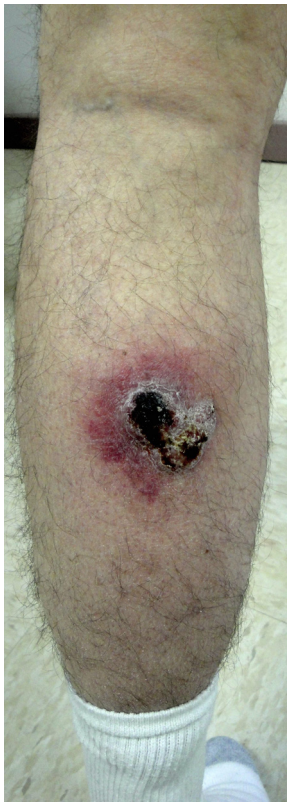

Fig 1. Extranodal NK-T cell presenting with rapidly expanding cutaneous ulcers in a previously healthy man.

(TCR)-β chain rearrangement in the sample from the left forearm, and TCR-γ chain rearrangement was indeterminate with polymerase chain reaction in the repeat biopsy owing to an inhibitor preventing amplification. EBV serology found significant elevation of VCA IgG antibody (>750 U/mL) and EBV nuclear antigen IgG (537 U/mL). Bone marrow examination was negative for lymphoma involvement.

Further evaluation and subsequent staging included a positron emission tomography (PET)/computed tomography (CT) scan, which found increased uptake in the left calf at the place of the original tumor as well as in tonsils and spleen (Fig 4). Enlarged lymph nodes were found in the cervical regions bilaterally; left superior mediastinum; and the retroperitoneal, splenic, and bilateral inguinal regions. An ear, nose, and throat examination was not performed but patient did not exhibit any of those symptoms.

Initially, after diagnosis, he was treated with radiation therapy to the lesion on his left leg and arm, and R-CHOP (cyclophosphamide, Adriamycin, vincristine, prednisone, plus rituximab). After six cycles of R-CHOP, he exhibited complete clinical remission. However, within 6 months, his disease recurred with subcutaneous nodules on his left chest wall, left lateral thigh, and the right scrotum. He was restarted on R-ICE (ifosfamide, carboplatin, and etoposide plus rituximab) for 3 cycles. His disease progressed despite initiation of intrathecal chemotherapy with depocyt, carmustine, etoposide, cytarabine, melphalan, and autologous stem cell transplant. He died 29 months after diagnosis.

DISCUSSION

ENKTL, nasal type, is a rare and aggressive malignancy. ENKTL accounts for a small minority of cutaneous lymphomas in the United States, where the condition is infrequently seen, as most often it presents in Asia and South America.[5] The correct diagnosis of ENKTL depends on cutaneous and extracutaneous manifestations, an involvement of the upper respiratory tract, histologic features, and immunophenotype.[6]

The most commonly affected site is the nasal cavity and nasopharynx.[6,7] The skin is involved in about 26% of cases.[8] Currently, the World Health Organization classification does not make a distinction for primary cutaneous disease presentation.[1,3,9] It is speculated that extranasal and nasal presentations fall on a spectrum of the same disease, as PET/CT reveals an occult primary tumor in most cases.[8] In concordance with this statement, our patient's PET/CT found tonsillar involvement with enlarged regional cervical lymph nodes.

ENKTL classically shows an angiocentric and angiodestructive polymorphic infiltrate of usually intermediate to larger lymphocytes with often elongated nuclei, sometimes admixed with other inflammatory cells and often associated with necrosis.[10] Although the original biopsy found extensive lymphohistiocytic infiltrate that was not further evaluated, the repeat biopsy found a more destructive pattern, typical of ENKTL, with a perivascular and periadnexal lymphocytic infiltrate invading the epidermis producing a large area of necrosis.

ENKTL shows CD2, CD56, and cytoplasmic CD3 positivity. CD56 was negative in our case. CD56 is a marker for NK cells, expressed in a subset of CD4 and CD8 cells, and is positive in 74% to 76% of cases of ENKTL.[11,12] A definite diagnosis of ENKTL in the case of CD56 negativity requires EBV positivity and expression of the cytotoxic proteins such as TIA1, granzyme B, or perforin.[3] Clonal TCR gene rearrangement is frequently nondetectable; however, a subset of tumors in some series do show evidence of T-cell lineage.[13] In this case, the T/NK cell antigen expression, positive EBER staining, TIA-1 positivity, granzyme B positivity, and a negative $\gamma\delta$ stain

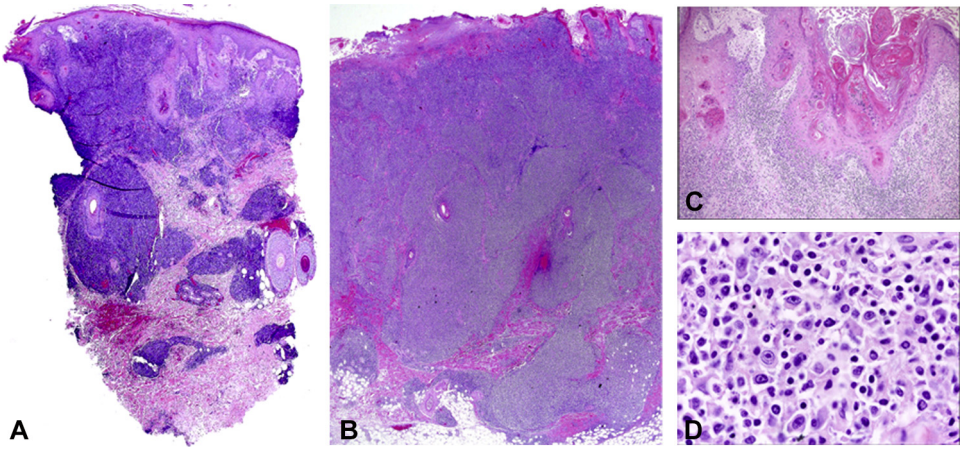

Fig 2. Biopsy from the left elbow. Hematoxylin-eosin stain shows a diffuse superficial and deep dermal infiltrate centered around skin appendages and blood vessels on a scanning (**A**) and close-up (**B**) magnification. A thinned epidermis with impending ulcer with a large area of necrosis, lymphocyte exocytosis, basal vacuolization, and Civatte bodies (**C**). Sheets of monotonous medium-sized cells with hyperchromatic nuclei and included numerous large atypical lymphocytes (**D**).

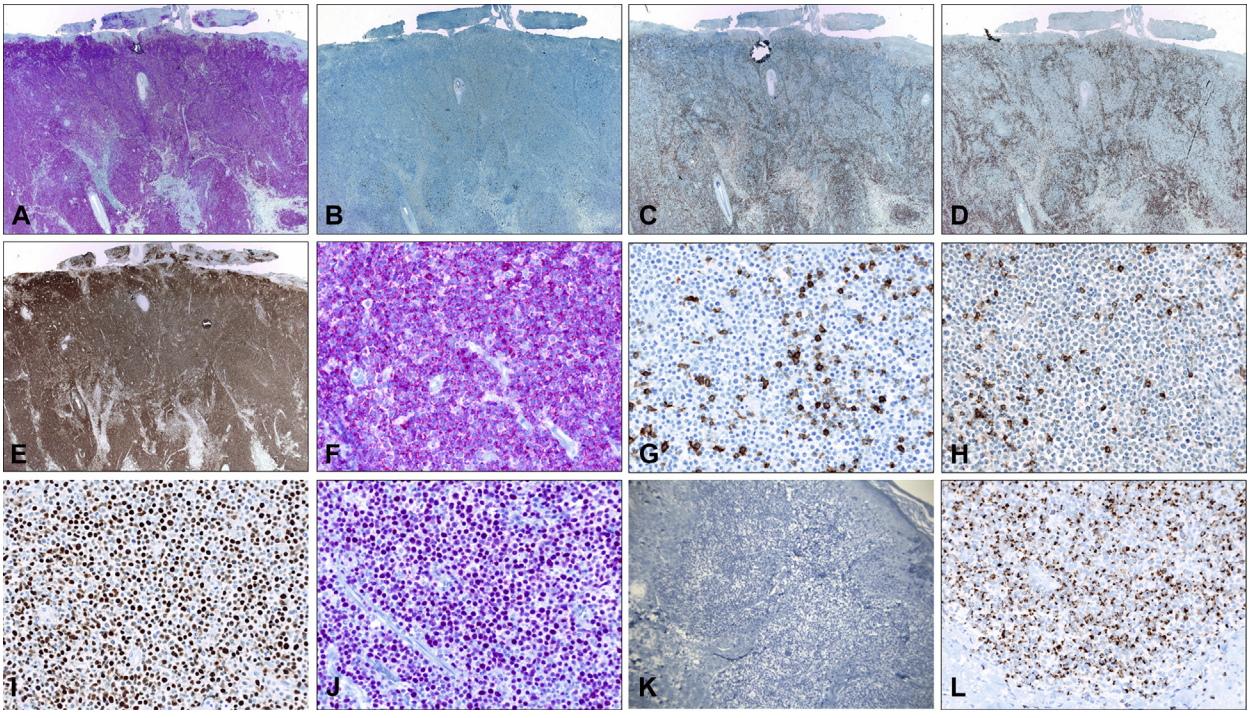

Fig 3. Immunohistochemical staining for CD3 (**A**), CD20 (**B**), CD4 (**C**), CD8 (**D**), CD43 (**E**), CD2 (**F**), CD5 (**G**), CD7 (**H**), EBER (**I**), Ki-67 (**J**), CD56 (**K**), granzyme B (**L**). CD2, CD3, CD43, Ki-67, EBER and granzyme B stain strongly. CD4, CD5, CD7, CD8 are somewhat diminished compared with CD2 and CD3 staining. CD56 is completely absent.

confirm the diagnosis of CD56^{-} ENKTL. TCR gene rearrangement was indeterminate. Whether the ENKTL reported here is of T cell or NK cell origin remains therefore undefined but does not impact the diagnosis.

Some investigators suggest that ENKTL with CD56 negativity should be described as a separate subtype, and some postulate that CD56 negativity is associated with a more aggressive clinical course.[14] In a retrospective study of 288 patients with early-stage

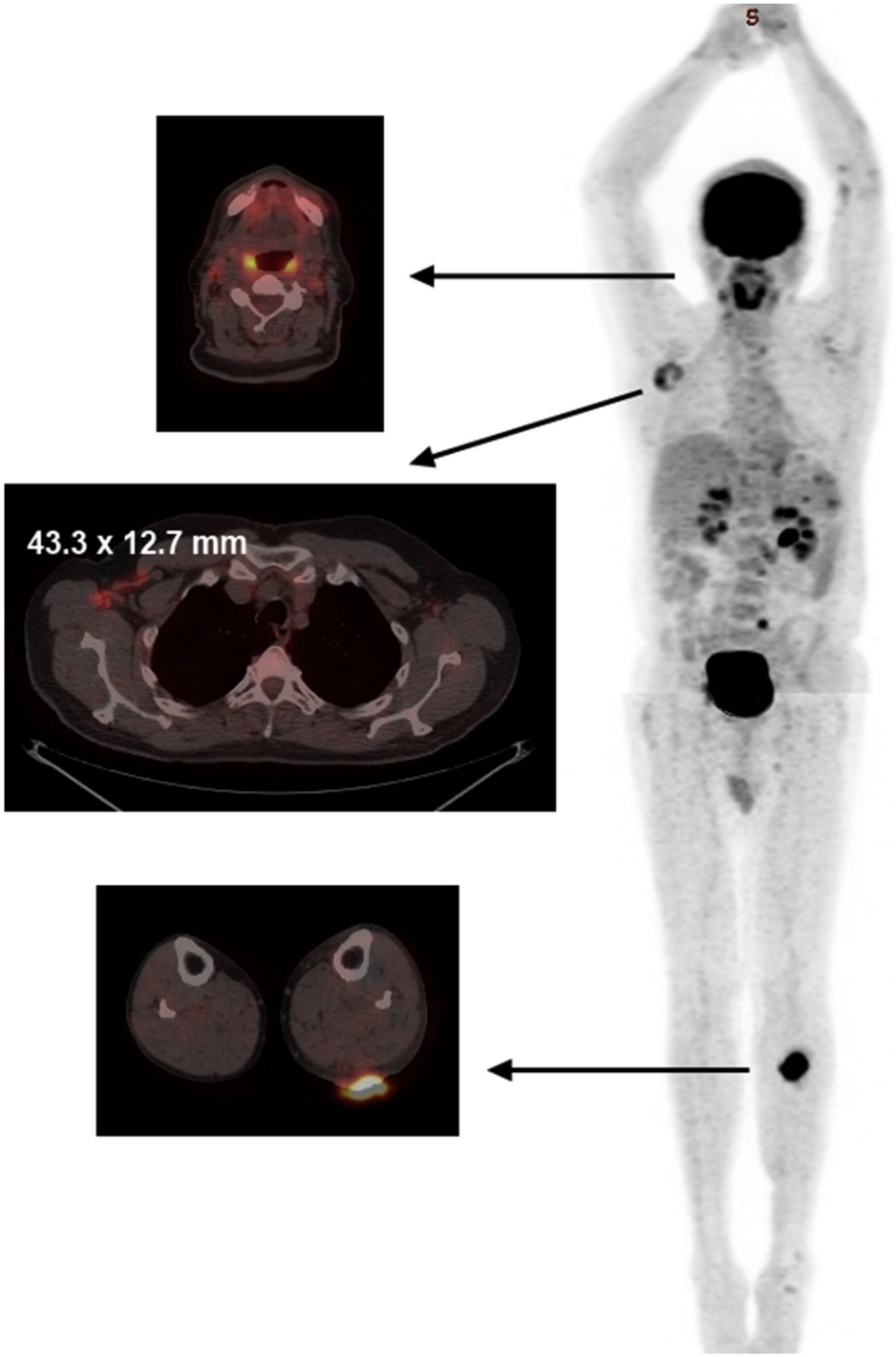

Fig 4. PET/CT scan image shows avid uptake in the tonsils, right axilla, and left calf.

upper aerodigestive tract ENKTL,[14] the remission rate of the $CD56^{+}$ group was 80.6%, whereas the $CD56^{-}$ group was 60.8%. Further, CD56 negativity also was associated with a lower 5- and 10-year progression-free survival. The case reported here, together with the previously published cases of $CD56^{-}$ ENKTL with cutaneous involvement, have many similarities regarding their clinical presentation and also appear to share a poor prognosis (Table I). All patients presented with an indurated plaque with frequent ulceration on the lower extremity. Histologic examination always found a heavy angiocentric lymphoid infiltrate with some degree of angioinvasion.

The differential diagnosis of an isolated necrotic rapidly evolving ulcer on the lower extremity is quite

Table I. Case reports of CD56$^-$ ENKTL with cutaneous involvement

	Kim et al[21]	Chia et al[6]	Little et al[22]	Lan et al[23] Patient 1	Lan et al[23] Patient 2	Lan et al[23] Patient 3
Gender	Female	Male	Male	Female	Male	Female
Age, y	35	51	60s	23	19	31
Location	Right thigh and upper arm	Left ankle	Left calf	Eyelid swelling lower extremities	Face, trunk, and upper/lower extremities	Trunk, upper/lower extremities
Morphology	Crusted plaque	Necrotic ulcer	Nodular plaque	Plaques	Plaques with ulceration and subcutaneous nodules	Plaques
Histology	Atypical lymphocytes with angiocentric infiltrate. Focal epidermal and dermal necrosis.	Atypical lymphocytes with prominent nuclei and angiocentric distribution	Atypical lymphoid cells, frequent mitosis, infiltration of blood vessels	Atypical lymphocytes with angiocentric growth and angioinvasion	Atypical lymphocytes with angiocentric growth and angioinvasion	Atypical lymphocytes with areas of necrosis and angioinvasion
Phenotype	CD3$^+$, CD8$^+$, granzyme$^+$, EBER$^+$, CD4$^-$, CD56$^-$, CD20$^-$	CD3$^+$, CD30$^+$, granzyme B$^+$, TIA1$^+$, CD5$^-$, CD56$^-$, EBER$^+$	CD2$^+$, CD3$^+$, CD5$^-$, CD7$^-$, CD4$^{+/-}$, CD8$^-$, CD30$^-$, CD56$^-$, TIA1$^+$, ALK$^-$, EBER$^+$	Cytoplasmic CD3$^+$, granzyme B$^+$, perforin+, CD8$^+$, EBER$^+$ CD56$^-$, CD4$^-$, CD5$^-$, CD20$^-$, CD3$^-$, CD68$^-$, CD79a$^-$, TdT$^-$, MPO$^-$	Cytoplasmic CD3$^+$, granzyme B$^+$, perforin$^+$, EBER$^+$, CD56$^-$, CD4$^-$, CD5$^-$, CD8$^-$, CD20$^-$, CD3$^-$, CD68$^-$, CD79a$^-$, TdT$^-$, MPO$^-$	Cytoplasmic CD3$^+$, granzyme B$^+$, perforin$^+$, EBER$^+$ CD56$^-$, CD4$^-$, CD8$^-$, CD5$^-$, CD20$^-$, CD3$^-$, CD68$^-$, CD79a$^-$, TdT$^-$, MPO$^-$
Treatment	Cisplatin-based regimen	SMILE, then ifosfamide/etoposide/dexamethasone, then DICE, then radiotherapy	EPOCH ×4, then SMILE ×2 then autologous SCT	CHOP	CHOP	CHOP
Response	Only moderate reduction in tumor size	SMILE - PD; ifosfamide/etoposide/dexamethasone − PR	2 months remission after EPOCH ×2; remission after SMILE ×2	PD	Died the day of treatment	
Survival from diagnosis	3 months and alive at presentation	9 months and alive at presentation	6 months and alive after SCT at presentation	3 mo		9 d

CHOP, Cyclophosphamide, vincristine, doxorubicin, and prednisone; *DICE*, dexamethasone, ifosfamide, cisplatin, etoposide; *EPOCH*, etoposide, prednisone, oncovin, cyclophosphamide, hydroxydaunorubicin; *PD*, progressive disease; *PR*, partial response; *SCT*, stem cell transplantation; *SMILE*, L-asparaginase, ifosfamide, methotrexate, etoposide, and dexamethasone.

extensive, whereas EBV positivity narrows the differential diagnosis to the following lymphomas and lymphoproliferative disorders: angioimmunoblastic T-cell lymphoma (although, the EBV^+ component is represented by the B cells and it is usually not neoplastic; if it is neoplastic, then it is classified as diffuse large B-cell lymphoma and not as angioimmunoblastic T-cell lymphoma); lymphomatoid granulomatosis; EBV^+ peripheral T-cell lymphoma, not otherwise specified; EBV-associated hemophagocytic lymphohistiocytosis; aggressive NK-cell leukemia; and 2 variants of cutaneous chronic active EBV infection—hydroa vaccinioforme–like lymphoproliferative disease (T/NK) and severe mosquito bite allergy (NK). EBV^+ lymphomas (both B- and T-) of many types can be encountered in the setting of immune suppression (grouped as posttransplant lymphoproliferative disorders). Immunohistochemistry, together with the morphologic and clinical findings, are essential in establishing the correct diagnosis.

Ann Arbor staging for nodal lymphoma rather than the classification for mycosis fungoides proposed by European Organization for Research and Treatment of Cancer is used for staging of ENKTL.[15] Because of the rarity of ENKTL and lack of randomized, controlled trials, current treatment protocols are consensus based.[15] For limited-stage disease (I/II), single modality such as radiotherapy or chemotherapy (if a patient is sufficiently fit) is recommended. Advanced disease (III/IV) is managed with a pegaspargase-based chemotherapeutic regimen (gemcitabine, pegaspargase, cisplatin, and dexamethasone or DDGP)[16] with or without chemoradiation (radiation and platinum-based chemotherapy) according to recent recommendations.[17] Our patient was treated 6 years ago initially with R-CHOP, which was prior to the DDGP regimen being reported. Clinical trials are an alternative option at any stage of ENKTL. If the patient is eligible, hematopoietic stem cell transplantation should be considered.[9,10] Previous studies confirmed low success rates with anthracycline-containing regimens. The overexpression of P-glycoprotein in tumor cells is deemed to be the cause of chemoresistance and early relapse.[18] In concordance with those data, 3 of 5 $CD56^-$ ENKTL patients responded poorly to CHOP (Table I). Two of 5 patients had some response to SMILE (L-asparaginase, ifosfamide, methotrexate, etoposide, and dexamethasone). L-asparaginase–based regimens such SMILE have been explored previously for advanced-stage and relapsed/refractory ENKTL, and significant responses were observed.[19] Recently, pegaspargase-based chemotherapeutic regimens were proposed as advantageous for pretreated ENKTL.[16] Our patient was treated with localized radiation, R-CHOP, R-ICE, intrathecal chemotherapy, and autologous stem cell transplant. He survived only 29 months after diagnosis, which is almost twice as long as reported median overall survival.

Interestingly, R-CHOP, in the case of our patient, provided a 6-month remission. There is a modern notion to include B-cell depletion strategies in the treatment of EBV^+ lymphoproliferative disorders, not of B-cell origin, based on the fact the EBV is harbored mainly in resting B lymphocytes.[20] During the T lymphocyte depletion, EBV-infected B cells have a higher potential for proliferation because of the diminishing of suppressive mechanisms. It would be interesting to know if a combination of rituximab with pegaspargase-based chemotherapy would improve overall survival, although its relevance in a case such as this in which the EBV is at least largely in the T-cells is uncertain.

Cutaneous manifestations of ENKTL must be considered in the case of rapidly progressing cutaneous ulcers even if the infiltrate is $CD56^-$.

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