

# Cutaneous extranodal natural killer/T-cell lymphoma mimicking cellulitis: A unique presentation



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## INTRODUCTION

Extranodal natural killer/T-cell lymphoma nasal type (ENKTL-NT) is a rare non-Hodgkin lymphoma associated with Epstein-Barr virus (EBV). It occurs most frequently at a median age of 50 years in men from Asia and Latin America.<sup>1</sup> Hallmark histopathologic features include an EBV-positive atypical lymphocytic infiltrate with extensive necrosis and vascular decimation.<sup>2</sup> Clinically, the majority of patients have a primary destructive mass in the midline nasal cavity, sinuses, and/or hard palate. Other common extranodal sites include skin, soft tissue, lungs, gastrointestinal tract, and testis. Cutaneous manifestations include erythematous plaques, ulcerations, or subcutaneous nodules in multiple areas of the trunk/extremities or a single lesion on the head/neck.<sup>1</sup> Herein, an unusual case of rapidly progressive ENKTL-NT in the lower extremity mimicking acute cellulitis is presented.

## CASE REPORT

A 53-year-old Hispanic male presented to the emergency department with painful left lower extremity swelling and erythema. He had recently completed a course of cephalexin for cellulitis of the left leg; yet, his symptoms worsened. Six months prior, enlarging bilateral adrenal and periaortic retroperitoneal masses were discovered incidentally on magnetic resonance imaging; however, the patient was lost to follow-up, preventing further work-up. On current presentation, he endorsed intermittent fevers, episodic night sweats, decreased appetite, and palpitations. He denied recent leg trauma or penetrating injury. Physical examination

### Abbreviations used:

EBV: Epstein-Barr virus  
ENKTL-NT: extranodal natural killer/T-cell lymphoma nasal type

revealed ill-defined, warm, confluent erythema, edema, and tender induration of the left calf (Fig 1).

Laboratory tests showed mild lymphocytopenia, moderate anemia, elevated creatinine protein kinase, elevated aldolase, and elevated lactate dehydrogenase. Peripheral blood flow cytometry did not show significant immunophenotypic abnormalities. Computed tomography and magnetic resonance imaging scans of the leg revealed myositis of the gastrocnemius muscle, extensive subcutaneous and superficial myofascial edema, and popliteal lymphadenopathy without lymphatic obstruction. The patient was started on intravenous ceftriaxone for high suspicion of cellulitis and pyomyositis.

A punch biopsy of the skin from the lower portion of the leg showed a sparse perivascular and interstitial infiltrate of enlarged atypical mononuclear cells in the reticular dermis and subcutis, not consistent with cellulitis. Given the findings of a gastrocnemius muscle biopsy flow cytometry performed just prior, which demonstrated 10% natural killer cells expressing CD2, CD3, CD7, CD56, as well as EBV, similar staining was performed on the skin. EBV-encoded RNA was detected by *in situ* hybridization (Fig 2, A), and immunohistochemical stains were CD 56<sup>+</sup> (Fig 2, B) and cytoplasmic CD3<sup>+</sup>. Cytotoxic markers TIA-1 and granzyme B were diffusely positive. Bacterial, mycobacterial, and

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**Fig 1.** Ill-defined, warm, confluent erythema, edema, and tender induration of the left calf.

fungal examinations were negative. A retroperitoneal mass core needle biopsy showed a similar population of neoplastic cells with Ki-67 immunostain, demonstrating a high proliferative activity of 70%-80%. There was no evidence of lymphoma cells in bone marrow biopsy. Polymerase chain reaction identified EBV DNA in the blood, with a viral load of 600,000 copies/mL. Fiberoptic rhinoscopy did not show a neoplasm of the nasopharynx. Positron emission tomography-computed tomography identified hypermetabolic tissue centered around the left para-aortic space and bilateral adrenal masses; no nasal lesions were found. Based on these findings, stage IV (both the tumor-node-metastasis staging system and the Ann Arbor staging system) extranodal natural killer/T-cell lymphoma, nasal type was diagnosed. The patient was started on 6 cycles of modified chemotherapy regimen (dexamethasone, ifosfamide, etoposide, and pegaspargase), with the ultimate plan of autologous hematopoietic stem cell transplantation.

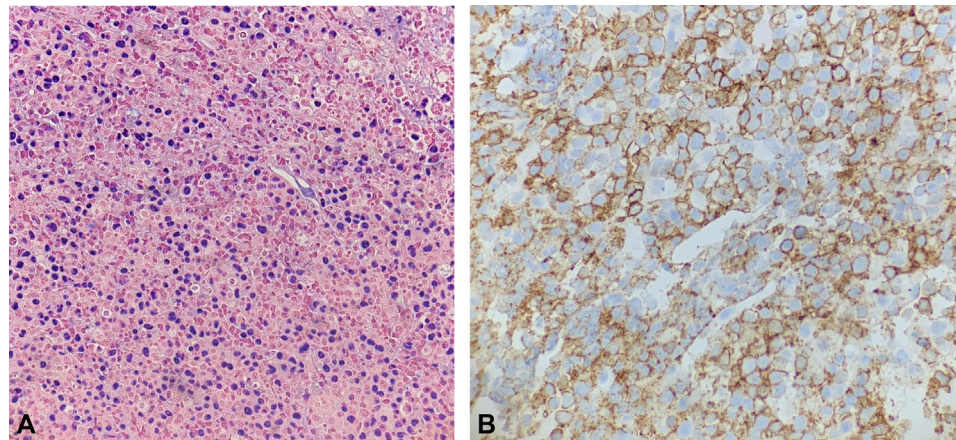
## DISCUSSION

This patient's previous abdominal imaging, multiple abnormal cell lines, and chronic B symptoms suggested an underlying hematologic malignancy of unknown type. Patients with hematologic malignancies are immunocompromised, and this patient's acute swelling, erythema, warmth, and tenderness of one lower extremity strongly suggested acute

cellulitis. Evidence of myositis on radiography along with delayed response to antibiotics suggested a progression to pyomyositis. While cutaneous ENKTL-NT can present as nodules or infiltrative plaques located on the trunk and extremities, this patient's unilateral cellulitis-like presentation in the absence of other cutaneous lesions is rare. Several other cases of cutaneous ENKTL-NT mimicking infectious skin conditions have been reported (Table 1).<sup>3-5</sup> In each case, the patients' underlying medical conditions and the frequency at which the favored diagnoses occurred in the general population led to initial misdiagnoses. However, these cases also illustrate the importance of comprehensive work-up when initial therapy is ineffective. In this case, histologic and immunophenotypic examination of the skin, muscle, and retroperitoneum confirmed the unifying diagnosis of ENKTL-NT.

Histopathologic analysis of ENKTL-NT demonstrated pervading necrosis with vascular findings of angiocentricity and angiodestruction. There were typically dense, polymorphous, perivascular infiltrates extending into the dermis and subcutaneous tissue. Tumor cells vary in size and feature pale cytoplasm, close-packed chromatin, and irregular nuclei.<sup>6</sup> EBV infection gives rise to natural killer cell lymphomagenesis, though the exact mechanism is unknown. EBV-encoded RNA was detected in the lymphocytic cells by *in situ* hybridization. Immunohistochemistry confirmed the diagnosis with CD2<sup>+</sup>, cytoplasmic CD3<sup>+</sup>, CD56<sup>+</sup>, and positive staining for cytotoxic proteins such as perforin, TIA-1, and granzyme B. If the cells are CD56<sup>-</sup>, diagnosis requires the presence of EBV and cytotoxic proteins.<sup>7</sup>

Prognosis of ENKTL-NT varies with the extent of disease involvement, but the overall 5-year survival rate is 30%. Serum lactate dehydrogenase is often elevated and associated with decreased survival along with increasing age, tumor stage, extranodal involvement, lymphadenopathy, and EBV DNA level.<sup>8</sup> Radiation may be used concurrently with chemotherapy in early disease; however, radiation alone results in high rates of relapse. Progressive disease requires multidrug treatment and often autologous hematopoietic stem cell transplantation. Natural killer cells express multidrug resistance-associated protein 1, leading to chemotherapy resistance to many types of drugs. The first-line chemotherapeutic regimen (steroid, methotrexate with leucovorin, ifosfamide, L-asparaginase, and etoposide) includes non-P glycoprotein efflux medications that are not affected by multidrug resistance-associated protein 1. Autologous hematopoietic stem cell transplantation has been shown to be advantageous when used during remission, although optimal use is yet to be determined.<sup>9,10</sup>



**Fig 2.** **A**, Densely packed mononuclear enlarged atypical cells in the gastrocnemius. EBV-encoded RNA was detected by *in situ* hybridization. **B**, Immunohistochemical staining was CD56<sup>+</sup>. *EBV*, Epstein-Barr virus.

**Table I.** Cases of ENKTL-NT mimicking other cutaneous conditions

Condition*	Age/Sex	Location	Associated condition	Biopsy	Ref
Diabetic ulcer	82, F	Lower portion of the leg	DM II	+	2
Abscess	28, M	Shoulder	HIV/AIDS	+	3
Panniculitis	14, F	Arms/legs	NR	+	4
Fasciitis	64, M	Upper portion of the arm	NR	+	5
Cellulitis	53, M	Lower portion of the leg	NR	+	CC

CC, Current case; *ENKTL-NT*, extranodal natural killer/T-cell lymphoma nasal type; *F*, female; *M*, male; *DM II*, diabetes mellitus type 2; *NR*, none reported; *Ref*, Reference.

\*This table includes selected examples of patients with of ENKTL-NT mimicking other cutaneous conditions. This list is not inclusive of all patients with atypical presentations of cutaneous ENKTL-NT.

When patients with hematologic malignancies present with signs of cellulitis, antimicrobial coverage is prudent during initial work-up. However, malignant cutaneous and soft tissue infiltration should be included in the differential diagnosis, especially for those who do not respond to broad-spectrum antibiotics. Multiple tissue sources aided in this patient's diagnosis; however, skin biopsy is the simplest procedure that can aid in the early diagnosis and treatment, which are imperative due to the aggressive nature of this disease.

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