A rare case of cutaneous Epstein-Barr virus–negative intravascular cytotoxic T-cell lymphoma

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Key words: CD4; cutaneous; cytotoxic; Epstein-Barr virus; intravascular; lymphoma; natural killer non-Hodgkin; T cell.

INTRODUCTION

Intravascular lymphoma is a rare type of non-Hodgkin lymphoma and is characterized by a malignant proliferation of lymphocytes inside the lumen of blood vessels.[1] Intravascular lymphoma is primarily an extranodal lymphoma, with skin and central nervous system reported as the most affected sites.[2] Most cases (approximately 90%) consist of B-cell origin, but T and natural killer (NK) cell lineages have also been reported.[3] Intravascular NK/T-cell lymphoma is typically related to the Epstein-Barr virus (EBV), expression of cytotoxic markers, and an aggressive course with an adverse prognosis.[2] Cutaneous intravascular NK/T-cell lymphoma can be difficult to differentiate, both clinically and immunohistologically, from other cutaneous lymphomas, such as intravascular cutaneous anaplastic large cell lymphoma, extranodal NK/T-cell lymphoma (nasal type), or blastic plasmacytoid dendritic cell neoplasm.[4,5] Within the cutaneous intravascular NK/T-cell lymphomas, most reported cases are of NK cell phenotype with a constant relation to EBV, and most patients die within 6 months.[2,6] Only sporadic cases with a (NK-like) T-cell phenotype are described, with a variable immunophenotype and disease course.[2,7,8] We describe the first case, to our knowledge, of a cutaneous EBV^- intravascular cytotoxic $CD4^+$ T-cell lymphoma, with a seemingly indolent disease course.

Abbreviations used:

EBER:	EBV-encoded RNA
EBV:	Epstein-Barr virus
NK:	natural killer
TCR:	T-cell receptor

CASE REPORT

An 87-year-old woman presented to our dermatology clinic with progressive, partly infiltrated, asymptomatic plaques with purpuric centers and telangiectases of 2 months' duration, mainly located on the trunk (Fig 1). A biopsy from the abdomen found a dermal infiltrate of large atypical lymphocytes located in the blood vessels. The atypical cells were confined to the vessel lumen and confirmed by endothelial CD34 staining. The intravascular lymphocytes expressed CD2, CD3, CD4, TIA-1, granzyme-B, and CD56, and showed a proliferation rate of more than 90% (Fig 2). T-cell receptor (TCR) rearrangements were positive for TCR-β (TCRb), and negative for TCR-γ. The atypical lymphocytes were negative for CD5, CD7, CD8, CD123, TDT, CD30, PAX-5, and CD20. EBV-encoded RNA (EBER) in situ hybridization was negative. Staging was performed with blood examination and positron emission tomography–computed tomography and showed no signs of extracutaneous involvement or active EBV infection. A primary cutaneous EBV^- intravascular cytotoxic $CD4^+$ T-cell lymphoma was

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Funding sources: None.
Conflicts of interest: None disclosed.
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JAAD Case Reports 2019;5:548-51.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.04.013

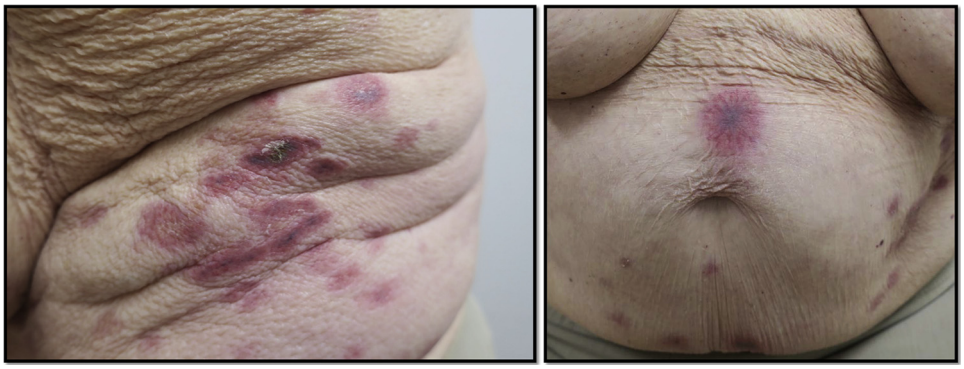

Fig 1. Progressive, partly infiltrated, asymptomatic plaques with purpuric center and telangiectasia, mainly located on the trunk.

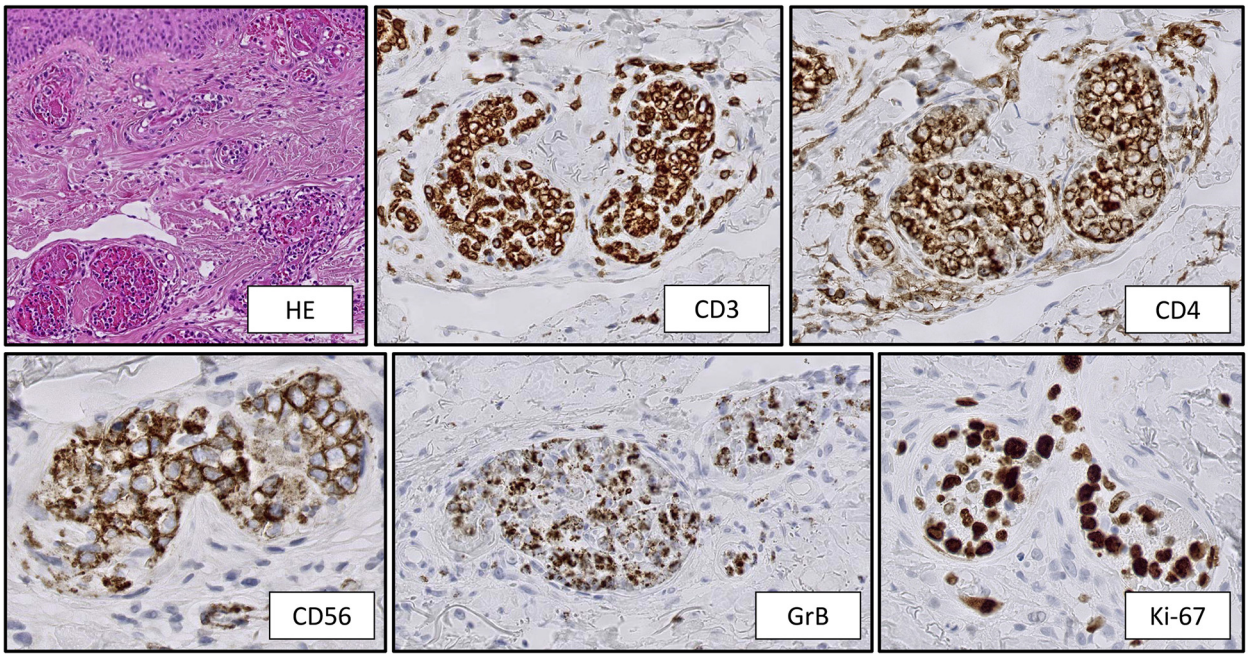

Fig 2. The atypical cells are confined to the vessel lumen. The intravascular lymphocytes express CD3, CD4, CD56, granzyme-B and Ki-67 greater than 90%.

diagnosed. Considering age and condition, the patient was not eligible for intensive systemic chemotherapy and, in cooperation with the department of radiotherapy, treatment was initiated with adjusted total skin irradiation restricted to the trunk. Considering the assumed aggressive nature of the disease, a relatively high palliative dose was used of 21 Gy in 12 fractions of 1.75 Gy, 2 times per week with 4 MeV electron beam. A complete response was observed; however, the patient relapsed after 2 months. Comparable to the initial presentation, multiple characteristic plaques were located mainly on the trunk. Because of the rapid relapse after radiotherapy and the impaired physical condition of the patient, prednisone, 10 mg/d, was administered with a partial response (>50% disappearance of lesions). After 12 months of follow-up, a second positron emission tomography scan and blood examination found no signs of extracutaneous disease, and patient was still alive with stable disease. However, the patient ultimately died 2 months later of cardiac failure (unrelated to disease).

DISCUSSION

Intravascular lymphoma, especially of NK/T-cell origin, is an extremely rare disease. Intravascular NK/T-cell lymphoma is usually primarily located in the skin, associated with EBV infection, a cytotoxic profile, and an aggressive disease course.

Table I. Characteristics of cutaneous (cytotoxic) intravascular T-cell lymphomas reported in the literature*

Case no.	Age	Gender	Type skin lesions	Immunophenotype/molecular analysis	Treatment	Status last follow up (mo)†
1. Cerroni et al[2]	87	M	Reddish-brownish lesions on the trunk	$CD3^+$, $CD4^-$, $CD8^-$, TIA^-, GrB^- $CD30^-$, $CD56^-$, $EBER^+$, PCR TCR^+	Died before treatment	D+ (0)
2. Alegria et al[6]	81	M	Purpuric plaques trunk	$CD3^+$, $CD4^-$, $CD8^-$, GrB^+, $CD30^+$, $CD56^-$, $EBER^+$, PCR TCR^+	Died before treatment	D+ (0)
3. Gleason et al[8]	62	M	Plaques on medial calves	$CD3^+$, $CD4^-$, $CD8^-$, TIA^+, GrB^+, $CD30^-$, $CD56^+$, $EBER^-$, PCR TCR^+,	Chemotherapy	A+ (8)
4. Martinez-Escala et al[9]	67	M	Purpuric patches on chest and abdomen	$CD3^+$, $CD4^-$, $CD8^-$, TIA^+, GrB^+, $CD56^-$, $EBER^-$, PCR TCR^+,	Chemotherapy and stem cell transplantation	Ao (6)
5. Okonkwo and Jaffe[11]	51	F	Plaques legs	$CD3^+$, $CD8^+$, GrB^+, TIA^+, $CD56^-$, $EBER^+$, TCR PCR^+	—	—
6. Sepp et al[12]	81	F	Hemorrhagic nodules trunk, face and extremities	$CD3^+$, $CD4^+$, $CD8^+$	Died before treatment	D+ (6)
7. Sepp et al[12]	75	F	Nodules upper legs	$CD4^+$, $CD8^{-/+}$, $CD30^{-/+}$, Southern blot TCR^+	Chemotherapy	D+ (18)
8. Jang et al[13]	23	F	Erythematous patches with fine red telangiectasias on trunk and extremities	$CD3^+$, $CD4^-$, $CD8^+$, TIA^+, GrB^+, $CD30^-$, $CD56^-$, $EBER^+$, PCR TCR^-	Chemotherapy	D+ (15)
9. Current case	87	F	Plaques trunk	$CD3^+$, $CD4^+$, $CD8^-$, TIA^+, GrB^+, $CD30^-$, $CD56^+$, $EBER^-$, PCR TCR^+	RT, prednisone	Do (14)

PCR, Polymerase chain reaction.
*With exclusion of intravascular cutaneous anaplastic large cell lymphoma.
†A+, alive with disease; Do, died of unrelated disease; D+, died of lymphoma.

Cutaneous intravascular NK/T-cell lymphoma can further be differentiated in intravascular NK-cell lymphoma and intravascular (NK-like) T-cell lymphoma. Most (cutaneous) intravascular NK/T-cell lymphomas reported in literature are $CD3^+$, $CD4^-$, $CD56^+$, TIA-1^+ and $EBER^+$ and suggest a NK-cell origin. T-cell receptor genes are not rearranged in true NK cells. Our current case showed expression of T-cell markers (CD2, CD3, CD4) and demonstrated TCRb rearrangements, which favors a T-cell origin. Besides the extremely rare intravascular T-cell phenotype, other peculiar findings are negativity for EBER/EBV and positivity for CD4 combined with a cytotoxic profile (CD56, TIA-1, granzyme-B).[7,9] This combination of an intravascular T-cell lymphoma with NK-cell characteristics can imply an NK/T-cell origin.[10] NK/T cells express or lack CD4 and CD8 and share features with NK cells such as CD56 expression and granzyme production and are important regulators of the immune response. We excluded blastic plasmacytoid dendritic cell neoplasm (intravascular distribution, $CD123^-$, $TCRb^+$), cutaneous anaplastic large T-cell lymphoma ($CD30^-$, no blasts), and extranodal NK/T-cell lymphoma (nasal type) ($EBER^-$, $CD4^+$, $TCRb^+$). In literature, only sporadic cases of cutaneous intravascular (cytotoxic) T-cell lymphomas have been described (Table I). Most patients were of older age (median age, 75; range, 23-87) and presented with purpuric plaques on the trunk. Of the patients with available data, 4 of 7 were $EBER^+$, 6 of 7 expressed cytotoxic markers, 4 of 5 were treated with systemic chemotherapy, and 5 of 8 died of disease.[2,6,8,9,11-13] Intravascular NK/T-cell lymphoma is extremely rare and usually associated with a poor prognosis. We report a new case of a cutaneous EBV^- intravascular cytotoxic $CD4^+$ (NK-like) T-cell lymphoma with an unusual phenotype and an indolent disease course.

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