A prominent cutaneous eruption as a harbinger for aggressive systemic disease: Gamma-delta T-cell lymphoma

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INTRODUCTION

Primary cutaneous gamma-delta T-cell lymphoma (PCGDTCL) and hepatosplenic gamma-delta T-cell lymphoma (HSGDTCL) are rare and aggressive neoplasms, both with an overall 5-year survival of 10%.[1,2] Even classic presentations of PCGDTCL and HGDTCL can be a diagnostic challenge due to the rarity of the conditions, variability of immunophenotypes presented in the literature, and variety of clinical presentations.[1-4] Hemophagocytic lymphohistiocytosis (HLH) is a severe condition caused by dysregulated immune activation that can be triggered by various conditions such as infections, malignancy, rheumatologic disease, and drug hypersensitivity.

We present a case of a patient who presented with a prominent cutaneous eruption and was diagnosed with gamma-delta T-cell lymphoma and HLH. The clinical and immunophenotypic presentation of this patient made distinguishing between PCDGTCL and HSGDTCL difficult. We identify key features of these conditions that provide a pathway to diagnosis.

Abbreviations used:

CHOEP:	cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone
HLH:	hemophagocytic lymphohistiocytosis
HSGDTCL:	hepatosplenic gamma-delta T-cell lymphoma
PCGDTCL:	primary cutaneous gamma-delta T-cell lymphoma

CASE

A 48-year-old, white male presented to the emergency department with a 4-month history of progressive, generalized weakness, constitutional symptoms, rigors, jaundice, anasarca, and a cutaneous eruption on his upper and lower extremities. He was immunocompetent and took no medications. The patient was alert and oriented. He was hypotensive (100/65 mmHg), tachycardic (109 beats/min), tachypneic (24 breaths/min) with normal oxygen saturation (99%, room air), and febrile (38.4 °C). He had light red coalescing plaques confined to the arms and legs (Fig 1), anasarca, and mild shifting dullness in his abdomen. There was no lymphadenopathy. The remainder of the exam was unremarkable.

Laboratory investigations showed pancytopenia, hyperferritinemia, elevated alanine aminotransferase, C-reactive protein, and elevated lactate

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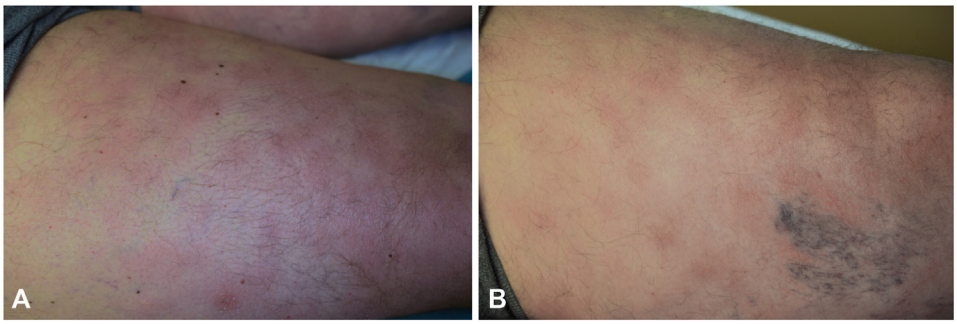

Fig 1. Clinical images, at initial presentation, of anterior (**A**) and anteromedial (**B**) leg with *light-red* to *violaceous*, coalescing plaques with telangiectasias (**B**). *Color photographs.*

dehydrogenase, and normal liver function tests and creatinine (Table I). A computed tomography scan of the chest, abdomen, pelvis, and lungs demonstrated fatty liver, moderate splenomegaly, no intrathoracic malignancy, diffuse anasarca, and scattered radiologically benign pulmonary nodules. Positron emission tomography scan showed no sign of internal malignancy.

Immunohistochemistry of a 4 mm punch biopsy of an indurated plaque identified a predominance of CD3-positive T-cells with co-expression of CD2, CD4, CD56, T-cell receptor delta, granzyme B, and TIA1 and appeared negative for CD8 and CD30. A significant loss in CD5, CD7, and BCL-2 was noted (Fig 2). In situ hybridization for Epstein-Barr virus-encoded RNA was negative. A DNA-based PCR assay identified a clonal T-cell receptor gamma gene rearrangement in the skin biopsy and was negative in the bone marrow. A bone marrow biopsy examination showed hematophagocytosis in a normocellular marrow with nondysplastic trilineage hematopoiesis. No abnormal lymphoid populations were identified by morphology, immunohistochemistry, and flow cytometry. A diagnosis of gamma-delta T-cell lymphoma and HLH was rendered.

The patient received one cycle cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone chemotherapy. He had minimal to no improvement. He developed an acute kidney injury and was started on hemodialysis. He was later transferred to the intensive care unit for continuous renal replacement therapy. His skin lesions became more eroded and hemorrhagic with increased exudate (Fig 3). After discussions with the clinical team, the patient declined further chemotherapy and chose to focus on comfort care. Nine days after comfort measures were initiated, the patient died.

Table I. Laboratory results of initial patient presentation

Laboratory investigation	Value	Reference range
White blood cell count, $\times 10^9$/L	4.0	4.5-11
Hemoglobin, g/L	136	140-180
Platelet count, $\times 10^9$/L	114	150-350
Ferritin, μ g/L	8285	6.5-204
Lactate dehydrogenase, U/L	922	120-130
C-reactive protein	47.91	0.00-7.99
Creatinine, u/L	88	64-104
Alanine aminotransferase, u/L	159	0-54
Alkaline phosphatase, IU/L	87	38-150
Total bilirubin, μ mol/L	20.3	0-20.4
INR	1.0	0.8-1.2

DISCUSSION

The defining feature of PCGDTCL is skin involvement. It most commonly presents as either ulcerating nodules, tumors, and deep plaques (panniculitis-like) or scaly erythematous plaques or patches that may progress to ulcers and tumors (mycosis fungoides-like).[1,4] These lesions typically present on the extremities and spare the trunk.[1] Patients often have constitutional symptoms and an elevated LDH.[3] The most common immunophenotype is CD2+, CD3+, CD4-, CD5-, CD7+, CD8-, positive/variable CD56, EBV-, and TCRδ+ ,β F1-.[1,3,4] Cytotoxic proteins are usually positive (eg TIA-1+, granzyme B+, and perforin+).[1,3,4] Molecular studies show TCR γ and TCR δ gene rearrangement.[1]

HSGDTCL rarely presents with cutaneous manifestations; however, several cases have been reported presenting as purpuric nodules, erythematous patches, hemorrhagic papules, and erythematous plaques.[5] It typically presents with constitutional symptoms, cytopenias, hepatosplenomegaly, and usually no lymphadenopathy.[2,3,6] The most common immunophenotype is CD2+, CD3+, CD4-, CD5-, CD8-, CD56+ (variable, usually positive), CD57-, EBV-, and TCR$\gamma\delta$+ showing in most cases, a nonactivated cytotoxic profile (TIA-1+, granzyme B-, perforin-), and CD7 loss has been frequently reported.[2,3,6] HSGDTCL usually infiltrates

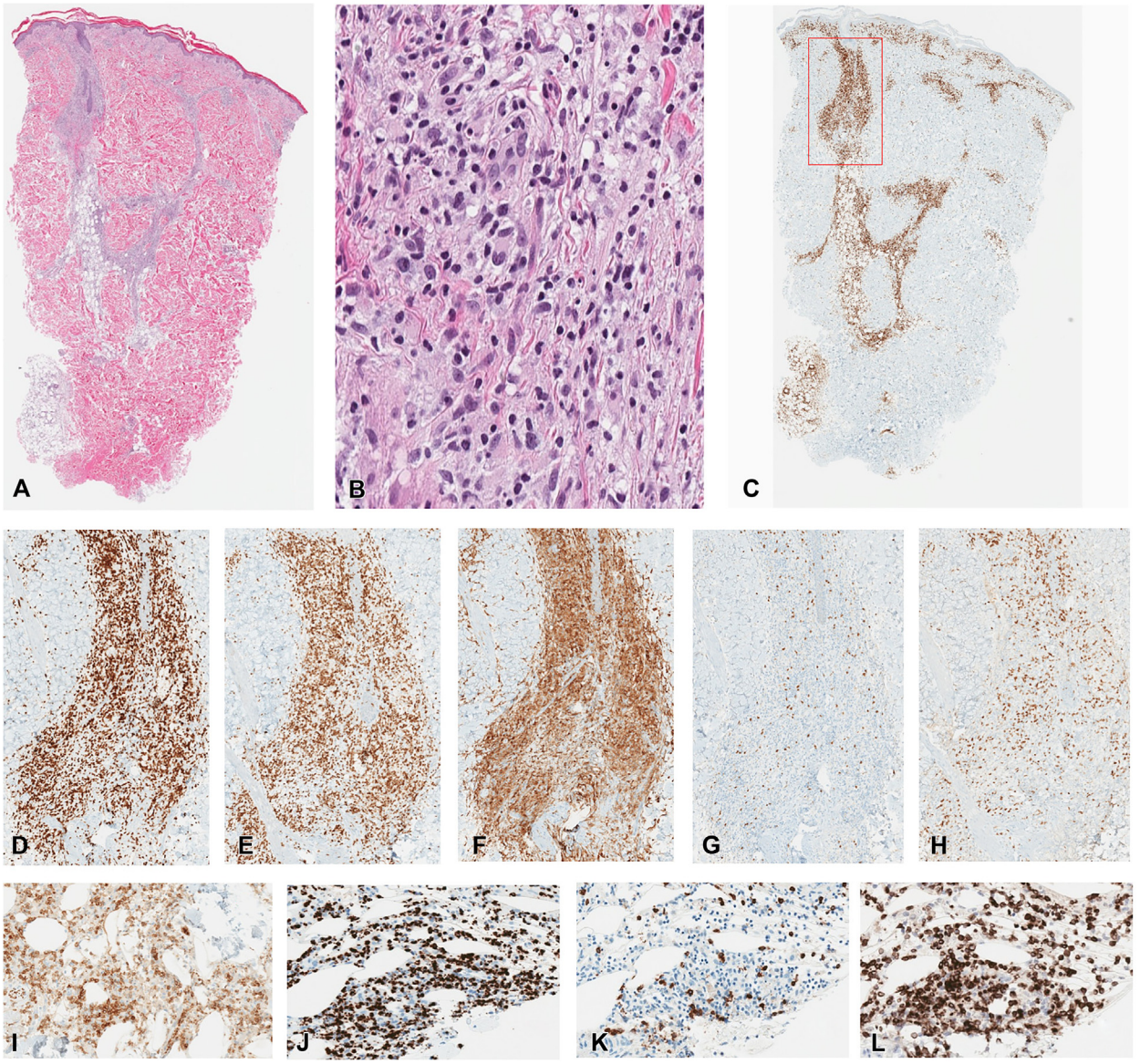

Fig 2. Photomicrographs. **A,** Whole mount H&E slide scan (**B**). High power view showing medium to large neoplastic cells with moderate nuclear atypia in a background of histiocytes and small lymphocytes (**C**). Scanning view showing CD3-positive staining and distribution of the T-cell infiltrate. The *red rectangle* highlights the area of additional T-associated immunostains (**D-H**). The neoplastic cells are positive for CD3 (**D**), CD2 (**E**), CD4 (**F**), and negative for CD8 (**G**). There is a reduced CD5 co-expression (**H**). Most neoplastic cells express strong and diffuse CD56 (**I**), granzyme B (**J**), and TCR delta (**L**). TCR beta F1 (**K**) stains reactive T cells. *Color photographs.*

the sinusoids of the splenic red pulp, liver, or bone marrow.[6] The latter is involved in 50% to >90% of cases and is frequently used for diagnosis.[6,7] The most common chromosomal abnormalities in HSGDTCL are isochromosome 7q and trisomy 8, which are found in approximately 50% to 60% of cases and help distinguish HSGDTCL from PCGDTCL when skin involvement is present.[2,3,5]

HLH has similar clinical findings including fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, and hemophagocytosis.[8] Skin manifestations such as generalized cutaneous eruptions, erythroderma, edema, purpura, and petechiae were reported in one-quarter of patients with HLH.[8]

PCGDTCL with constitutional symptoms[9] and/or HLH[10] may mimic the clinical presentation of HSGDTCL with cutaneous involvement. Our patient had constitutional symptoms and HLH. Because of the dominant skin involvement, a diagnosis of primary cutaneous gamma-delta T-cell lymphoma

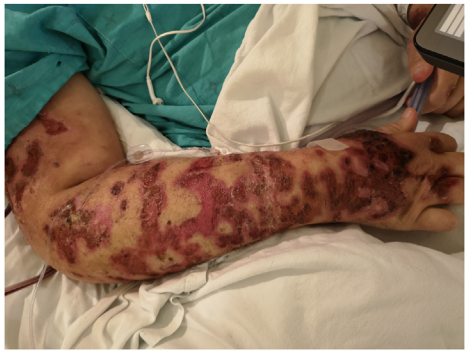

Fig 3. Right dorsal forearm 2 weeks postadmission demonstrating *dark pink* to *red*, erosive plaques, some with scale and thick overlying crust.

was made. Testing for chromosomal abnormalities was not clinically indicated, however, testing for isochromosome 7q and trisomy 8 may have provided diagnostic clarity.

PCGDTCL and HSGDTCL are 2 aggressive and rare lymphomas that are diagnostically challenging entities. The presence of cutaneous involvement, negative bone marrow biopsy, and cytotoxic profile favors a diagnosis of PCGDTCL in this case.

Conflicts of interest

None disclosed.

REFERENCES

1. Ramachandran P, Aggarwal A, Chin Wang J. Gamma-delta T-cell lymphoma: an overview. In: Paolo Piccaluga P, ed. Peripheral T-cell lymphomas. IntechOpen; 2019.
2. Pro B, Allen P, Behdad A. Hepatosplenic T-cell lymphoma: a rare but challenging entity. *Blood*. 2020;136(18):2018-2026. https://doi.org/10.1182/blood.2019004118
3. Foppoli M, Ferreri AJM. Gamma-delta T-cell lymphomas. *Eur J Haematol*. 2015;94(3):206-218. https://doi.org/10.1111/ejh.12439
4. Stoll JR, Willner J, Oh Y, et al. Primary cutaneous T-cell lymphomas other than mycosis fungoides and Sézary syndrome. Part I: clinical and histologic features and diagnosis. *J Am Acad Dermatol*. 2021; 85(5):1073-1090. https://doi.org/10.1016/j.jaad.2021.04.080
5. Santonja C, Carrasco L, Pérez-Sáenz MDLÁ, Rodríguez-Pinilla SM. A skin plaque preceding systemic relapse of gamma-delta hepatosplenic T-cell lymphoma. *Am J Dermatopathol*. 2020; 42(5):364-367. https://doi.org/10.1097/DAD.0000000000001569
6. Yabe M, Miranda RN, Medeiros LJ. Hepatosplenic T-cell lymphoma: a review of clinicopathologic features, pathogenesis, and prognostic factors. *Hum Pathol*. 2018;74:5-16. https://doi.org/10.1016/j.humpath.2018.01.005
7. Bojanini L, Jiang L, Tun AJ, et al. Outcomes of hepatosplenic T-cell lymphoma: the mayo clinic experience. *Clin Lymphoma Myeloma Leuk*. 2021;21(2):106-112.e1. https://doi.org/10.1016/j.clml.2020.09.013
8. Freedman AS, Aster JC. Clinical manifestations, pathologic features, and diagnosis of hepatosplenic T cell lymphoma. 2023. Accessed October 23, 2023. https://www.uptodate.com/contents/clinical-manifestations-pathologic-features-and-diagnosis-of-hepatosplenic-t-cell-lymphoma?search=hepatosplenic%20t%20cell%20lymphoma&source=search_result&selectedTitle=1~44&usage_type=default&display_rank=1#H13
9. Guitart J, Weisenburger DD, Subtil A, et al. Cutaneous γδ T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. *Am J Surg Pathol*. 2012;36(11): 1656-1665. https://doi.org/10.1097/PAS.0b013e31826a5038
10. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood*. 2008;111(2):838-845. https://doi.org/10.1182/blood-2007-04-087288