Received: 5 May 2023 | Revised: 1 June 2023 | Accepted: 8 June 2023

DOI: 10.1002/jha2.737

eJHaem

HAEMATOLOGY IMAGES

Primary cutaneous T-follicular helper lymphoma

Elena M. Fenu[1] | **Tatyana Milman**[2] | **Robert Penne**[2] | **Farah El-Sharkawy Navarro**[1] | **Guang Yang**[1] | **Adam Bagg**[1]

[1]Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]Department of Ophthalmology, Wills Eye Hospital and Jefferson University Hospital, Philadelphia, Pennsylvania, USA

Correspondence
Elena M. Fenu, Department of Pathology and Laboratory Medicine, Division of Hematopathology, 7 East Gates Pavilion, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA, USA.
Email: Elena.Fenu@Pennmedicine.upenn.edu

KEYWORDS
haematological malignancies, lymphoid malignancies, T cells

A 76-year-old woman presented with a subcutaneous left eyelid mass (Figure 1, top left) present for 3 months, along with pruritic eruptive skin lesions of the face, chest, neck, and arms, which developed days to weeks later. A staging positron emission tomography (PET) performed 2 months after diagnosis highlighted the left lacrimal gland and cutaneous nodules on the face, chest, and back, but did not show associated lymphadenopathy (top center). She underwent a surgical biopsy of the eyelid lesion.

Histopathology revealed that the soft tissue was involved by an extensive, vaguely nodular infiltrate of small lymphocytes with irregular nuclei, compact chromatin, and inconspicuous nucleoli (top right). Skin was not present for evaluation. The cells stained for CD3, CD5, CD4, TCR-beta, PD1, and ICOS (top right insert upper); negative for CD10, BCL6, CXCL13, TCR-delta, TCL1, CD25, CD56, CD57, granzyme B, perforin, and TIA1. Scattered larger $CD20^+$ $PAX5^+$ B cells (5% of cellularity) expressed CD30, MUM1, and EBER1 (top right insert lower). Polymerase chain reaction (PCR) followed by next-generation sequencing (NGS) studies revealed both a monoclonal TRG (graphical representation of dominant clones, bottom left), while a monoclonal IGH rearrangement (capillary electrophoresis, bottom right) was detected by PCR using Biomed-2 FR2 and FR3 primers. Targeted mutational analysis using an NGS panel detected disease-associated variants in *TET2*, *RHOA* (specifically c.50G>T, p.G17V, NM_001664.4), *DNMT3A*, and *KRAS*, leading to a diagnosis of follicular helper T-cell (TFH) lymphoma [1]. She subsequently received brentuximab (anti-CD30 monoclonal antibody) with partial clinical response. No obvious nodal disease has developed 8 months following initial development of the eyelid mass.

Lymphomas of T-follicular helper (TFH) origin show a characteristic phenotype involving expression of CD4 and at least two TFH markers (PD1, CD10, CXCL13, BCL6, ICOS). They are often associated with an EBV+ B-cell proliferation, which may be clonal [2]. TFH neoplasms are primarily nodal disease processes. However, although this is not a formally recognized category by the WHO or ICC, very rare cases of primary cutaneous T-cell neoplasms with a TFH phenotype and molecular profile have also been reported [3]. These patients present with multiple cutaneous lesions composed of a dense dermal lymphoid infiltrate, but no nodal involvement. Importantly, TFH neoplasms that remain localized to the skin have a better prognosis than their nodal counterparts [4].

The differential diagnosis for a primary cutaneous lymphoma with a TFH phenotype includes mycosis fungoides (MF), which can often express PD1 [5]. In MF, however, diffuse expression or TFH markers, or expression of multiple markers, is less likely [6]. Clinically, cutaneous TFH neoplasms will present as nodules rather than plaques, and without erythroderma. Histologically, epidermotropism (the hallmark of MF) should not be seen [7]. A lack of nodal involvement on staging imaging studies will differentiate a primary cutaneous TFH lesion

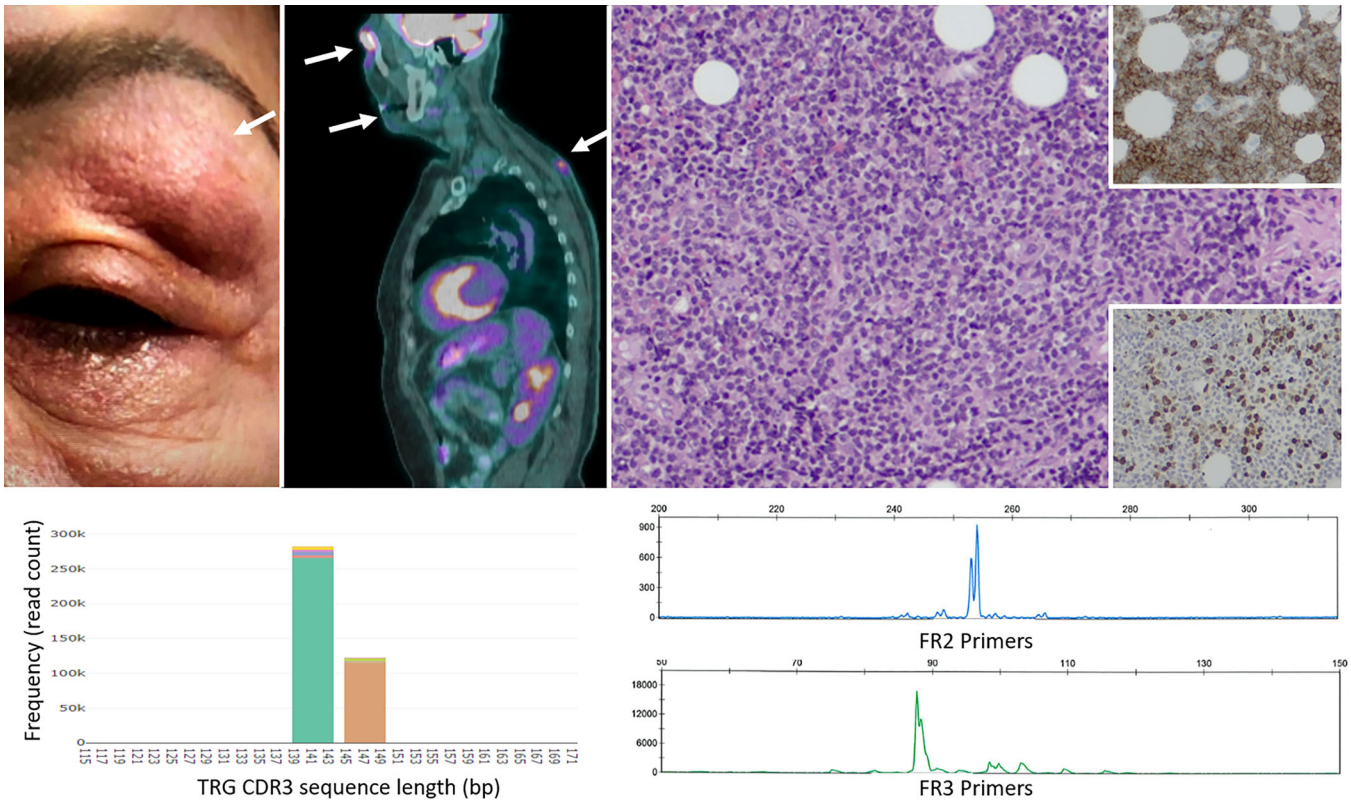

FIGURE 1 Composite image showing the patient's left eyelid mass (top left) and positron emission tomography (PET) scan (top center), the histology of the lesion (top right; hematoxylin and eosin stain, 100× magnification) with ICOS immunohistochemistry (top right insert upper; 100× magnification) and EBER1 in situ hybridization (top right insert lower; 100× magnification), and the monoclonal TRG (bottom left) and IGH rearrangements (bottom right).

from secondary skin involvement by a nodal TFH neoplasm, something which may be seen, particularly in the case of angioimmunoblastic T-cell lymphoma [8, 9].

AUTHOR CONTRIBUTIONS

Robert Penne and Tatyana Milman identified the patient and contributed the clinical history. Elena M. Fenu took photomicrographs and drafted the manuscript. Guang Yang and Farah El-Sharkawy Navarro provided molecular pathology expertise. Adam Bagg rendered the diagnosis, and initiated and supervised this report. All authors reviewed and approved the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

FUNDING INFORMATION

No funding was obtained during the course of this project.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS APPROVAL STATEMENT

Ethics committee/IRB approval was not required for this case report.

PATIENT CONSENT STATEMENT

Patient-identifying information was not used in this report. Thus, the authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION (INCLUDING TRIAL NUMBER)

The authors have confirmed clinical trial registration is not needed for this submission.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No material from other sources was used during this project.

ORCID

Elena M. Fenu https://orcid.org/0000-0001-9523-9222
Farah El-Sharkawy Navarro https://orcid.org/0000-0001-6425-8404
Adam Bagg https://orcid.org/0000-0002-1669-468X

REFERENCES

1. Cortes JR, Ambesi-Impiombato A, Couronné L, Quinn SA, Kim CS, da Silva Almeida AC, et al. RHOA G17V induces T follicular helper cell specification and promotes lymphomagenesis. Cancer Cell. 2018;33(2):259–73.e7.

2. Kishimoto W, Takiuchi Y, Nakae Y, Tabata S, Fukunaga A, Matsuzaki N, et al. A case of AITL complicated by EBV-positive B cell and monoclonal plasma cell proliferation and effectively treated with lenalidomide. Int J Hematol. 2019;109(4):499–504.
3. Santonja C, Soto C, Manso R, Requena L, Piris MA, Rodríguez-Pinilla SM. Primary cutaneous follicular helper T-cell lymphoma. J Cutan Pathol. 2016;43(2):164–70.
4. Xie Y, Jaffe ES. How I diagnose angioimmunoblastic T-cell lymphoma. Am J Clin Pathol. 2021;156(1):1–14. doi:10.1093/ajcp/aqab090
5. Kantekure K, Yang Y, Raghunath P, Schaffer A, Woetmann A, Zhang Q, et al. Expression patterns of the immunosuppressive proteins PD-1/CD279 and PD-L1/CD274 at different stages of cutaneous T-cell lymphoma/mycosis fungoides. Am J Dermatopathol. 2012;34:126–8.
6. Bosisio FM, Cerroni L. Expression of T-follicular helper markers in sequential biopsies of progressive mycosis fungoides and other primary cutaneous T-cell lymphomas. Am J Dermatopathol. 2015;37:115–21.
7. Wang L, Rocas D, Dalle S, Sako N, Pelletier L, Martin N, et al. Primary cutaneous peripheral T-cell lymphomas with a T-follicular helper phenotype: an integrative clinical, pathological and molecular case series study. Br J Dermatol. 2022;187(6):970–80.
8. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720–48.
9. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229–53.

How to cite this article: Fenu EM, Milman T, Penne R, Navarro FS, Yang G, Bagg A. Primary cutaneous T-follicular helper lymphoma. eJHaem. 2023;4:1176–1178.
https://doi.org/10.1002/jha2.737