TIM-3 deficiency presenting with two clonally unrelated episodes of mesenteric and subcutaneous panniculitis-like T-cell lymphoma and hemophagocytic lymphohistiocytosis

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Abstract
This report offers novel clinical and diagnostic aspects of the association between germline mutations in HAVCR2 and subcutaneous panniculitis-like T-cell lymphoma (SPTCL). The patient presented with panniculitis-like T-cell lymphoma involving mesenteric fatty tissue associated with hemophagocytic lymphohistiocytosis (HLH). Five years later, he developed a clonally unrelated SPTCL and underwent hematopoietic stem cell transplantation. Retrospectively, he was found to carry germline mutations in HAVCR2 associated with reduced T-cell immunoglobulin mucin-3 (TIM-3) expression. We show that mesenteric fatty tissue localization of SPTCL can be the presenting manifestation of TIM-3 deficiency, that this condition predisposes to recurrent lymphoma, and that flow cytometry is a possible screening tool.

Keywords
congenital immunodeficiency (not HIV), hemophagocytic lymphohistiocytosis, non-Hodgkin’s lymphoma, stem cell transplantation, subcutaneous panniculitis-like T-cell lymphoma

1 INTRODUCTION

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare peripheral lymphoma of cytotoxic T-cells that commonly mimics panniculitis and is associated with hemophagocytic lymphohistiocytosis in one-third of patients. Note that 20% of patients are under the age of 20. Clinical presentation typically includes subcutaneous nodules that, on pathologic evaluation, demonstrate cellular infiltrates...
in the subcutaneous fat. General prognosis is favorable with a 5-year overall survival rate of around 80%. The main predictor of a poor prognosis is presentation with hemophagocytic lymphohistiocytosis (HLH). SPTCL has recently been associated with germline mutations in \( \text{HAVCR2} \) encoding T-cell immunoglobulin mucin-3 (TIM-3), an inhibitory receptor expressed on T cells and innate immune cells. Abrogation of TIM-3 expression leads to persistent T-cell activation and increased production of inflammatory cytokines (TNF-\( \alpha \), IL-1\( \beta \)). \( \text{HAVCR2} \) mutations were found in 60-85% of SPTCL cases and were associated with younger age at onset and more frequent association with HLH. Here, we report a patient who adds novel clinical and diagnostic aspects to TIM-3 deficiency.

## 2 | CASE DESCRIPTION

A previously healthy Caucasian male presented at age 17 with persistent high fever, lethargy, and diarrhea. He had moderate leukopenia and thrombopenia. He exhibited elevated concentrations of transaminases, lactate dehydrogenase, lipase, and amylase. The bone marrow showed reactive trilineage hematopoietic hyperplasia with slightly increased eosinophils and plasma cells. Imaging showed splenomegaly and an inflammatory process in the ileocecal region with infiltration of the local fatty tissue (Figure 1A-C). Exploratory laparotomy revealed mesenteric panniculitis with beginning fibrosis. The appendix was unremarkable. Shortly after referral to our center, the patient developed bicytopenia (leukocytes 1.3 G/L; neutrophils 0.79 G/L, hemoglobin 8.7 g/dL; thrombocytes 111 G/L) with evidence of hemolysis. In addition, he showed signs of liver damage (ALT 280 U/L, AST 458 U/L), inflammation (ferritin 1996 ng/mL, soluble IL-2R 3716 U/mL), and hypertriglyceridemia (304 mg/dL). Fibrinogen levels were normal. Bone marrow and liver biopsies exhibited hemophagocytosis by abundant histiocytes (Figure 2A). NK-cell cytotoxicity was normal. IgA, IgG, and IgM were within the normal range. IgE was elevated (791 IU/mL). Autoantibodies (ANA, ANCA, AMA/LKM, and SMA) were negative. No infectious etiology was reported. Because seven of eight of the HLH-2004 criteria were met by the patient (Table S1), he was treated with the etoposide-based HLH2004 protocol for 8 weeks and achieved rapid remission. Pathologic examination of the mesenterial biopsy showed a rimming of fat by pleomorphic CD3\(^\text{−} \), CD8\(^\text{−} \), alpha/beta-positive, and CD4-negative T-cells reminiscent of an SPTCL (Figure 2B). The tumor cells expressed a cytotoxic phenotype and harbored a clonal TCR-gamma gene rearrangement that was characterized by a prominent reproducible peak at 143 bp in V-gamma 9-PCR.
FIGURE 2  Histopathological findings. (A and B) At age 17. (A) Hemophagocytosis is evident in bone marrow trephine (left, CD68 IH ×63) and liver biopsies (right, H&E ×20; inlet ×63). (B) Mesenterial adipose tissue shows lobular infiltration by small- to medium-sized lymphocytes (upper left, H&E ×2.5; inlet ×63) with prominent rimming of fat cells (see inlets). Predominance of CD8+ T-cells (upper right, ×10; inlet ×63) that have a cytotoxic profile with expression of granzyme B (lower left, ×10; inlet ×63) and perforin (lower right, ×100). Note presence of cellular debris. (C) At age 25. Biopsy of subcutaneous lesion on the right thigh showing the typical pattern of SPTCL. Pleomorphic lymphocyte infiltrates spare fibrous septa but diffusely involve subcutaneous fat lobules (upper left, PAS ×2.5; inlet ×40). Cytotoxic CD8+ T-cells (upper right, ×20; inlet ×40) and perforin+ T-cells (lower left, ×63) form characteristic rims around adipocytes and have an increased Ki67+ proliferative fraction (lower right, ×63).

The patient remained asymptomatic showing persistent splenomegaly but no recurrence of the abdominal fat inflammation in yearly MRI scans. Eight years after the initial presentation, he developed fever, night sweats, leukopenia (1.7 g/L), neutropenia (0.85 g/L), and thrombocytopenia (112 g/L). He showed an enlargement of two inguinal lymph nodes and radiologic evidence of mesenteric fat inflammation. Lymph node biopsy and bone marrow aspiration showed no evidence of hemophagocytosis or T-cell lymphoma. Clinical HLH criteria were not fulfilled (Table S1). One month later, the patient developed a lesion on his right thigh (Figure 1D-F) and histology confirmed SPTCL (Figure 2C). Treatment was initiated with polychemotherapy (1× CHOP, 2× DHAP, 1× VIP-E) with initial response, but progress after 3 months. Therapy was switched to etoposide and radiotherapy of the primary SPTCL lesion. Allogenic peripheral hematopoietic stem cell transplantation from an unrelated partially mismatched donor (8/10) was performed for progressive disease of the SPTCL after myeloablative conditioning with fludarabine (90 mg/m²), BCNU (300 mg/m²), and thiopeta (10 mg/kg), and graft-versus-host disease (GvHD) prophylaxis with Alemtuzumab (20 mg total) and Cyclosporine A. The early posttransplant course was complicated by HHV-6 reactivation, psychosis, and acute, steroid sensitive stage 1 skin GvHD. Six years later, the patient remains in complete remission with full donor chimerism. Clonality analysis by TCRgamma PCR of the SPTCL present in the subcutaneous biopsy revealed oligoclonal T-cell receptor gamma rearrangements with reproducible peaks at 153 bp (Vgamma10), 199 bp (VG1-8), and 178 and 181 bp (VG9).

Sequencing of pre-hematopoietic stem cell transplantation (pre-HSCT) PBMC DNA retrospectively established the diagnosis of TIM-3 deficiency caused by the compound heterozygous mutations p.Ile97Met and p.Thr101Ile in HAVCR2 (Figure S1A). While I97M has been described to abolish protein expression, no expression or functional data have so far been published on the T101I mutation, which has been described in a single patient in association with the Y82C mutation5 (Figure S1B). Flow cytometry revealed reduced TIM-3 expression on activated T cells, illustrating that the T101I mutation also leads to reduced protein expression (Figure S1C).

3 | DISCUSSION

Several interesting aspects are revealed by this case. Panniculitis-like T-cell lymphoma rarely occurs in the mesenteric fat with few cases published.6,7 We show that this uncommon localization in the mesenteric fatty tissue can be the presenting manifestation of TIM-3 deficiency in the context of HLH. HLH has been observed in one-third of pediatric patients with SPTCL.8 Remarkably, five of nine patients in a
pediatric SPTCL cohort had recurrence of their lymphoma and it has been observed that clonal populations can differ between the original biopsy and after recurrence. Our case shows that TIM-3 deficiency can be associated with such recurrent, clonally unrelated lymphoma. Notably, also in patients with atypical mesenteric panniculitis-like T-cell lymphoma, in particular if presenting with HLH, TIM-3 deficiency is an important differential diagnosis. TIM-3 expression analysis by flow cytometry is a simple screening tool for all mutations described so far, but should be followed by genetic testing for HAVCR2 mutations. Detection of TIM-3 deficiency provides a rationale for anti-inflammatory treatment rather than polychemotherapy. However, caregivers have to be aware of the lifelong risk of recurrence of SPTCL lesions and the associated potentially life-threatening immune activation in TIM-3-deficient patients unless allogeneic HSCT has been performed.

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CONFLICT OF INTEREST
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AUTHORS’ CONTRIBUTION
Oliver Wegehaupt wrote the manuscript and arranged the figures. Miriam Gross performed the TIM-3 stainings. Annette Schmitt-Graeff was responsible for the histopathology of both episodes. Markus Uhl provided images of radiological findings for both episodes. Myriam Lorenz and Klaus Schwarz performed the HAVCR2 genetic analysis of the patient and his parents. Christian Kratz, Charlotte Niemeyer, Claudia Wehr, and Reinhard Marks provided patient data. Stephan Ehl compiled the case and contributed to manuscript revision.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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