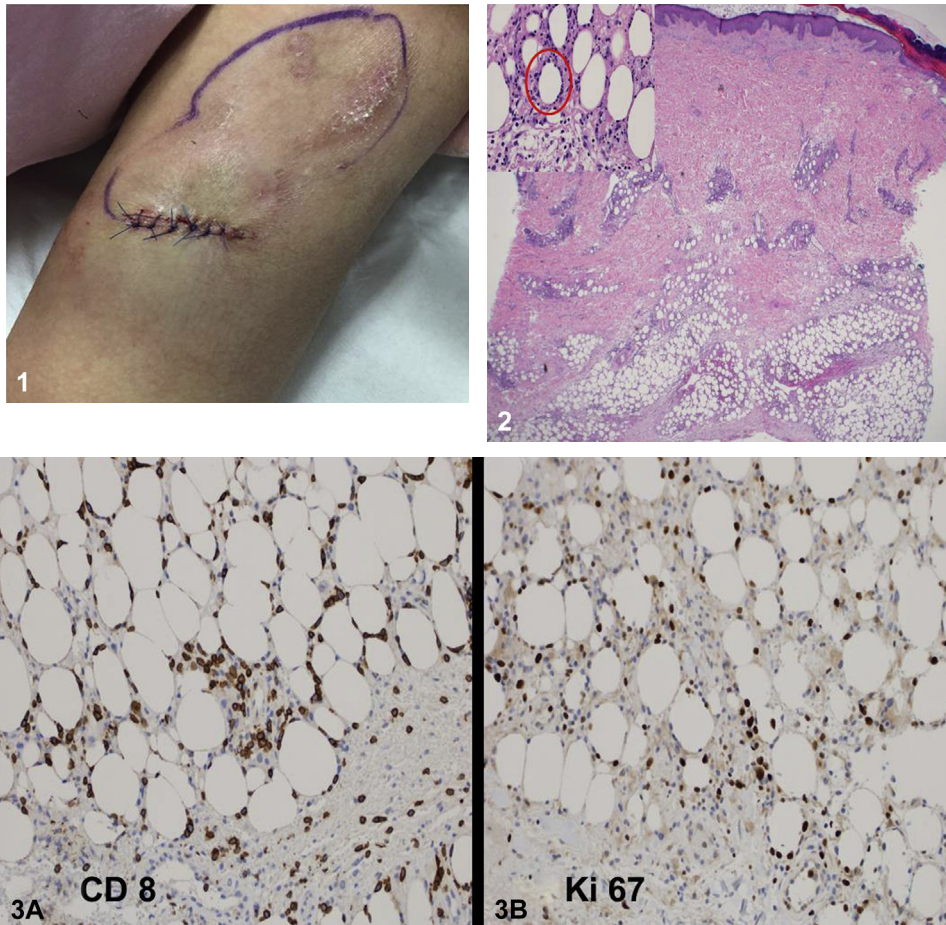


# Fever and indurated subcutaneous plaques



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**Key words:** hemophagocytic syndrome; subcutaneous panniculitislike T-cell lymphoma.



A 21-year-old Chinese woman presented with a 1-week history of high fever, myalgia, and a 2-month history of firm lumps. Examination found 2 large nontender erythematous indurated subcutaneous plaques with central atrophy on the left arm (Fig 1) and right buttock. There was no ulceration, Raynaud's phenomenon, or livedo reticularis.

Investigations found leukopenia of  $1.36 \times 10^9/L$  ( $4.0-10.0 \times 10^9/L$ ), hemoglobin 10.8 g/dL (13.0-17.0 g/dL), elevated alanine transaminase of 144 U/L (10-55 U/L), and aspartate transaminase of 205 U/L (10-45 U/L). Blood

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cultures, HIV results, and viral hepatitis serology results were negative. A biopsy specimen was taken from her arm plaque (Figs 2 and 3).

**Question 1: What is the most likely diagnosis?**

- A. Lupus profundus
- B. Subcutaneous panniculitislike T-cell lymphoma (SPTCL)
- C. Erythema nodosum
- D. Polyarteritis nodosa (PAN)
- E. Erythema induratum

**Answers:**

**A.** Lupus profundus — Incorrect. Lupus profundus is more common in women and presents as subcutaneous nodules on arms, shoulders, buttocks, and face. It occurs in 2% to 5% of systemic lupus erythematosus (SLE) patients. Conversely, 10% to 15% of patients with lupus panniculitis have SLE. Histopathology findings show lobular lymphocytic panniculitis with epidermal and dermal changes of lupus, such as thickened basement membrane, interface changes, and superficial and deep, perivascular, periadnexal, lymphocytic inflammation with increased dermal mucin. In less than half of the cases, biopsy findings show lobular lymphocytic panniculitis without epidermal and dermal lupus changes.<sup>1</sup> There are increased plasma cells and B-cell aggregates, and are less likely to have Ki-67/MIB-1–positive T cells or monoclonal *TCR* gene rearrangement compared with SPTCL.

**B.** SPTCL — Correct. The infiltration of fat lobules by large lymphocytes with hyperchromatic irregular nuclei rimming the adipocytes with fat necrosis is consistent with a diagnosis of SPTCL. The World Health Organization criteria classify SPTCL to cases expressing  $\alpha\beta$  T-cell receptor, commonly CD8<sup>+</sup>, with solely subcutis involvement, which often runs an indolent course. Primary cutaneous  $\gamma\delta$  T-cell lymphoma is commonly CD4<sup>-</sup>, CD8<sup>+</sup>, CD56<sup>+</sup>, with infiltration into epidermis and dermis and portends a poor prognosis. Approximately 19% of SPTCL patients also have autoimmune disorders including SLE, rheumatoid arthritis, and Sjögren disease.<sup>2</sup>

**C.** Erythema nodosum — Incorrect. There are tender erythematous subcutaneous nodules on the lower legs.

**D.** PAN — Incorrect. Livedo reticularis, Raynaud phenomenon, subcutaneous nodules, and ulceration often occur on legs.

**E.** Erythema induratum — Incorrect. It presents with tender nodules on calves, which may ulcerate,

with septal and lobular granulomatous panniculitis and neutrophilic vasculitis on histology.

**Question 2: What systemic complication may be present in this patient?**

- A. Miliary tuberculosis
- B. Sarcoidosis
- C. Systemic PAN
- D. Acute SLE
- E. Hemophagocytic syndrome

**Answers:**

**A.** Miliary tuberculosis — Incorrect. Erythema induratum may be an immunologic hypersensitivity reaction to antigenic components of *Mycobacterium tuberculosis* and has been associated with miliary tuberculosis.<sup>3</sup> However, miliary tuberculosis is unrelated to SPTCL.

**B.** Sarcoidosis — Incorrect. Sarcoidosis may be associated with erythema nodosum.

**C.** Systemic PAN — Incorrect. Fever, myalgia, fatigue, peripheral neuropathy, and bowel and renal ischemia are manifestations, but the histopathology is not consistent with that of PAN.

**D.** Acute SLE — Incorrect. There is significant overlap of clinical and histologic features in SPTCL and SLE with both conditions often presenting with a constellation of fever, constitutional symptoms, hepatitis, cytopenia, similar cutaneous manifestations, and associated autoimmune disorders. However, the skin biopsy result is not consistent with that of lupus panniculitis.

**E.** Hemophagocytic syndrome — Correct. Approximately 15% of SPTCL cases have underlying systemic involvement or hemophagocytic syndrome (HPS). These patients have a reduced 5-year overall survival rate of 46% compared with 80% in patients without HPS. HPS is diagnosed by at least 5 features including fever greater than 38.5°C; splenomegaly; blood cytopenia; hypertriglyceridemia or hypofibrinogenemia; hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver; low natural killer cell activity; elevated ferritin; and elevated soluble CD25 (soluble interleukin-2 receptor  $\alpha$ ). Bone marrow aspiration is important to detect marrow involvement.<sup>4</sup> Our patient had a constellation of fever, splenomegaly, cytopenia, hypertriglyceridemia, high ferritin, and bone

marrow involvement, thereby confirming the presence of HPS. For systemic involvement, positron emission tomography-fludeoxyglucose body scan and computerized tomographic scans of the thorax, abdomen and pelvis are useful to characterize the location, size and depth of extracutaneous lesions.

**Question 3: In addition to the stains shown in Fig 3, which immunohistochemical staining would likely be positive in this patient?**

- A. CD3
- B. CD20
- C. CD30
- D. CD45
- E. CD56

**Answers:**

- A.** CD3 — Correct. CD3, CD43, Ki67, perforin, granzyme B, and TIA1 are positive in SPTCL. It is also commonly CD4<sup>+</sup> and CD8<sup>+</sup> as shown in Fig 3, A. In contrast, lupus panniculitis commonly shows a mixture of CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Foci of Ki-67 hotspots within regions of atypical CD8<sup>+</sup> T cells was observed in our case (Fig 3, B) and has been reported in SPTCL. The Ki-67 hotspots are not present in lupus panniculitis, which can help distinguish it from SPTCL.<sup>5</sup>
- B.** CD20 — Incorrect. CD20 is negative in SPTCL. Lupus panniculitis usually has aggregates of CD20<sup>+</sup> B cells mixed with CD4<sup>+</sup> and CD8<sup>+</sup> T cells.

- C.** CD30 — Incorrect. CD30 is negative in SPTCL. However, it may be positive in primary cutaneous  $\gamma\delta$  T-cell lymphoma.
- D.** CD45 — Incorrect. CD45 is negative in SPTCL.
- E.** CD56 — Incorrect. CD56 positivity is seen in primary cutaneous  $\gamma\delta$  T-cell lymphoma but not SPTCL.

**Abbreviations used:**

HPS: hemophagocytic syndrome

PAN: polyarteritis nodosa

SLE: systemic lupus erythematosus

SPTCL: subcutaneous panniculitislike T-cell lymphoma

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