

## **Pralatrexate Induces Long-Term Remission in Relapsed Subcutaneous Panniculitis-Like T-Cell Lymphoma**

### **Dear Editor,**

In subcutaneous panniculitis-like T-cell lymphoma (SPTL), infiltration of subcutaneous tissue by pleomorphic T-cells and benign macrophages is seen in skin nodules that mimic lobular panniculitis. SPTL affects young patients and about 20% develop haemophagocytic syndrome (HPS) which worsens survival significantly.<sup>1,2</sup> We describe a case of aggressive SPTL in a patient with HPS who relapsed after multiple lines of therapy, but achieved complete and durable remission after extended pralatrexate therapy.

Although the PROPEL trial had demonstrated that pralatrexate, an antifolate, induced a durable response in relapsed/refractory peripheral T-cell lymphoma (PTCL), it did not include patients with SPTL.<sup>3</sup> To our knowledge, treatment beyond 6 cycles of pralatrexate has not been reported. Our case illustrates, for the first time, the use of extended pralatrexate therapy in the treatment of aggressive SPTL.

### **Case Report**

A 39-year-old man presented with fever of 2 weeks' duration and tender abdominal nodules. There was no lymphadenopathy or hepatosplenomegaly. Laboratory data revealed raised lactate dehydrogenase, raised ferritin (22,060 µg/L), pancytopenia (haemoglobin, 9.7 g/dL; absolute neutrophil count,  $0.81 \times 10^9/L$ ; platelet,  $91 \times 10^9/L$ ) and low fibrinogen (0.69 g/L). Positron emission tomography (PET) and computed tomography (CT) showed hypermetabolic activity in the subcutaneous fat of the abdominal wall. Abdominal nodule biopsy demonstrated atypical lymphocytes rimming adipocytes in the subcutis that are CD8+CD4- alpha/beta cells with high Ki67 expressing granzyme, CD2 and CD7, but losing CD5 (Fig. 1). Epstein-Barr virus-encoded small ribonucleic acid by in situ hybridisation was negative and lymphocytes did not stain for gamma/delta T-cell receptor. Bone marrow biopsy showed histiocytic proliferation with haemophagocytosis.

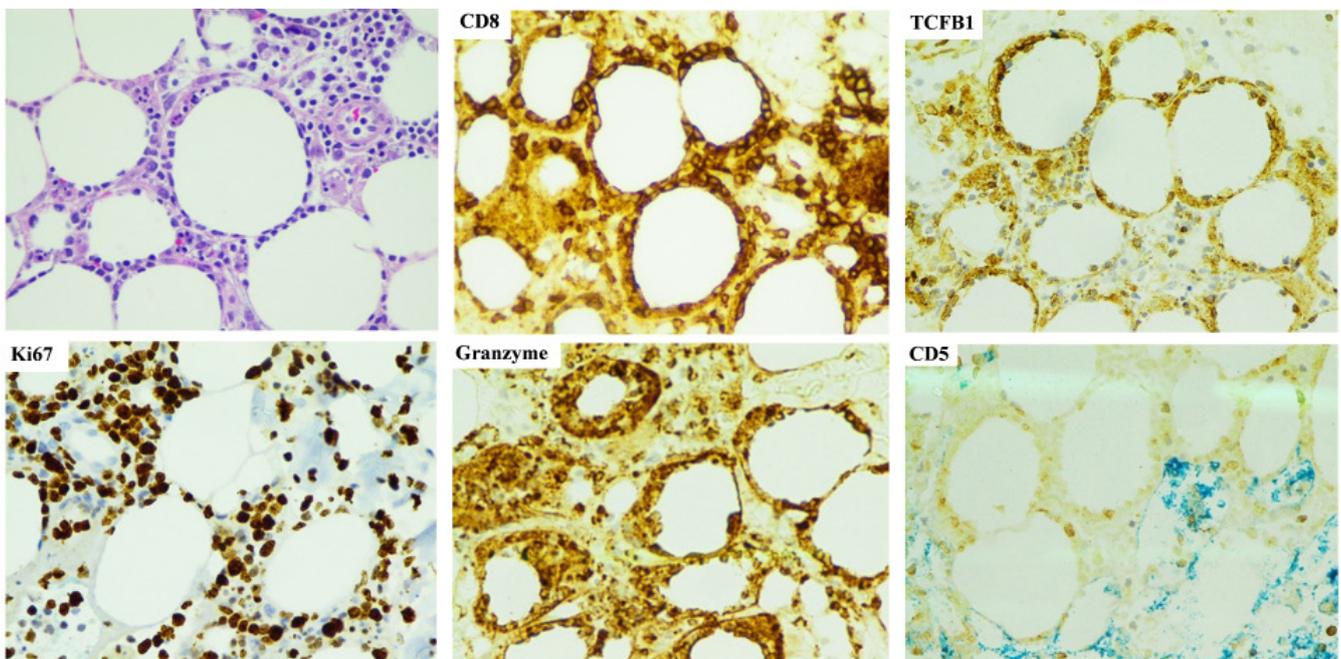


Fig. 1. Photomicrographs ( $\times 40$ ) showed subcutaneous infiltration by atypical lymphoid cells with rimming of adipocytes that are CD8+ alpha/beta subtype, expressing granzyme, high Ki67 (60-70%) and loss of CD5.

The patient was started on cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). However, fever returned after a brief respite and he was given romidepsin and cyclosporine in view of clinical non-response. After 5 cycles of romidepsin/cyclosporine, PET and CT scans showed progression with increased abdominal and new gluteal lesions. He was then given gemcitabine, dexamethasone and cisplatin for 6 cycles and achieved complete metabolic remission. He declined allogeneic stem cell transplantation as consolidation for long-term disease control.

Eight months later, he presented with a left axillary nodule and biopsy showed recurrence of SPTL (Fig. 2). According to the protocol for PTCL, he was started on pralatrexate at 30 mg/m<sup>2</sup> weekly for 6 of the 7 weeks for each cycle. To prevent mucositis, he was treated prophylactically with folinic acid and methylcobalamin. After the first cycle, treatment was administered in the outpatient clinic without mucositis or significant toxicity. He achieved metabolic remission after 6 cycles, but relapsed 3 months after cessation of pralatrexate. He was then restarted on

pralatrexate for 1 year. At 18 months, he remained in complete metabolic response.

**Discussion**

For indolent SPTL, immunosuppressive agents such as prednisolone and cyclosporine—or systemic biologic agents such as bexarotene and methotrexate—may be used.<sup>4</sup> In cases of aggressive presentation with haemophagocytic syndrome, intensive chemotherapy such as CHOP or CHOP-like regimens—followed by consolidation with autologous stem cell transplantation—is commonly used.<sup>5</sup> However, this intervention has high failure and relapse rates.

On the other hand, novel drugs such as pralatrexate and romidepsin may achieve a durable response in a small group of patients.<sup>6,7</sup> This case suggests that patients who had initially benefitted from pralatrexate can be re-treated when there is disease progression. Additionally, an extended treatment regimen can maintain response.

Extended pralatrexate therapy offers a treatment regimen that is well tolerated in responding patients. It also provides

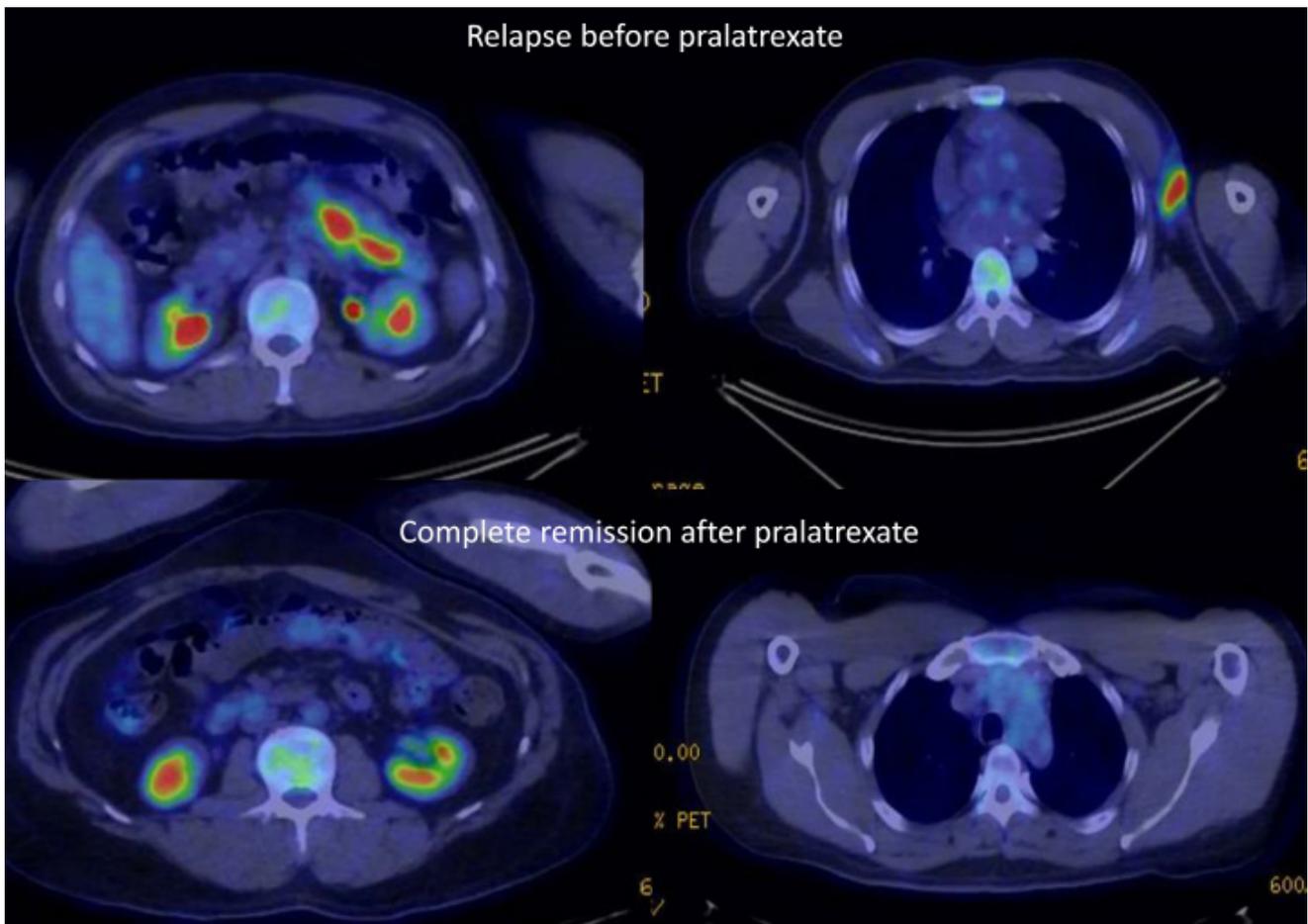


Fig. 2. Positron emission tomography at relapse (top) showed hypermetabolic soft tissue in the small bowel mesentery abutting the duodenum, jejunum and axilla and remission (bottom) post-treatment with pralatrexate.

time to organise a transplant or to maintain the quality of life in patients who are not eligible for the procedure. Additionally, it can provide a basis for studies that compare novel agents to time-limited intensive chemotherapy. Due to the selective activity of novel therapies, more research is needed to identify predictive biomarkers so that treatment strategies can be personalised for patients with this rare condition.

## REFERENCES

1. Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood* 2008;111:838-45.
2. Giam YC, Ong BH. Clinicopathological and immunohistological correlation of malignant lymphomas of the skin. *Ann Acad Med Singapore* 1994;23:412-7.
3. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol* 2011;29:1182-9.
4. Briki H, Bouaziz JD, Molinier-Frenkel V, Delfau-Larue MH, Ortonne N, Bagot M. Subcutaneous panniculitis-like T-cell lymphoma alpha/beta: complete sustained remission with corticosteroids and methotrexate. *Br J Dermatol* 2010;163:1136-8.
5. Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. *Cancer* 2004;101:1404-13.
6. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol* 2012;30:631-6.
7. Amengual JE, Lichtenstein R, Lue J, Sawas A, Deng C, Lichtenstein E, et al. A phase I study of romidepsin and pralatrexate reveals marked activity in relapsed and refractory T-cell lymphoma. *Blood* 2018;131:397-407.

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