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CASE REPORT

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Primary cutaneous CD4+ small-/medium-sized T-cell lymphoproliferative disorder: A case report

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Key Clinical Message

Primary cutaneous CD4+ small-/medium-sized T-cell lymphoproliferative disorder is usually characterized by nodules and plaques affecting the upper part of the body. The present case presented with a large, single tumor located on a lower extremity. The patient did not respond to surgical therapy but responded to cyclophosphamide, methotrexate, and radiotherapy.

KEYWORDS

cyclophosphamide, Hodgkin lymphoma, small/medium T cell

1 | INTRODUCTION

Primary cutaneous CD4+ small-/medium-sized T-cell lymphoproliferative disorder (PCSM-TCLPD) is a rare and heterogeneous entity, with suggested derivation from follicular T-helper lymphocytes. Most of the cases present as a solitary lesion in the upper part of the body and good response to surgical excision or local radiotherapy.[1-6] The report describes a case of this rare disease with some peculiarities compared the typical described forms.

2 | CASE REPORT

We describe the case of a 55-year-old man who developed PCSM-TCLPD 10 years after successful treatment of Hodgkin lymphoma (HL). The PCSM-TCLPD developed in an atypical site, that is on the lower extremity, relapsed shortly after surgical excision but responded to cyclophosphamide therapy.

A 55-year-old man was consulted in our clinic in 2014, with a three-year history of a progressive 7×3-cm-sized tumorous infiltration, which affected the dermis and hypodermis and was localized in the upper and medial part of the right thigh. Before our first examination, a diagnosis of panniculitis was rendered based on clinical presentation and histopathology result. He was treated with glucocorticosteroids and antibiotics and showed progression.

The past medical history was significant for HL, diagnosed in July 2001. The lymphoma was asymptomatic, and ultrasonography performed due to nephrolithiasis revealed some abnormalities. Following computed tomography revealed the presence of a solid tumor ($9 \times 6 \times 4$ cm) in the pelvis, on the right side of the urinary bladder and the lymph node packets around the iliac vessels, without infiltration of the surrounding tissue. Exploratory laparotomy with excisional biopsy of the enlarged lymph nodes was performed, and the tissue was subjected to pathological examination. The results of bone marrow examination were normal. The patient was diagnosed with mixed-cellularity classical HL at stage II A and began treatment in the middle of July 2001. He received six cycles of ABV/COPP (doxorubicin, bleomycin, vinblastine/cyclophosphamide, vincristine, procarbazine, and prednisone). Two months after chemotherapy, radiotherapy of the subdiaphragmatic lymph nodes was initiated using

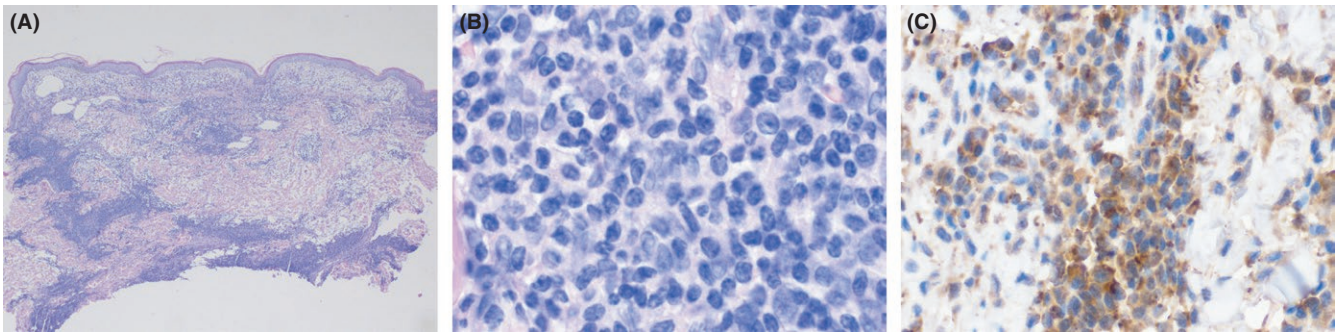

FIGURE 1 *PCSM-TCLPD.* A, H&E stained *histopathological image* shows lymphocytic infiltration involving deep portion of the dermis. B, Higher magnification shows mixed infiltrate of small- and medium-sized lymphocytes with scattered plasma cells and macrophages. C, Immunophenotyping results show the lymphoma cells are positive for CXCL13

a 9 MeV photon beam; the patient received cumulative doses of 33.6 and 43.2 Gy for the aortic lymph nodes and iliac inguinal-femoral nodes, respectively. The treatment ended in the end of April 2002 and produced sustained complete remission during a follow-up period continuing to December 2005.

Family medical history revealed one case of malignant neoplasm. The patient's father, a long-term smoker, was diagnosed with lung cancer at the age of 53.

In July 2014, a second biopsy specimen was taken. Hematoxylin and eosin (H&E) staining revealed intensive infiltration of small to medium-sized lymphocytes intermingled with scattered histiocytes and plasma cells involving a deep portion of the dermis (Figure 1A,B). Immunohistochemistry demonstrated follicular T-helper phenotype of the lymphocytes (CD3+, CD4+, CD8−, CD7−, PD1−, CXCL13+ [Figure 1C], bcl6−, and TIA1−/+). No molecular studies have been undertaken to confirm monoclonality; however, loss of CD7, a pan-T-cell marker, seemed to be an indirect proof of malignant transformation, although not unequivocal determinant of TCR rearrangement. Epstein-Barr virus and cytomegalovirus status have not been analyzed.

Physical examination showed neither systemic symptoms nor lymphadenopathy. The results of laboratory examinations, including a complete blood cell count with differential count, liver function tests, renal function tests, and urinalysis, were all within normal limits. Computed tomography examination of the neck, chest, abdomen, and pelvis revealed no abnormalities. Bone marrow aspiration showed no evidence of malignancy. Relapse of HL was excluded.

Based on these findings, the patient was diagnosed as having PCSM-TCLPD, as it seemed to be most consistent diagnosis with the clinical and histological findings. He underwent surgical excision of the affected area but surgery turned out to be ineffective: The surgical wound was not healing, and the skin lesion developed again at the original site and gradually increased in size.

One year after surgical treatment, the patient returned to the clinic for assessment. Physical examination revealed a red-livid, ulcerative, solitary nodular infiltration of the skin, and subcutaneous tissue, 20 × 15 cm in diameter (Figure 2A,B).

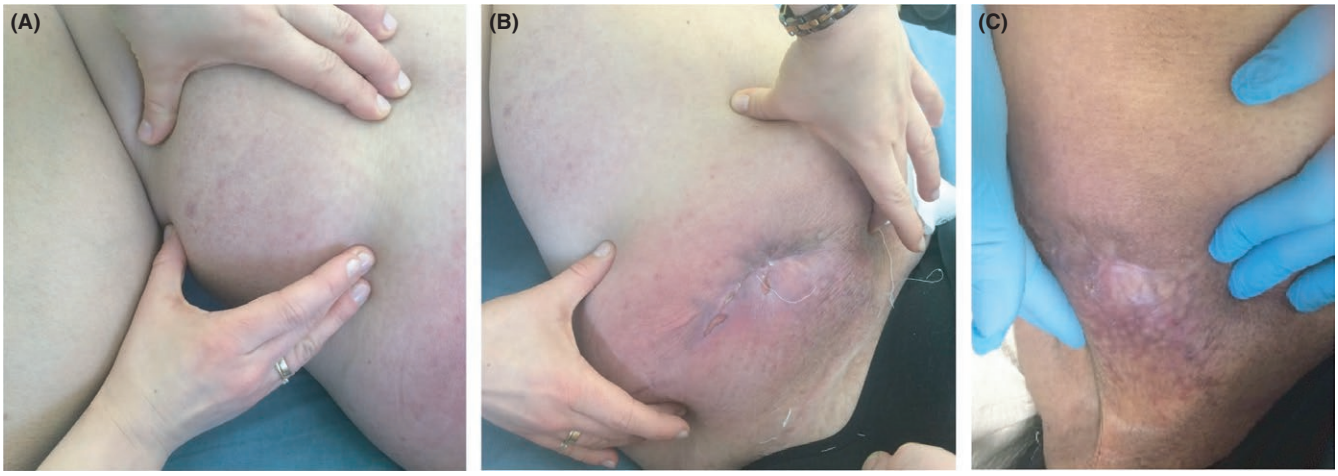

FIGURE 2 *PCSM-TCLPD.* A and B, Before cyclophosphamide use. Note the extent of the lesion. C, Two weeks after cyclophosphamide therapy was commenced

Due to the infiltration, the right thigh was enlarged twice to its normal size, which impaired his movement. Staging for extracutaneous involvement was negative. The presence of ulcers was a factor which disqualified from radiotherapy. The patient was started on a course of cyclophosphamide (0.9 mg/kg/d po) and methylprednisolone (0.35 mg/kg/d po). After two weeks of treatment, 90% regression of the skin lesion was observed (Figure 2C). As such, a good response was observed during the follow-up, and methylprednisolone was gradually tapered and discontinued after eight weeks. Cyclophosphamide was tapered to 75 mg per day after 10 weeks.

Four months after the initiation of cyclophosphamide therapy, the patient developed hemorrhagic cystitis and the drug had to be discontinued. As a consequence, the lesion relapsed in the same area over a period of two weeks grew up to 10 × 8 cm in size, and hard-to-heal wounds formed within the lesion. In May 2016, computed tomography of the abdomen and pelvis and laboratory tests demonstrated no abnormalities. The patient was put on a course of 20 mg oral methotrexate once a week for ten months, resulting in the disease stabilizing. Methotrexate was found to be clearly less effective than the combination of cyclophosphamide and methylprednisolone administered previously, with the 6-cm-sized infiltration persisting, despite the wounds within the lesion almost healing. Therefore, in March 2017, methotrexate therapy was interrupted and the patient started radiation therapy. In the third week of radiotherapy, the lesion decreased to 2.5 cm in size. Subsequently, the tumor disappeared and only healing persisted in the place of tumor. The patient has been seen in our outpatient clinic in November 2018 without any symptoms of lymphoma.

3 | DISCUSSION

We would like to note a possible link between HL treatment and PCSM-TCLPD in the presented case. Many reports demonstrate over twofold increased risk of subsequent malignancies for HL survivors compared with general population. The relative risk of subsequent malignancy increased between five and nine years after chemotherapy alone and remained elevated for 25 years and longer when combined therapies (with radiotherapy) were used. The risk was markedly higher when a chemotherapy included alkylators, as in our case.[7-9] In addition, in our case the subsequent tumor developed in the area exposed to radiation during HL treatment, which might be responsible for the unusual localization.

The lesion size in case described herein was larger than other reported cases (1-2.5 cm), it might be one of the possible reason why the first-line therapy failed.[5,6]

Cyclophosphamide is believed to be an effective form of second-line therapy for PCSM-TCLPD, when given as a single chemotherapeutic agent. Only few reports of this therapy for PCSM-TCLPD exist in the literature.[4,10] Wawrzycki at al. observed good response in the case presenting with widespread nodules after ineffective PUVA therapy.[10] Alberti-Violetti et al[4] described two cases with initial response and relapse in further course, and the third patient demonstrated progression.

Not only is this the first case report of the development of PCSM-TCLPD as secondary neoplasm in a patient previously treated for HL, it also describes an atypical presentation of this rare entity.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

AUTHOR CONTRIBUTIONS

ER: involved in conception and case report drafting and design. MK: managed and collected the data and wrote the report. M P-P: managed and collected the data. WB: involved in pathological diagnosis and interpretation the tissue biopsy slides. AW: peer reviewed and helped in report writing.

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