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Concise Report

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorders: demographic, clinical, therapeutic and prognostic aspects. A retrospective monocentric analysis

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Abstract

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorders (PCSM-LPDs), represent a rare group of haematological diseases primarily affecting the skin. In this retrospective single-centre case series study, we aimed to investigate the demographic, clinical, therapeutic and prognostic aspects of PCSM-LPD. We collected data from cases diagnosed between 2010 and the present, employing histopathological and immunohistochemical methods following the World Health Organization criteria. We included 22 patients with a median age of 61.5 years and a median time between clinical onset and diagnosis of 3.0 months. Surgical excision with conservative margins was the primary choice, showing clinical remission in 17 cases, while nonsurgical treatments, including radiotherapy, high-potency steroids and ablative laser, achieved clinical remission in four cases. Clinical presentations varied, but the most common was a single violaceous nodule or papule on the upper body parts. In conclusion, our single-centre case series provides valuable insights into PCSM-LPD, highlighting the effectiveness of surgical treatments and the potential of nonsurgical ones. Even if controversial, the benign nature of PCSM-LPD emphasizes the importance of achieving tumour clearance with acceptable aesthetic outcomes.

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorders (PCSM-LPD) encompass a distinctive group of rare haematological diseases primarily affecting the skin.[1] These disorders are characterized by clonal expansion of CD4+ T cells with small-to-medium-sized nuclei. They have garnered increasing attention in recent years due to their unique clinical and histopathological features. Traditionally encompassed within the spectrum of primary cutaneous T-cell lymphomas (CTCLs), they have more recently been considered a separate entity due to their indolent and benign course.[2,3] They are considered a recent entity,[4] and data are relatively scarce compared with more numerous and detailed findings in mycosis fungoides (MF), which is increasingly being studied in depth.[5,6] The aetiopathogenesis is still debated, although potential triggers due to infection or immune system stimulation are described in the literature.[7]

The age of onset and clinical presentation of PCSM-LPD may vary among patients, but the classic appearance is a single violaceous nodule or papule on the head, neck, upper extremities or upper trunk, even if uncommon variants have been described.[8] Skin biopsies are crucial for diagnosis, as they reveal the characteristic histopathological features and immunophenotypic profile of CD4+ T-cell involvement. Biopsies can be characterized by epidermotropism, with atypical T-cell infiltration into the papillary dermis and an altered epidermal architecture. A slow growth rate characterizes them, but they may become bulky if recognized late.

To date, it is known that, apart from clinical characteristics and resistance to conventional therapies, only a skin biopsy can provide the correct diagnosis, and it is essential to underline that most evidence comes from collections of case reports and small case series.

We describe our single-centre, tertiary-centre case studies reporting the main demographic, clinical and therapeutic characteristics associated with PCSM-LPD. We report the related outcomes for this type of proliferation in order to increase the knowledge of this cutaneous neoplasm.

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Report

We retrospectively collected data on all cases diagnosed from 2010 to the present by histopathological and immunohistochemical methods (Figure 1) according to the World Health Organization criteria.[9] We then retrieved images for the qualitative clinical data collected from our electronic medical archive, including age, sex, timing of onset, reported symptoms, associated haematological comorbidities (if any), the type of therapy performed, the outcome and the follow-up. All data were analysed with SPSS 26 software (IBM, Armonk, NY, USA).

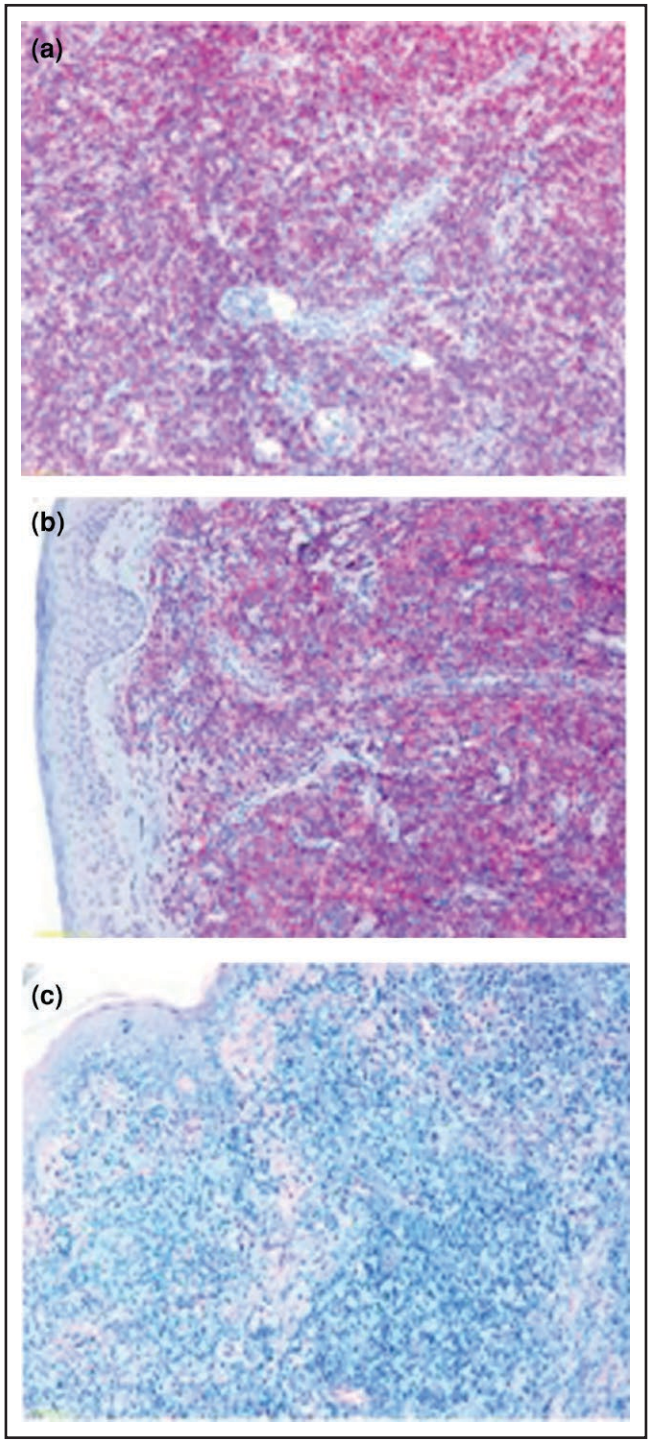

Figure 1 Histopathology of primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorders. The infiltrative population is positive for (a) CD3 and (b) CD4. Original magnification × 10. (c) Note the dense superficial and deep dermal lymphoid infiltrate separated from the epidermis by a grenz zone. Lymphoid cells are small to medium in size with nuclear pleomorphism. Original magnification × 10, Giemsa stain.

We report 22 patients, with the mean age in the study being 59.1 years (median 61.5, range 7–87); 17 were male and 5 were female (Table 1).

The majority presented with either nodules (10 cases) or plaques (10 cases), while a smaller number exhibited patches (1 case) or papules (1 case). Regarding the number of lesions, most patients had a unique neoformation (21 cases), although there was a single instance of multiple localized nodules. Regarding body sites, the most common site of presentation was the head and neck region (11 cases, with 5 on the scalp, which was the most frequently affected area), followed by the trunk (4 cases), arms (4 cases) and legs (3 cases). The mean time reported between clinical onset and diagnosis was 3.1 years (range 1–5).

Overall, the most common treatment was surgical therapy, specifically surgical excision with conservative margins (between 0.5 and 1 cm), as reported in 18 cases. Three other therapies were noted: (i) local electron beam therapy, for a total of 4 Gy over four sessions (two patients); (ii) high-potency steroid treatment (clobetasol dipropionate cream) once per day until complete clinical resolution, then applied for another 2 weeks, for a total of 10 weeks (one patient); and (iii) ablative CO_2 laser therapy, ultrapulse setting at 20–40 Hz, 0.8 J ms^{-1} fluency until reaching the dermis, with the endpoint of ablating 0.2–0.3-cm observable margins (one patient).

Outcomes for the patients who underwent surgical excision included 17 clinical remissions, with 1 case in doubt due to a subsequent diagnosis of cutaneous lymphoma. Clinical remission was observed for nonsurgical therapies in four cases out of four; nonsignificant differences were observed between these two groups ($P = 0.63$) (Table 2). The mean follow-up period was 44.0 months (median 28.5) for patients who underwent surgical therapy and 29.5 months (median 21) for those receiving nonsurgical therapies, again with no statistical difference ($P = 0.52$).

Kaplan–Meier survival curves showed a similar pattern and comparable outcomes between surgical and nonsurgical interventions (Figure 2). No patients died from a disease-specific event.

Of the surgically treated patients, one was codiagnosed with plaque MF, and another developed non-Hodgkin lymphoma type B, 27 months later. These conditions led us to consider conservatively that at least one patient had a possible relapse or disease progression.

Most evidence surrounding PCSM-LPD in the literature comes from collections of case reports and small case series. Our study contributes to this limited body of knowledge by presenting a series of single-centre cases. This allows us to provide a comprehensive overview of the demographic, clinical and therapeutic characteristics of PCSM-LPD.

Our results confirm how the clinical presentation of PCSM-LPD may be variable, but the classic manifestation typically involves a single violaceous nodule or papule on the head, neck, upper extremities or upper trunk. This heterogeneity of location can often pose a diagnostic challenge, making skin biopsies essential for confirmation.

Table 1 Patient demographics and clinical characteristics

	n	Range	Mean (SD)	Median (IQR)
Age (years)	22	7–87	59.1 (16.5)	61.5 (50.75–66.25)
Sex				
Male	17			
Female	5			
Reported clinical onset (months)	22	1–5	3.1 (1.1)	3 (2–4)
Clinical appearance				
Patch	1			
Nodule	10			
Papule	1			
Plaque	10			
Number of lesions				
Single	21			
Multiple	1			
Localization				
Arm	4			
Leg	3			
Trunk	4			
Head and neck	11			

			Follow-up period	
Reported treatment	***n***	**Outcomes**	**Mean (SD)**	**Median**
Surgical therapy				
Surgical excision	18	17 CR (1 in doubt)	44.0 (42.5)	28.5
Nonsurgical therapies				
All	4	4 CR	21.0 (12.7)	21.0
Radiotherapy	2	2 CR		
High-potency steroid	1	1 CR		
Ablative CO_2 laser[a]	1	1 CR		

CR, clinical remission; IQR, interquartile range. [a]Patient's details previously published as a case report.[10]

Molecularly, PCSM-LPD is marked by a monotonous population of $CD4^+$ T cells expressing mature T-cell receptor markers. These lymphocytes exhibit an indolent behaviour, growing slowly and demonstrating a lack of aggressive invasion into other organs. Despite their relatively slow growth, PCSM-LPD lesions can become bulky if diagnosed late. Thus, timely diagnosis through skin biopsy remains crucial.

Among the demographic aspects, we should note that the mean time between clinical onset and diagnosis appeared to be 3 months, but these results may be excessively optimistic due to the study being conducted in a tertiary centre. Still, they emphasize the importance of early detection.

Regarding treatments, surgical excision with conservative margins was the most common therapy, showing clinical remission in almost all cases. Nonsurgical therapies, including radiotherapy and high-potency steroid treatment, also demonstrated positive outcomes.

Table 2 Clinical outcomes in 18 patients treated with surgical excision and 4 with nonsurgical therapies

	Value	*P*-value[a]
Mean follow-up time (months)		
Surgical excision	44.0	0.52
Nonsurgical therapies	29.5	
Clinical remission, *n*		
Surgical excision	17	0.63
Nonsurgical therapies	4	
Disease-related deaths, *n*		
Surgical excision	0	–[b]
Nonsurgical therapies	0	

[a]Two-tailed significance. [b]Not calculable.

Notably, we also identified a patient with a single nodule treated by ablative CO_2 laser, which achieved a complete resolution of the manifestation with no relapse after 33 months of follow-up. Finally, our analysis did not reveal significant differences in outcomes between surgical and nonsurgical interventions, with maintenance of clearance and no relapses over 10 years.

Considering the described benign nature of the lesions, the main objective is to carry out radical treatments with acceptable aesthetic outcomes. Therefore, surgical therapy is preferable, but nonsurgical techniques should not be discarded a priori if these can guarantee simpler management of the case or a better aesthetic outcome.

Our study also found a codiagnosis of plaque MF in one patient and the later development of non-Hodgkin lymphoma type B in another patient, which raised questions about the diagnostic and management challenges posed by overlapping conditions, and whether this disorder might be linked to the development of more severe forms of lymphoma.

The study's limitations include the small sample size, an uneven distribution of patients among treatment groups (with a majority undergoing surgical excision), and the fact that patients were primarily enrolled in a tertiary medical centre, causing a selection bias that might have led to shorter reported time between onset and diagnosis compared with other contexts. These factors can affect the generalizability of the findings and may introduce bias in treatment comparisons and data collection due to variations in care settings.

Finally, our work lacks molecular investigations due to the study design and current technical limitations. Such studies

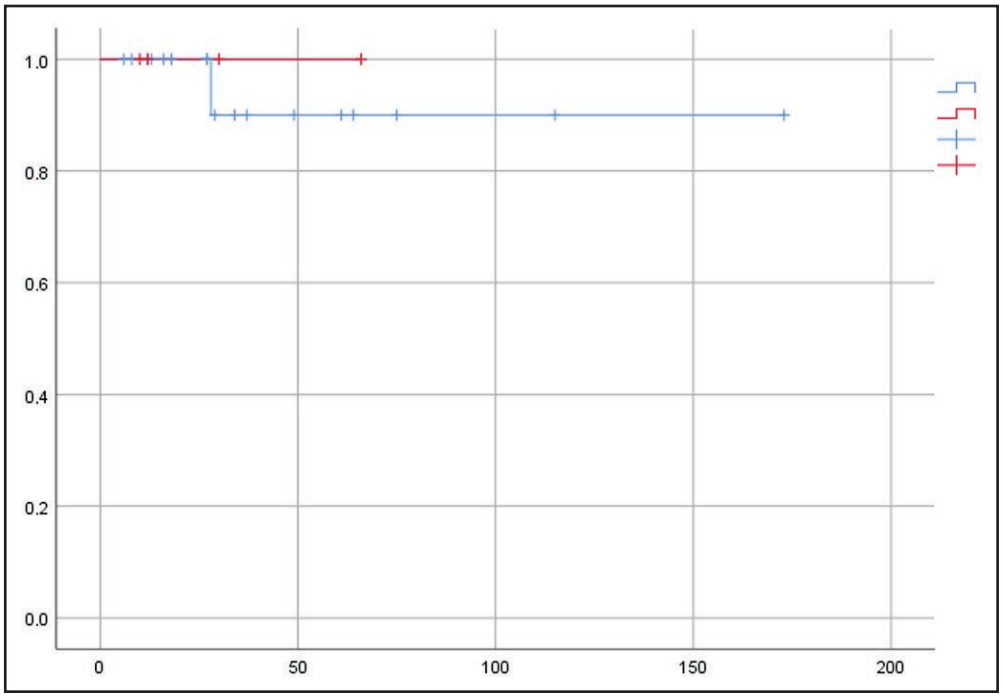

Figure 2 Kaplan–Meyer relapse curves. In blue: follow-up and outcomes after surgical excision. In red: follow-up and outcomes of nonsurgical interventions (radiotherapy, steroids and ablative laser).

would have provided further data on the genesis and prognosis of this disease.

Still, our retrospective analysis of cases of PCSM-LPD provides valuable insights into this rare skin disorder's demographic, clinical, therapeutic and prognostic aspects. Although the small sample size is a limitation, our findings suggest that surgical and nonsurgical treatments can be effective, with comparable outcomes. Moreover, the study confirms the benign evolutive nature of the disease, with the concomitant diagnosis of MF considered as disease progression, and the patient later affected by non-Hodgkin lymphoma still under investigation.

Further research and more extensive studies are needed to refine treatment approaches and to better understand the long-term prognosis of PCSM-LPD.

Learning points

- Early detection remains crucial in primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCSM-LPD) to prevent the mass from becoming bulky and complicating any treatment.
- Surgical excision with conservative margins emerged as the predominant treatment, with clinical remission in almost all cases.
- Nonsurgical interventions like radiotherapy and high-potency steroid treatment demonstrated comparable positive outcomes.
- One case highlighted the efficacy of ablative CO_2 laser, which provided complete resolution with no relapse over 33 months.
- The study underscores the benign nature of the lesions but cautions against potential codiagnosis or the subsequent finding of other lymphomas, whose aetiopathogenetic correlation remains to be determined.
- Despite the study limitations, the findings provide invaluable insights into the clinical, therapeutic and prognostic dimensions of PCSM-LPD.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethical statement

The study was approved by the Bologna local ethics committee (no. Clin.Isto.Tp.19). The patients in this manuscript have given written informed consent for the publication of their case details.

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