Primary Cutaneous CD4+ Small/Medium T-Cell Lymphoproliferative Disorders (SMPLPD), demographical, clinical, therapeutic and prognostic aspects: a retrospective monocentric analysis

Running head: Insights into Primary Cutaneous CD4+ Lymphoproliferative Disorders

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Learning Points

- Early detection remains crucial to prevent the mass from becoming bulky and complicating any treatment.
- Surgical excision with conservative margins emerged as the predominant treatment, showcasing clinical remission in almost all cases.
- Non-surgical interventions like radiotherapy and high-potency steroid treatment demonstrated comparable positive outcomes.
- A case highlighted the efficacy of ablative Co2-laser demolition, achieving complete resolution with no relapse over 33 months.
- The study underscores the benign nature of the lesions but cautions against potential co-diagnosis or the subsequent finding of other lymphomas, whose etiopathogenetic correlation remains to be determined.

- Despite study limitations, the findings provide invaluable insights into the clinical, therapeutic, and prognostic dimensions of SMPLPD.

Abstract

Primary Cutaneous CD4+ Small/Medium T-Cell Lymphoproliferative Disorders (SMPLPD), also known as PCS-TCLPD, represent a rare group of hematologic 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 SMPLPD.

We collected data from cases diagnosed between 2010 and the present, employing histopathological and immunohistochemical methods following WHO criteria.

We included 22 patients with a median age of 61.50 years and median time between clinical onset and diagnosis of 3.00 months. Surgical excision with conservative margins was the primary choice, showing clinical remission in 17 cases, while non-surgical treatments, including radiotherapy, high-potency steroid treatment and ablative laser, achieved clinical remission in four cases.

Clinical presentations varied, but the most common one was a single violaceous nodule/papule on upper body parts.

In conclusion, our single-centre case series provides valuable insights into SMPLPD, highlighting the effectiveness of surgical treatments and the potential of non-surgical ones.

Even if controversial, the benign nature of SMPLPD emphasizes the importance of achieving tumour clearance with acceptable aesthetic outcomes.

Introduction

Primary Cutaneous CD4+ Small/Medium T-cell lymphoproliferative Disorders (SMPLPD or PCS-TCLPD) encompass a distinctive group of rare hematologic diseases primarily affecting the skin[1]. These disorders are characterized by clonal expansion of CD4+ T-cells with small to medium-sized nuclei and have garnered increasing attention in recent years due to their unique clinical and histopathological feature: traditionally encompassed within the spectrum of primary cutaneous T-cell lymphomas (CTCLs), they have later been considered a separate entity due to their indolent and benign course[2,3]. Considered a recent entity[4] its data are relatively immature compared to the more numerous and detailed ones About mycosis fungoides (MF), which is increasingly studied in depth [5,6].

The aetiopathogenesis is still debated, although potential triggers due to infectious or immune system-stimulating are described in the literature[7].

Age and clinical presentation of SMPLPD 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, and they can be characterized by epidermotropism, i.e. 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 lately. To date, it is known that, apart from clinical characteristics and resistance to conventional therapies, only a skin biopsy can address the diagnosis correctly, 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 the related outcomes to investigate this type of proliferation in order to increase the knowledge of this cutaneous neoplasm.

Report

We retrospectively collected all cases diagnosed from 2010 to the present by histopathological and immunohistochemical methods [Image 2] according to WHO's criteria[9]. We then retrieved images for the qualitative clinical data collected from our electronic medical archive withage, gender, timing of onset, reported symptoms, associated haematological comorbidities (if any), the type of therapy performed, the outcome and follow-up. All data were analysed with SPSS 26 (IBM) software.

We report 22 patients, with the average age in the study being 59.06 years (median 61.50), ranging from 7 to 87 years; 17 were male, and 5 were female.

The majority presented 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. About body sites, we found 11 cases located in the head and neck region, 5 of them on the scalp, being the most frequently affected area, followed by the trunk (5 cases), arms (4 cases) and legs (3 cases).
The mean time reported between clinical onset and diagnosis was 3.09 years, ranging from 1 to 5 years.
Of the total treated patients, surgical therapy, specifically surgical excision with conservative margins (between 0.5 and 1 cm) was the most common treatment in 18 cases. Among other therapies, we have enlisted:

- Local electron beam therapy, for a total of 4 Grays partitioned in 4 sessions (2 patients);
- High-potency steroid treatment (clobetasol di-propionate cream) once per day in use until achieving a complete clinical resolution and then applied for other two weeks, for a total of 10 weeks (1 patient);
- Ablative CO2 laser therapy, ultra-pulse setting 20-40hz, 0.8 j/ms fluency until reaching the dermis, with the end-point of ablating 0.2-0.3 cm observable margins (1 patient).

Outcomes for the patients who underwent surgical excision accounted for 17 clinical remissions (with 1 case in doubt due to a subsequent cutaneous lymphoma diagnosis). Clinical remission was observed for non-surgical therapies in 4 cases out of 4; non-significative differences were observed between these two groups (P 0.629). The mean follow-up period was 44.00 months (median 28.5) for patients who underwent surgical therapy and 29.50 months (median 21) for those receiving non-surgical therapies, still without any statistical differences (P 0.524).
Conversely, Kaplan-Meier Survival Curves showed a similar pattern and comparable outcomes between surgical and non-surgical interventions [Image 1].
No patients died from a disease-specified event.

Of the surgically treated patients, one patient was co-diagnosed with plaque MF and another developed non-Hodgkin's lymphoma type B 27 months later. These conditions led us to consider conservatively at least one patient as possible relapse/disease progression of the disease.

Discussion

Most evidence surrounding SMPLPD 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 SMPLPD.

Our results confirm how the clinical presentation of SMPLPD 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 location heterogeneity often can pose a diagnostic challenge, making skin biopsies essential for confirmation.

Molecularly, SMPLPD is marked by a monotonous population of CD4+ T-cells expressing mature T-cell receptor (TCR) markers. These lymphocytes exhibit an indolent behaviour, growing slowly and demonstrating a lack of aggressive invasion into other organs. Despite their relatively slow growth, SMPLPD 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 three months, but these results may be excessively optimistic due to the study being conducted in a tertiary centre. Still, it emphasizes the importance of early detection.

Regarding treatments, surgical excision with conservative margins was the most common therapy, showing clinical remission in almost all cases. Non-surgical therapies, including radiotherapy and high-potency steroid treatment, also demonstrated positive outcomes.
Notably, our cases also reported a patient with a single nodule treated by ablative Co2-laser demolition, 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 non-surgical interventions, with maintenance of clearance and no relapses over ten 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 without discarding non-surgical techniques *a priori* if these can guarantee simpler management of the case or a better aesthetic outcome.

Our study also found a co-diagnosis of plaque MF in one patient and the later development of non-Hodgkin's lymphoma type B in another patient, which raised questions about the diagnostic and management challenges posed by overlapping conditions and if this disorder may be linked or not to the development of more severe form of lymphomas.

The study's limitations include 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 which may have led to shorter reported time between onset and diagnosis compared 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 a molecular investigations perspective due to the study design and current technical impossibility, which would have provided further data on the genesis and prognosis of this disease.

Still, our retrospective analysis of SMPLPD cases provides valuable insights into this rare skin disorder's demographic, clinical, therapeutic, and prognostic aspects. Although the limited sample size is a limitation, our findings suggest that surgical and non-surgical treatments can be effective, with comparable outcomes. Moreover, it confirms the benign evolutive nature of the disease, with the concomitant diagnosis of MF considered as a 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 better understand the long-term prognosis of SMPLPD.

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Figure legends

Figure 1: Kaplan-Meyer relapse curves.
1) in blue, follow-up and outcomes after surgical excision
2) in red follow-up and outcomes of non-surgical interventions (radiotherapy, steroids and ablative laser).

Figure 2: Histopathology of primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder.
The infiltrative population is positive for CD3 (a) and CD4 (b). 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

Table 1: Patient demographic and clinical characteristics.

* Patient previously published as a case report[10]

			N	Range		Mean - median value - std dev. – IQR
Age (Years)			**22**	**7-87**		**59.06 – 61. 50 - 16.546 – 15.5**
Sex (M: F)			**22**	**17:5**		**17:5**
Reported clinical onset (Months)			**22**	**1-5**		**3.09 - 3 - 1.109 - 2**
Clinical appearance						
	Patch		**1**			
	Nodule		**10**			
	Papule		**1**			
	Plaque		**10**			
Lesions number						
	Single		**22**			
	Multiple		**0**			
Localization						
	Arm		**4**			
	Leg		**3**			
	Trunk		**4**			
	Head and neck		**11**			
Reported treatment			**N**		**Outcomes**	**Mean and median follow-up time and std dev**
	Surgical therapy	**Surgical excision**	**18**		**17 CR (1 in doubt)**	**44.00 - 28.5 - 42.530 – 46.5**
	Non-surgical therapies	**Non-surgical therapies (All)**	**4**		**4 CR**	**21.00 – 21.0 - 12,728 – 46.5**
		Radiotherapy	**2**		**2 CR**	
		High potency steroid	**1**		**1 CR**	
		Ablative Co2 laser*	**1**		**1 CR**	

Table 2: Clinical outcomes.

Legend: * 2-tail significance, # it's a constant

Follow-up time (months)		N		P Value
	Surgical excision	18	44.00	0.524*
	Non-surgical therapies	4	29.50	
Clinical remissions				
	Surgical excision	18	17	0.233
	Non-surgical therapies	4	4	
Disease-related deaths				
	Surgical excision	18	0	#
	Non-surgical therapies	4	0	

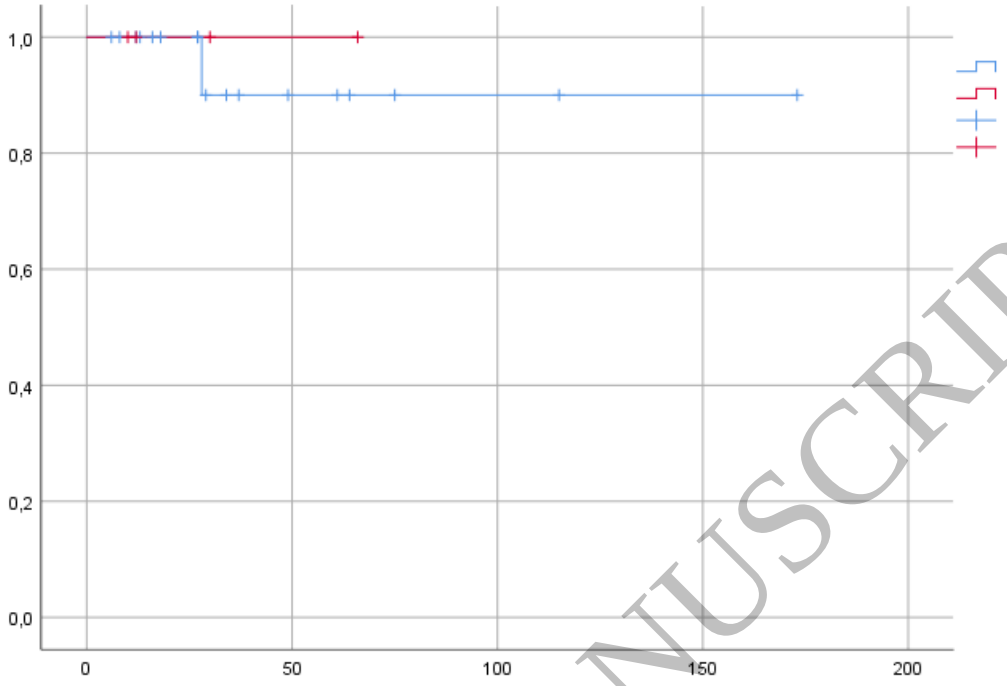

Figure 1
142x97 mm (x DPI)

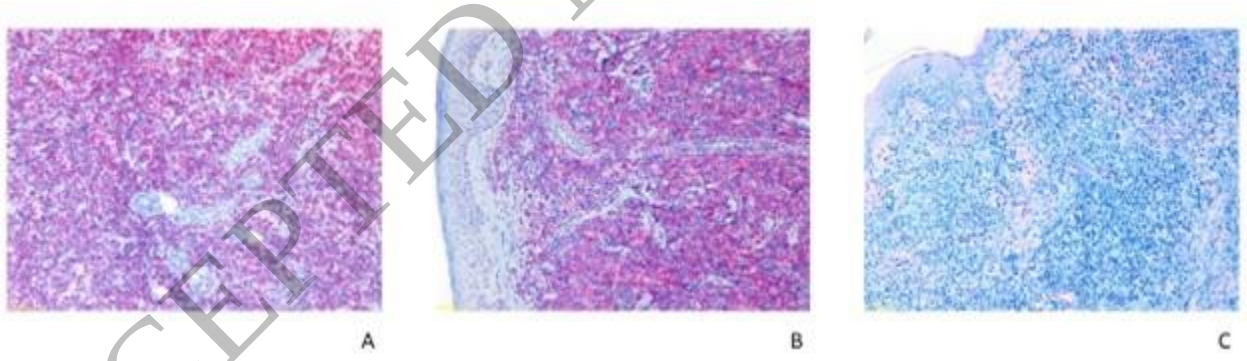

Figure 2
169x48 mm (x DPI)