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Single Case

A Longstanding, Persistent and Recurrent Case of Cryptogenic Panniculitis

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Abstract
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare subtype of cutaneous T-cell lymphoma. There may be a significant histologic overlap with traumatic panniculitis and lupus profundus. We describe a 54-year-old woman who had received a diagnosis of SPTCL based upon a left parietal scalp biopsy 5 years earlier. This diagnosis was supported by immunohistochemistry (IHC) demonstrating a CD8+ predominant lymphocyte population in the subcutis. T-cell gene rearrangement studies were not performed at that time. The patient was treated and showed significant clinical improvement. When several tender erythematous subcutaneous nodules appeared on the upper back, left plantar surface and pretibial region, repeat biopsy was performed. Histology revealed a lobular and septal panniculitis with no vasculitis. The infiltrate contained abundant eosinophils and histiocytes not seen in the original biopsy specimen. IHC demonstrated a mixture of CD4+, CD8+ and CD7+ lymphocytes with abundant CD68+ histiocytes. T-cell gene rearrangement studies performed on one of the lesions failed to demonstrate clonality. It is important to recognize that patients with SPTCL are not exempt

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from other types of panniculitis, and complete histologic, IHC and molecular workups are essential to properly classify all cutaneous lesions in these patients.

Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare subtype of cutaneous T-cell lymphoma that is localized primarily to the subcutaneous adipose tissue. It is slightly more common in females and occurs in a broad age range, with a median age at presentation of 35 years [1]. Up to 20% of patients have, at presentation, an associated autoimmune disease such as systemic lupus erythematosus, juvenile idiopathic arthritis, Sjögren's syndrome or type 1 diabetes mellitus. SPTCL is characterized by single or multiple nodules and/or plaques mainly on the legs and trunk. The lesions might become necrotic, but they do not ulcerate and in rare cases might present as alopecia.

Less than 20% of cases are associated with the hemophagocytic syndrome, which may present with high fevers, maculopapular rash, failure to thrive, central nervous system symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, coagulopathy, abnormal liver function tests or an extremely high serum ferritin level. Typically, there is an indolent course without extracutaneous spread. The histologic picture reveals a subcutaneous infiltrate which generally spares the epidermis and dermis, composed of pleomorphic small, medium or large lymphocytes and histiocytes. The infiltrate is confined to lobules, producing a lobular panniculitis-like pattern. Areas of fat necrosis and karyorrhectic nuclear fragments are frequently present [2]. Lipotrophic neoplastic cells form a rim around individual fat cells and by definition have an alpha/beta T-cell receptor (TCR) T-cell phenotype, and they express CD3, CD45RO, CD43 and CD8 but not CD4. The degree of lymphoid atypia is variable between cases [1]. The neoplastic cells may also show angiocentricity and vascular invasion [1]. Plasma cells are present in some cases, but neutrophils and eosinophils are generally absent.

It is typical of SPTCL that the epidermis and dermis are spared. However, interface dermatitis, periadnexal inflammation and dermal mucin deposition can be identified, creating a markedly similar histologic picture to lupus profundus. Cases with overlapping features between lupus profundus and SPTCL have been described [3, 4]. Classically, TCR gene rearrangement studies help to determine the clonality of the neoplastic cells and confirm the diagnosis of SPTCL.

SPTCL is often mimicked by other types of panniculitides histologically presenting as a lobular pattern of inflammation without presence of vasculitis. Such entities include sclerosing panniculitis [5], lupus panniculitis [5], cold panniculitis [5], traumatic panniculitis and other lesser diseases [5].

Lupus panniculitis typically presents as a deep indurated nodule or plaques involving the arms, face, buttocks and chest – as well as, less frequently, the abdomen, back and neck. The lesions may be painful. The overlying skin can be normal or show erythema, atrophy or ulceration. The lesions heal with atrophy and scarring. Patients sometimes recall a history of trauma. The lesions tend to resolve spontaneously and follow a chronic course characterized by periods of remission and exacerbation. The most common histologic finding is a lobular-

predominant lymphocytic panniculitis. Plasma cells are often present on the periphery of the fat lobules, and a characteristic hyalinization is seen in many cases.

In contrast, traumatic panniculitis clinically presents as warm, tender, indurated plaques or nodules and might be unrelated in its severity to the intensity of the causative trauma [6]. The histologic picture of traumatic panniculitis is not entirely specific and therefore can be challenging and easily mistaken for other skin and subcutaneous lesions [7]. Initial changes are characterized by the presence of a mixed inflammatory infiltrate composed of lymphocytes and macrophages, mostly around vessels and septae. As the lesion progresses, there is an associated rupture of fat cells and formation of fat microcysts surrounded by histiocytes [6]. There are also collections of foam cells admixed with inflammatory cells that can include neutrophils and eosinophils [6]. Late lesions show fibrotic replacement of damaged fat and residual small fat cysts surrounded by macrophages and foreign-body-type giant cells [6]. Traumatic panniculitis is usually a self-limiting disorder and requires only symptomatic treatment, whereas SPTCL and lupus panniculitis are treated aggressively with radiation and/or chemotherapy [8].

Case Report

A healthy 54-year-old woman presented with a 1-year history of a large smooth plaque on the scalp with associated alopecia (Fig. 1a). The lesion was tender, had slowly increased in size and had not been treated prior to the visit. She had no other symptoms, organomegaly or lymphadenopathy. Excisional biopsy was performed, which revealed a lobular infiltrate of atypical lymphocytes (Fig. 1b, c) predominantly expressing CD8 and displaying rimming of adipocytes (Fig. 1d, e). The immunoperoxidase workup also showed moderately dense dermal and subcutaneous lymphocytes expressing CD4, a minority of lymphocytes expressing CD56 and an elevated Ki-67 labeling rate with rimming around adipocytes. There were associated necrosis and sclerosis of fatty lobules and increased dermal and subcutaneous mucin. Bacterial and fungal cultures and stains were negative. There also was superficial perivascular and perifollicular mixed lymphocytic infiltrate with vacuolar alteration of the basal layer of the epidermis and follicular epithelium. A diagnosis of SPTCL was made by the dermatopathology unit at a large, academic medical center, based upon the clinical, histologic and immunohistochemical studies. T-cell gene rearrangement studies were not performed on the original biopsy, and the tissue was no longer available for subsequent testing. Some of the histologic features described might also have suggested lupus profundus. The patient was referred to the oncologist and treated with radiotherapy with complete resolution of the lesion and hair regrowth.

Four years later the patient returned to her original dermatology clinic with new multiple firm, tender and enlarging subcutaneous nodules on the upper back, left shoulder, left forearm and both shins (Fig. 2a, b). Based on the patient's prior history and the clinical appearance of the lesions, the differential diagnosis included recurrent SPTCL, as well as traumatic panniculitis, lupus profundus and erythema nodosum. Punch biopsies of the two lesions were performed, which demonstrated a pathological process centered upon the subcutis, similar to that observed in the prior SPTCL specimen (Fig. 2c). However, the new lesions displayed more abundant fat necrosis and a mixed inflammatory infiltrate that consisted of equal numbers of

CD4+ and CD8+ T cells, with retention of CD7 expression. Eosinophils, scattered plasma cells and abundant histiocytes were also present (Fig. 2d). The pattern was both lobular and septal. Weber-Christian disease also entered the differential diagnosis, but the predominance of lymphocytes over neutrophils, along with the long and complicated history, made this diagnosis less likely. No hyalinization characteristically seen in lupus profundus was identified. The presence of eosinophils is not usually a feature of lupus profundus. A T-cell gene rearrangement test failed to demonstrate any clonal population, and an α_1-antitrypsin serological evaluation was normal. The histological findings were best explained by panniculitis resulting from trauma (traumatic panniculitis), but thorough questioning of the patient did not reveal such a possibility.

Thus, 6 years into the course of the disease process, multiple biopsies have yielded confusing and conflicting patterns that have been reviewed by pathologists at several large academic institutions and the diagnosis remains elusive. This is clearly a case of cryptogenic panniculitis.

Discussion

Skin is the second most common extranodal site for the presentation of primary non-Hodgkin lymphoma [9]. SPTCL is an uncommon cutaneous T-cell lymphoma accounting for less than 1% of all non-Hodgkin lymphoma subtypes.

SPTCL may demonstrate a significant clinical and histologic overlap with other cutaneous lymphomas, autoimmune conditions and diseases presenting with lobular panniculitis (Table 1). Traumatic panniculitis is a subcutaneous inflammatory process that enters the differential diagnosis and could potentially mimic SPTCL, presenting with deep-seated indurated plaques and nodules. Despite our usual ability to differentiate these entities on conventional light microscopy of hematoxylin and eosin-stained slides, the rarity of these entities warrants particular attention in the situation where neither seems to fit, nor does lupus profundus, another possible mimic.

We presented a case where a patient with presumptively treated SPTCL and seemingly in complete remission developed clinically similar lesions. The lesions were initially thought by the clinician to be a recurrence of the previous diagnosed SPTCL. However, the histologic picture initially revealed a pattern with necrosis of the subcutaneous fat and a dense inflammatory infiltrate that was both septal and lobular. On careful examination, a more varied inflammatory infiltrate composed of T cells, eosinophils and abundant histiocytes was present. T-cell rearrangement studies were negative and failed to support the initial hypothesis of possible SPTCL recurrence. The initial biopsy, diagnosed as SPTCL, showed the classic histology with a predominantly lobular pattern and characteristic rimming of adipocytes. However, as there was no T-cell confirmation and no evidence of disease progression, this initial diagnosis is uncertain.

The patient demonstrates no clinical or serologic evidence for lupus erythematosus, so lupus profundus also seems unlikely. Histologically, lupus panniculitis commonly presents with basal vacuolar changes, as well as superficial and deep perivascular lymphocytic infiltrate and lymphocytic lobular panniculitis. Concomitant septal involvement is often present [10]. A lymphocytic vasculitis with lymphocytic nuclear dust sometimes occurs. The major

characteristic histologic features of lupus have not been present in the biopsies at any point in the course of the disease. It appears unlikely that the patient can be categorized as having lupus profundus.

Although SPTCL, lupus panniculitis and traumatic panniculitis are rare, there is the possibility of a common genetic alteration or other association whereby one begets the other. The underlying genetic cause of SPTCL remains unknown, but a familial predisposition has been suggested [11]. Gayden et al. [12] studied a series of 27 patients with SPTCL to identify genetic variants underlying this disease. They identified missense variants in *HAVCR2*, which encodes T-cell immunoglobulin mucin 3 (TIM-3), in 16 of their 27 patients. TIM-3 is a member of the TIM family and is expressed by several cell types of the immune system and acts as a negative immune checkpoint regulating peripheral tolerance, antitumoral immunity and innate immune responses [12]. The main function of TIM-3 is to terminate the immune response. Mutation leads to TIM-3 loss and uncontrolled immune activation and therefore promotes the disease. Gayden et al. [12] propose that TIM-3-mutant SPTCL should be viewed as an inflammatory condition.

In contrast, there are no data in the literature regarding genetic impairments or predisposition to traumatic panniculitis and its relation to underlying clinical or biologic abnormalities. Subcutaneous fat has a limited repertoire of responses to noxious stimuli, with the most common response being fat necrosis, which could in turn be secondary to innumerable conditions [13]. Fat necrosis is subsequently accompanied by a varied degree of inflammation. Interestingly, this inflammation plays a significant role in cutaneous T-cell lymphomas. These tumors are very sensitive to changes in the tumor-associated inflammatory environment that serves as a critical checkpoint in the transition from early indolent to progressive and advanced disease [14]. In early cutaneous T-cell lymphoma, the skin lesions contain a small population of malignant T cells immersed within a dense infiltrate of reactive immune cells. A significant proportion of the immune cells are activated CD8+ T cells and T-helper 1 cells expressing cytotoxic molecules, implying that early inflammation encompasses a cell-mediated antitumor response that actively suppresses the expansion of malignant cells [14]. Disease progression is associated with increasing expression of T-helper 2 markers that is driven by nonmalignant immune cells in the lesion [14]. Hence, inflammation in these tumors serves as a "conductor of the orchestra" directing the tumor's behavior. A similar evolution has not been described for SPTCL, and its pathogenesis remains completely unknown. Traumatic panniculitis could therefore progress from a spectrum of autoimmune inflammatory conditions where prolonged chronic subclinical inflammation creates a favorable microenvironment for transition from nonneoplastic to neoplastic cells and further progression into lymphoma.

It is also important to mention that in the above-described case, the biopsy of the primary lesion displayed the classic histology of SPTCL, albeit with a few features of lupus profundus. The clinical and histologic similarities between SPTCL and lupus profundus are well described in multiple case reports [1, 3, 4]. Magro et al. [3] have suggested that such lesions represent a form of cutaneous lymphoid dyscrasia with a pattern of lobular lymphocytic panniculitis. The fact that patients having mixed features of lupus profundus and SPTCL may further develop/progress to lymphoma [1] further supports the hypothesis of autoimmune panniculitis as a possible initial insult that may trigger progression to lymphoma.

There is only 1 case report in the literature, of a 36-year-old woman with a 6-year history of recurrent panniculitis who developed an angiocentric and angiodestructive cutaneous T-

cell lymphoma. She subsequently developed a rapidly progressive fatal syndrome characterized by cytophagocytic histiocytosis and hyperlipidemia [15]. In contrast, our patient has followed an indolent course with no evidence of disease progression and remains relatively healthy 6 years following the initial diagnosis.

In conclusion, it remains important that all available diagnostic information be examined and reviewed within the overall individual clinical context. The histologic and clinical discriminants of benign and malignant panniculitides may not yet be so sharply defined, and in some cases, a definitive diagnosis may remain elusive for years. Given the uncertainty about the ultimate diagnosis in this case, it seems that one ought to exercise extreme caution prior to giving an unequivocal diagnosis of SPTCL, relying on a full complement of clinical, histologic, immunologic and molecular factors before rendering an unequivocal diagnosis.

Statement of Ethics

The patient has given written informed consent to publish this case (including publication of images). Information revealing the patient's identity has been avoided. The research in this case report was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T. Pukhalskaya and B.R. Smoller are the URMC resident physician pathologist and consulting pathologist, respectively, on this case. J.A. Brown is the pathologist who worked initially on the case and referred the patient to the URMC. A.A. Sills is the dermatologist who performed the biopsy.

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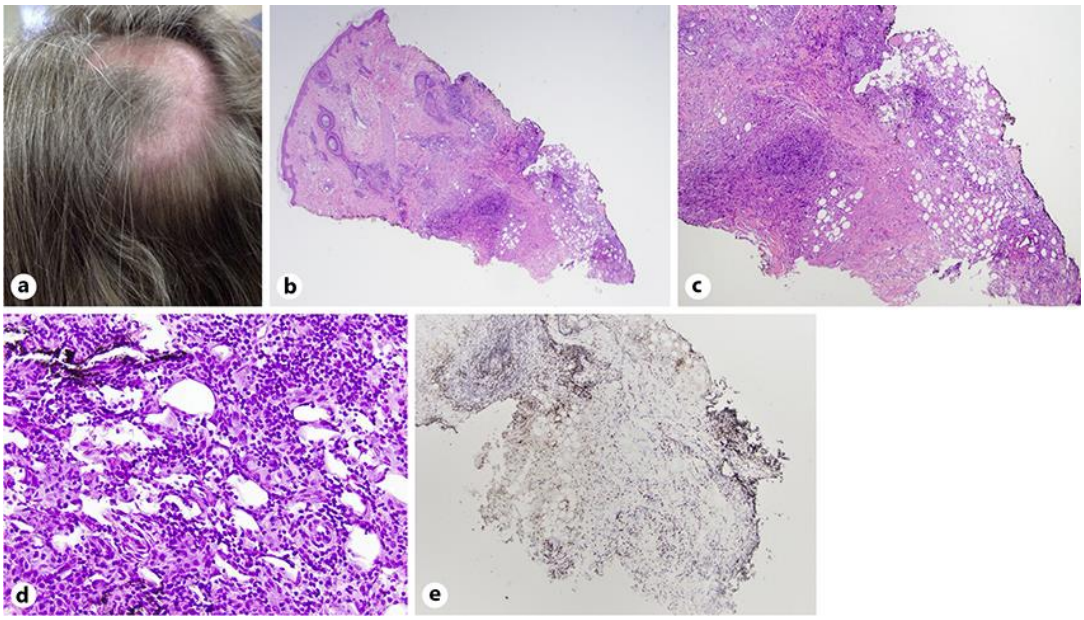

Fig. 1. **a** Clinical presentation of the primary scalp lesion. **b** Histology of the primary scalp lesion. H&E. ×20. **c** Histology of the primary scalp lesion. H&E. ×40. **d** Histology of the primary scalp lesion. H&E. ×100. **e** CD8 immunohistochemical profile of the primary lesion. ×40.

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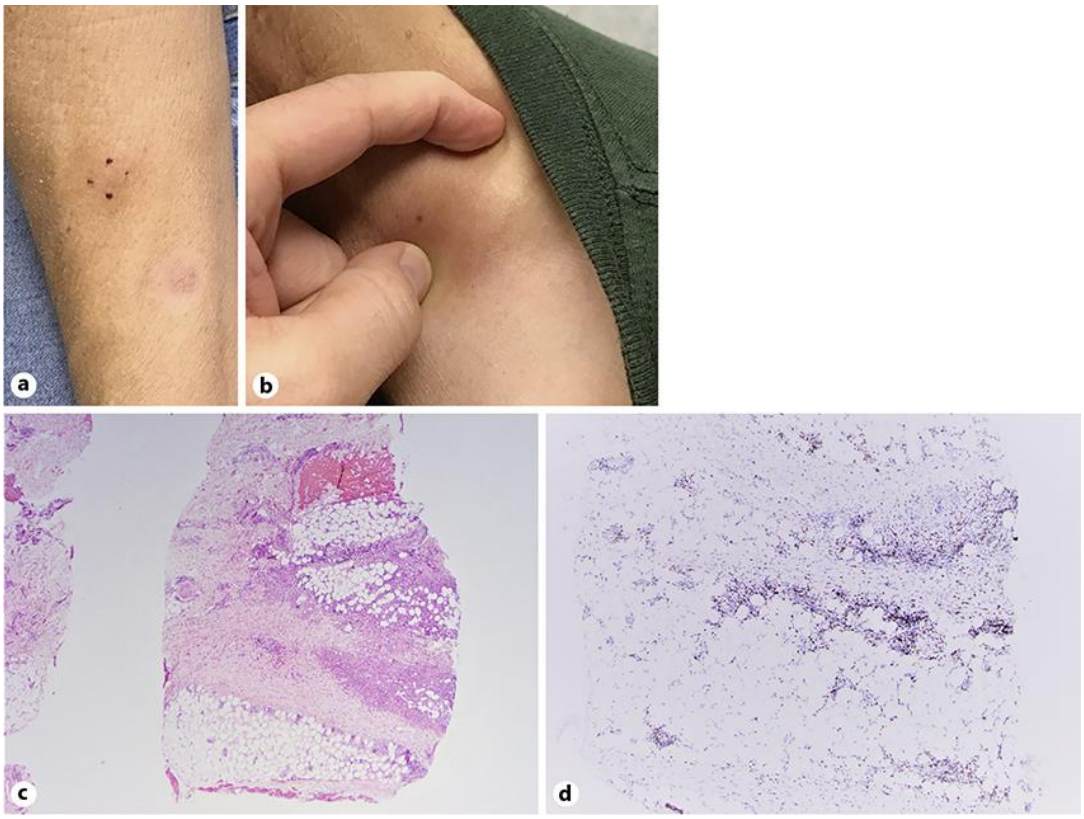

Fig. 2. **a**, **b** Clinical presentation of the recurrent lesion. **c** Histology of the recurrent lesion. ×40. **d** CD8 immunohistochemical profile of the recurrent lesion. ×40.

Table 1. Classification of predominantly lobular panniculitis

Lobular panniculitis with vasculitis	Lobular panniculitis without vasculitis
	Subcutaneous panniculitis-like T-cell lymphoma[1]
	Cryptogenic panniculitis[1]
Erythema induratum of Bazin	Sclerosing panniculitis
Lucio's phenomenon	Calciphylaxis
Neutrophilic lobular panniculitis associated with rheumatoid arthritis	Scleroderma neonatorum
Erythema nodosum leprosum	Cold panniculitis
Crohn's disease	Lupus erythematosus profundus[1]
	Pancreatic panniculitis
	Infective panniculitis
	Traumatic panniculitis
	Factitious panniculitis
	Subcutaneous fat necrosis of newborn
	Subcutaneous sarcoidosis
	Post-steroid panniculitis
	Gout-related panniculitis
	Post-irradiation sclerodermatous panniculitis
	Crystal-storing histiocytosis

[1] Most likely diagnoses for the patient described in the case report.