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The development of primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder at the site of a melanoma excision scar

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Abstract

Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder (PCSM-LPD) is a rare and low-grade form of cutaneous T-cell lymphoma (CTCL), representing 2% of all primary cutaneous lymphomas. Because of its rarity, the etiology or exact clinicopathology of PCSM-LPD remains unclear. We present the first case of PCSM-LPD, to our knowledge, arising at a past melanoma excision site. A 72-year-old woman with a past medical history significant for melanoma-in-situ excised 36 years ago presented to our clinic for evaluation of a single, erythematous plaque of the posterior arm within a melanoma excision scar. A biopsy was performed, revealing PCSM-LPD. Reports of the development of other T-cell lymphoproliferative disorders after prior skin trauma such as chemical burns, thermal injury, and mechanical trauma exist in the literature. Physicians should be aware of the possibility of the appearance of T-cell lymphoproliferative disorders at the site of scars or prior trauma with a time lag of months to years.

Keywords: cutaneous T-cell lymphoma (CTCL), scar, melanoma, surgery, primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder

Introduction

Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder (PCSM-LPD) is a rare and low-grade form of cutaneous T-cell lymphoma (CTCL), representing 2% of all primary cutaneous lymphomas [1]. PCSM-LPD, originally called primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma, has been reclassified from peripheral T-cell lymphoma not otherwise specified to a benign lymphoproliferative disorder owing to its limited clinical risk and indolent nature [2]. PCSM-LPD has an average age of diagnosis of 54 years and usually presents as a single papule or nodule on the face, neck, or upper trunk [1]. The five-year survival rate is over 90% [2]. Excision, radiation therapy, and skin-directed therapies are usually sufficient to cure this disorder [1].

Because of its rarity, the etiology or exact clinicopathology of PCSM-LPD remains unclear. A case of PCSM-LPD co-existing with myelodysplastic syndrome with transformation into chronic myelomonocytic leukemia as well as a case of methotrexate and etanercept-induced PCSM-LPD have been reported, but no other associations or causative agents have been proposed [3, 4]. We present the first case of PCSM-LPD arising at a prior melanoma excision scar site.

Case Synopsis

A 72-year-old woman with a past medical history significant for melanoma-in-situ excised 36 years ago presented to our clinic for evaluation of a single,

erythematous plaque on the posterior arm at the site of a melanoma excision scar (**Figure 1**). She first noticed erythema, pruritus, and stinging of the lesion two months prior to presentation. At that time, her local dermatologist performed a shave biopsy that revealed an atypical lymphoid infiltrate consistent with a CD4+ T-cell lymphoproliferative disorder. She had no prior history of non-melanoma skin cancers. Her family history was negative for melanoma and lymphoma. Her medications included 80-12.5mg valsartan-hydrochlorothiazide and 25mg metoprolol for 13 years for treatment of hypertension. Otherwise, her review of systems and medical history were noncontributory. Physical exam revealed a 12×12 mm erythematous, scaly plaque on the right posterior upper arm on a portion of a 10cm well-healed melanoma excision scar.

A biopsy of the lesion at our clinic demonstrated a dense dermal infiltrate of small to medium sized lymphocytes (**Figure 2**). No definite germinal center formation, eosinophils, or prominent epidermotropism was identified. The atypical cells were positive for CD3 with a predominant expression of CD4 over CD8 (CD4:CD8 is >6:1). CD30 stained scattered cells. CD20 highlighted admixed B lymphocytes. A subpopulation of lymphocytes expressed PD-1 and a focal and patchy CXCL13 expression was noted. We also performed the molecular study for T-cell receptor beta and gamma chain gene (TCRB and TCRG) rearrangements by PCR analysis, which showed a monoclonal T-cell receptor beta and gamma chain gene (TCRB and TCRG) rearrangements, supporting the diagnosis of CD4-positive T cell lymphoproliferative disorder. Taken together, the histopathological findings are interpreted as those of a CD4 predominant atypical T cell lymphocytic infiltrate with an adjacent scar. On histologic grounds alone, the findings are indicative of a small/medium size pleomorphic CD4-positive T cell lymphoma.

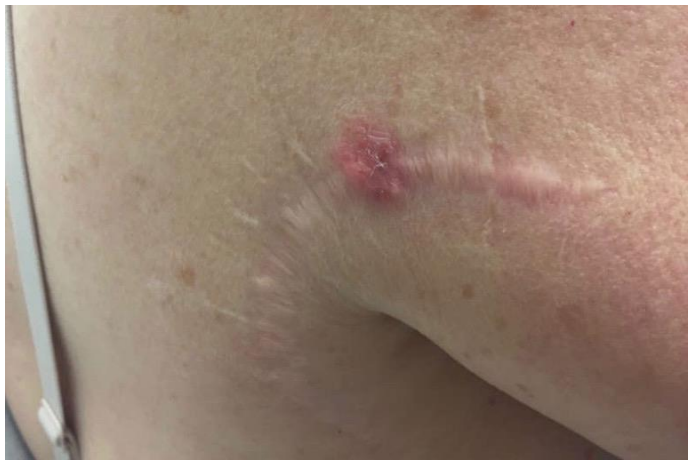

Figure 1. *Melanoma excision site scar with an erythematous plaque.*

Clobetasol 0.1% cream was prescribed to apply to the affected area daily. Two months later, the patient's lesion improved to a non-pruritic, non-painful, scaly, erythematous plaque measuring 10×10 mm. Flattening and decreased erythema of the lesion occurred after the patient received 4 Gy of local radiation to the lesion in two fractions. The

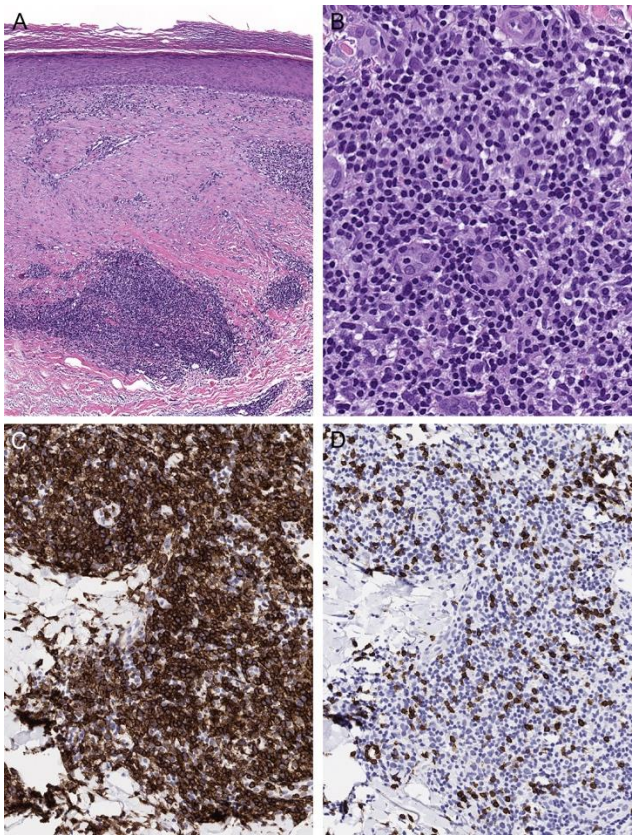

Figure 2. *Representative H&E image of skin shave biopsy showing nodular aggregates of lymphohistiocytic infiltrate predominantly in the dermis underlying the scar, 40× (**A**). The lesional cells were primarily composed of lymphocytes and histiocytes, 400× (**B**). The atypical lymphocytes were small-to-medium in size with admixed histiocytes and reactive B lymphocytes. Immunohistochemical staining showed that the lesional cells were primarily composed of CD4 positive T cells with a CD4 to CD8 ratio of approximately more than 6:1 (immunohistochemical study with CD4 staining **(C)** and CD8 staining (**D**), 200×.*

patient was instructed to continue applying clobetasol 0.1% cream until further follow-up.

Case Discussion

To our knowledge, this is the first reported case of PCSM-TCL occurring at the site of a prior surgical scar or prior melanoma in-situ site. Reports of the development of other T-cell lymphoproliferative disorders after prior skin trauma exist in the literature. There have been three reported cases of primary cutaneous anaplastic large cell lymphoma (PCALCL) arising from a prior burn scar [5-7]. Amoh et al. reported the development of two red nodules at the site of a burn scar on the right upper arm in a 35-year-old Japanese male four months after a thermal burn [5]. A biopsy was performed and immunohistochemical analysis showed positivity for CD3, CD4, CD25, and CD30. The patient had a monoclonal T-cell receptor rearrangement in the beta chain on southern blot analysis. A diagnosis of PCALCL was made and the patient was treated successfully with a total of 40 Gy of focal radiation therapy. Morihara et al. encountered a 64-year-old woman with biopsy-proven PCALCL surrounding the site of a thermal burn scar 13 years after the initial thermal burn [6]. Finally, Yeung et al. described a case of a 58-year-old man with PCALCL which appeared in a scar on the palm at the site of a prior chemical burn 18 months prior. The patient also had recurrent bacterial infections in the same area as well as a psoriatic plaque. Moreover, other skin trauma etiologies have been implicated in the development of T-cell lymphoma. Paul et al. encountered four male patients who all developed mycosis fungoides (MF) after skin trauma, with a median time of 10 years between exposure and diagnosis [8]. Exposures/ trauma included gravel embedded into the thigh of a runner, super glue inoculation of the right buttock, poison oak dermatitis of the right thigh, and a chronic hematoma of the right anterior lower extremity caused by a motor vehicle accident.

Although there is a paucity of data regarding the relationship between PCSM-LPD and melanoma, other subtypes of T-cell lymphoma, such as MF, are associated with melanoma [9]. For example, Chen et al. found that there is a relationship between an increased number of melanomas in one first degree relative and an increased risk of development of MF [10]. The authors acknowledge that this relationship is significant, but not overwhelming owing to a limited number of cases and borderline standardized incidence ratios (SIRS), [10]. Moreover, it is possible that melanoma and CTCL are genetically linked [9]. The histocompatibility locus antigen (HLA) class II alleles *HLA-DR5* and *DQB1*03* are increased in both melanoma and CTCL patients [11]. Additionally, alterations in tumor suppressor protein p16 are present in both melanoma and CTCL patients [12, 13]. Although our patient developed a T-cell lymphoproliferative disorder many years after her melanoma, the relationship between the two disease states still requires further consideration. One other risk factor for the development of CTCL in our patient is her history of hydrochlorothiazide use, which is implicated as a triggering agent for MF [14].

Conclusion

The pathophysiology behind the development of T-cell lymphoproliferative disorders after cutaneous injury/scar formation remains unknown. For PCALCL specifically, it has been shown that CD30+ T-cells are generated after thermal injury [15]. Interestingly, Morihara et al. reported high expression of vascular endothelial growth factor (VEGF) by their patient's tumor cells as well as the expression of VEGF receptors on these same cells. It is possible that neovascularization in the setting of tissue injury could predispose patients for the development of PCALCL. Baum et al. postulate that PCSM- TCLPD may be a reactive process based on the absence of substantial cytologic atypia and the presence of a reactive infiltrate of inflammatory cells [16]. Skin trauma resulting in chronic antigenic exposure and T-cell stimulation/accumulation fits the hypothesis of Tan et al. regarding the autoimmune nature of CTCL [17]. Physicians should be aware of the possibility of the appearance of T-cell lymphoproliferative disorders at the site of scars or prior trauma with a time lag of months to years. Further investigations are warranted to elucidate the etiology and pathophysiology of this phenomenon.

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