1 INTRODUCTION

Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder (PCSM-TCLD) is a provisional entity since 2005.\(^1\) Previous to that, it was considered a cutaneous T-cell lymphoma until 2016, at which point the terminology was modified due to its uncertain malignant potential.\(^2\)

PCSM-TCLD is characterized by a predominance of small to medium-sized CD4\(^{+}\) pleomorphic T-cell phenotype with a distinct clinical presentation from mycosis fungoides.\(^1,3\)

The median age at diagnosis is 51-53 years, with a slight male predominance.\(^3,4\) Most cases usually present with an asymptomatic solitary nodule, plaque, or tumor, most commonly on the head or neck region, though, cases involving other parts of the body, and multifocal disease have been reported.\(^3,6\)

The clinical outcome is frequently favorable with 5-year survival rates of up to 98.4\%, especially when solitary lesions are present, according to a recently published systematic review.\(^4\)

Atypical clinical features include generalized skin lesions, large rapidly growing tumors, >30\% large pleomorphic T cells, and/or a high proportion of proliferative cells. These cases should prompt the clinician to think about a peripheral T-cell lymphoma, NOS instead of a PCSM-TCLD.\(^6\)

**Abstract**

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder is a provisional entity according to the last WHO-EORTC classification. The treatment of choice has not yet been defined. Local therapies have been used with variable response. Doxycycline as a main treatment option is a potential low-cost and effective alternative for this disorder.

**Keywords**

CD4-positive T-lymphocyte, cutaneous T-cell lymphoma, doxycycline, drug repurposing, lymphoproliferative disorder
Herein, we report the first Latin-American case of doxycycline treatment in a young male with this rare condition.

2 | CASE REPORT

A previously healthy 30-year-old Chilean male presented with a 4-month history of multiple, multifocal erythematous to violaceous nodules and plaques on the face. The skin lesions were intermittently itchy and had gradually increased in size and number. Physical examination showed multiple bean-sized erythematous nodules and plaques on the right frontal and mandibular area (Figure 1A). There were neither systemic symptoms nor lymphadenopathy. Incisional skin biopsies were performed, and the histopathological examination revealed a dense infiltration involving the entire dermis and subcutis (Figure 2A). This infiltrate had a polymorphous composition with predominance of small to medium-sized atypical lymphocytes with pleomorphism without epidermotropism (Figure 2B) which also showed a vasculocentric pattern (Figure 2C). Few plasma cells were present. On the immunohistochemical studies, most of the infiltrating cells were positive for CD3, and CD4 (Figure 3A and 3B), CD5, and CD7, while negative for CD30, CD23, CD56, and CD10. There was a subset of these cells positive for PD1. Few CD8$^+$ T cells were present in the mixed infiltrate (Figure 3C), and CD10 was positive in stromal cells. In addition, there was a moderate amount of B cells which were positive for CD20 (Figure 3D) and Bcl-2. A low Ki-67 proliferation index was found. Epstein-Barr virus was not detected by in situ hybridization. No human T-lymphotropic virus type I DNA was detected in the skin biopsy by polymerase chain reaction (PCR). Monoclonality was demonstrated by means of T-cell receptor $\beta$ and $\gamma$-chain consensus PCR. The laboratory examinations at the time of diagnosis, including a complete blood cell count with differential, liver function tests, renal function tests, antinuclear antibody test, serum protein electrophoresis, and urinalysis were within normal limits. The chest X-ray and whole-body computed tomography revealed no abnormalities.

A clinicopathological diagnosis of primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder was made. During the first month of treatment, the patient received doxycycline 100 mg twice daily along with topical fluticasone 0.05% cream twice a day. After that period of time, topical fluticasone was suspended, and doxycycline was continued at the same dosage for another 3 months. From the fourth month on, the dosage of doxycycline was decreased to 100 mg daily, and the patient is currently under the same treatment. Approximately four weeks after initiation of treatment, there was evidence of flattening of the skin lesions and decreased facial erythema, although by that time the lesion had not completely resolved, with a fifteen percent improvement. At his fourth-month follow-up visit, there was an important clinical improvement without evidence of local spread or metastasis (Figure 1B). The response has been sustained during the 6 months of clinical and laboratory monitoring, with excellent tolerance to therapy (Figure 1C).
DISCUSSION

Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder is a rare disease that represents about 2%-3% of cutaneous lymphomas.1 This condition portends an excellent prognosis, mainly if solitary lesions are present. Also, it is characterized by an indolent clinical behavior and its local recurrence is rare.2,4-6 Because of the aforementioned reasons, staging is not recommended in typical cases. According to some experts, it may not represent a true malignancy due to clinical and histopathological features similar to cutaneous pseudo–T-cell lymphomas with a nodular growth pattern.2,3,8

The histopathological hallmark of this disorder is a dense nodular or diffuse T-cell infiltrate, mainly located in the dermis.4-6 There is a small proportion of large pleomorphic cells that does not exceed 30%, and epidermotropism or folliculotropism are not significant.9 CD4+ T cells are small to medium in size with pleomorphic nuclei which are the predominant cell type in a mixed reactive infiltrate of small CD8+ T cells, B cells, histiocytes, and plasma cells.5,6,9 By definition, the offending T cells are always CD4+ and CD3+, and almost all cases are CD8- and CD30-.4,6 The Ki-67 proliferation index is usually low, and loss of CD5 and CD7 is uncommon.3-6 Interestingly, CD20+ B cells are numerous and compose around 10%-60% of the infiltrate.4,9 As for molecular analysis, monoclonal T-cell receptor β and/or γ chain rearrangement has been detected in most cases.3,4 In addition, a variable proportion of the atypical CD4+ T cells express follicular helper T-cell markers such as PD1, BCL6, CXCL13, CD10, and ICOS.4,6,8 It has been suggested that these cells can induce B-cell proliferation and differentiation, hence the presence of numerous B cells in some cases.3,9,10

In consideration of these features, the clinical, histopathological, and molecular findings of our case were compatible with those usually reported in PCSM-TCLD patients which led us to make this diagnosis.

The optimal treatment for this condition has not been established. Conservative approach is an option, as there have been case reports of spontaneous resolution after biopsy.11-13 For those patients with persistent lesions, preferred treatment choices include topical or intralesional steroids, surgical excision, and, occasionally, low dose radiotherapy.9,14 An alternative approach is doxycycline, a widely used tetracycline with antimicrobial, anti-inflammatory, immune-modulating, and neuroprotective properties.15 Different studies have demonstrated its effects on multiple signaling pathways necessary for tumor genesis and survival. These antineoplastic actions include
inhibition of nuclear transcription factor NF-κβ, signal transducer and transcription factor STAT3, ERK, AKT, and HSP90 pathways.\cite{16,17} Induction of apoptosis through caspases 3 and 8 activation, and decreased levels in BCL2 alpha, have also been described.\cite{15,17,18} One of the consequences of NF-κβ signaling inhibition is the excess mitochondrial production of reactive oxygen species which in turn contributes, in another way, to apoptosis.\cite{16,19}

Concerning the anti-inflammatory properties of tetracyclines, this ability stems from the inhibition of matrix metalloproteinases (MMPs), hydrolases, and cytokine production.\cite{20} Moreover, it is believed that MMPs contribute to tumor cell growth, invasion, and metastasis via previous activation of growth factors, hence, another potential role of these antibiotics in cancer.\cite{21}

Bearing in mind these multiple actions, the address of common pathways in tumor cells of diverse origins with doxycycline seems reasonable as has been demonstrated in studies about the effect of this drug in diffuse large B-cell lymphoma, lung cancer, breast cancer, prostate cancer, melanoma, and one case of PCSM-TCLD,\cite{7,17,22-25} among others. With respect to the latter, the patient had a 5-year history of a slow-growing tumor on the right cheek and treatment with oral doxycycline, 200 mg daily for 21 days, achieved a temporary complete remission of 13 months.\cite{7}

In view of all these concepts, doxycycline was the first therapeutic choice in our patient, achieving a substantial clinical response. Nevertheless, since this is the second PCSM-TCLD case reported worldwide in which this agent was used as first-line treatment, it is necessary to explore its mechanisms of action and affected molecular pathways in further studies, in the context of this kind of T-cell lymphoproliferative disorder.

In summary, this report demonstrates that doxycycline is a potential low-cost and safe alternative for PCSM-TCLD and possibly other cutaneous and noncutaneous lymphomas.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTION

CE and PMGF: shared co-first authorship in drafting the manuscript. CE and NAJ: took overall responsibility for patient care. CC: structured the introduction and part of case description. PMGF and CC: shared responsibility in collecting references. PMGF, NAJ and FBB: took overall responsibility for critical manuscript review. CE, PMGF, CC: involved in final manuscript corrections. CEF and PMGF: contributed equally to this paper.

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REFERENCES

1. Willemze R, Jaffe ES, Cerroni L, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768-3785.

2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.

3. Beltraminelli H, Leinweber B, Kerl H, Cerroni L. Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior. *Mod Pathol*. 2008;21:708-715.

4. Messeguer F, Gimeno E, Agusti-Mejias A, et al. Primary cutaneous CD4+ small-to-medium-sized pleomorphic T-cell lymphoma: report of a case with spontaneous resolution. *Actas Dermosifiliogr*. 2011;102:636-638.

5. González Fernández D, Valdés Pineda F, Gómez Díez S, et al. Primary cutaneous CD4+ small/medium-sized T-cell lymphoma with spontaneous regression after biopsy. *Actas Dermosifiliogr*. 2015;106:767-768.

6. Garcia-Herrera A, Colomo L, Camos M, et al. Primary cutaneous small/medium CD4 + T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. *J Clin Oncol*. 2008;26:3364-3371.

7. Cetinözeman F, Jansen PM, Willemze R. Expression of programmed death-1 in primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma, cutaneous pseudo-T-cell lymphoma, and other types of cutaneous T-cell lymphoma. *Am J Surg Pathol*. 2012;36:109-116.

8. Golub LM. Introduction and background. *Pharmacol Res*. 2011;63:99-101.

9. Rodríguez Pinilla SM, Roncador G, Rodríguez-Peralto JL, et al. Doxycycline induces apoptotic cell death in malignant T-cells. *Oncotarget*. 2016;7:75954-75967.

10. García-Herrera A, Colomo L, Camos M, et al. Primary cutaneous small/medium T-cell lymphoproliferative disorder: Where do we stand? A systematic review. *J Dtsch Dermatol Ges*. 2019;17:123-136.

11. Grogg KL, Jung S, Erickson LA, et al. Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoproliferative disorder. *Hematol Oncol Clin North Am*. 2019;33:135-148.

12. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.

13. Beltraminelli H, Leinweber B, Kerl H, Cerroni L. Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior. *Mod Pathol*. 2008;21:708-715.

14. Messeguer F, Gimeno E, Agusti-Mejias A, et al. Primary cutaneous CD4+ small-to-medium-sized pleomorphic T-cell lymphoma: report of a case with spontaneous resolution. *Actas Dermosifiliogr*. 2011;102:636-638.

15. Bahrami F, Morris DL, Pourgholami MH. Tetracyclines drugs with huge therapeutic potential. *Mini Rev Med Chem*. 2012;12:44-52.

16. Alexander-Savino CV, Hayden MS, Richardson C, et al. Doxycycline is an NF-κB inhibitor that induces apoptotic cell death in malignant T-cells. *Oncotarget*. 2016;7:75954-75967.

17. Pulvino M, Chen L, Oleksyn D, et al. Inhibition of COP9-signalosome (CSN) deneddylating activity and tumor growth of diffuse large B-cell lymphomas by doxycycline. *Oncotarget*. 2015;6:14796-14813.

18. Iwasaki H, Inoue H, Mitsuke Y, et al. Doxycycline induces apoptosis by way of caspase-3 activation with inhibition of matrix metalloproteinase in human T-lymphoblastic leukemia CCRF-CEM cells. *J Lab Clin Med*. 2002;140:382-386.

19. Kiessling MK, Klemke CD, Kamiński MM, et al. Inhibition of constitutively activated nuclear factor-κB induces reactive oxygen species- and iron-dependent cell death in cutaneous T-Cell lymphoma. *Cancer Res*. 2009;69:2365-2374.

20. Golub LM. Introduction and background. *Pharmacol Res*. 2011;63:99-101.

21. Rooprai HK, Rucklidge GJ, Panou C, et al. The effects of exogenous growth factors on matrix metalloproteinase secretion by human brain tumour cells. *Br J Cancer*. 2000;82:52-55.

22. Qin Y, Zhang Q, Lee S, et al. Doxycycline reverses epithelial-to-mesenchymal transition and suppresses the proliferation and metastasis of lung cancer cell. *Oncotarget*. 2015;6:40667-40679.

23. Tang X, Wang X, Zhao YY, et al. Doxycycline attenuates breast cancer related inflammation by decreasing plasma lysophosphatidylcholine concentrations and inhibiting NF-κB activation. *Mol Cancer*. 2017;16:36.

24. Oğut D, Reel B, Gonen Korkmaz C, et al. Doxycycline down-regulates matrix metalloproteinase expression and inhibits NF-κB signaling in LPS-induced PC3 cells. *Folia Histochem Cytobiol*. 2016;54:171-180.

25. Sun T, Zhao N, Ni CS, et al. Doxycycline inhibits the adhesion and migration of melanoma cells by inhibiting the expression and phosphorylation of focal adhesion kinase (FAK). *Cancer Lett*. 2009;285:141-150.

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