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A diagnostically challenging case of CD8+ primary cutaneous gamma/delta T-cell lymphoma

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Abstract

Primary cutaneous gamma/delta T-cell lymphoma (PC $\gamma\delta$ TCL) is a rare form of cutaneous lymphoma characterized by abnormal clonal proliferation of mature, activated gamma-delta T cells expressing the $\gamma\delta$ heterodimer of the T-cell receptor (TCR). As an entity, PC $\gamma\delta$ TCL has recently undergone diagnostic revision since its introduction in the 2008 WHO classification of cutaneous lymphomas and confirmed in 2016. Nonetheless, diagnosis remains difficult both clinically and histologically, given its broad range of clinical manifestations and immunohistochemical phenotypes. Herein, we present a rare case of CD8+ PC $\gamma\delta$ TCL with a discussion highlighting the heterogeneity within this entity.

Keywords: general dermatology; medical dermatology; oncology; cutaneous lymphoma, CD8, gamma-delta T cells

Introduction

Primary cutaneous lymphomas are a heterogeneous group of lymphoproliferative neoplasms that are, by vast majority, T-cell in origin. Still undergoing ongoing molecular and pathologic analysis, this group was among those that recently underwent revision in the 2016 WHO guidelines to encompass a growing number of discrete entities. They are broadly characterized by a clonal population of T-cells and rearrangement of TCR, which exists physiologically as a heterodimer of either alpha-beta ($\alpha\beta$) or gamma-delta ($\gamma\delta$) receptors. The $\alpha\beta$ TCR phenotype is most common, with a much smaller percentage of

cutaneous T-cell lymphoid neoplasms expressing $\gamma\delta$.

Primary cutaneous gamma/delta T-cell lymphoma (PC $\gamma\delta$ TCL) is a rare disease, accounting for less than 1% of all primary cutaneous lymphomas. It consists of an abnormal clonal proliferation of mature, activated gamma-delta T cells expressing the $\gamma\delta$ heterodimer of the TCR. The $\gamma\delta$ phenotype is expressed by 5% of circulating T cells and up to 30% of the total number of T cells in some organs, including the skin [1, 2]. Its rarity, coupled with a wide range of clinical and histologic patterns, makes this a diagnostically challenging disease. Rapid diagnosis is crucial, given its aggressive clinical course with a 5-year survival rate of 20-33% [3, 4].

The clinical and histologic appearances of PC $\gamma\delta$ TCL and other T-cell lymphomas, as well as seemingly benign-appearing entities, may show overlapping features. As such, careful histopathologic examination, immunohistochemical analysis of surface markers, and clinicopathologic correlation are crucial; molecular studies are sometimes necessary to make this diagnosis [4, 5]. The cytotoxic phenotype of PC $\gamma\delta$ TCL has been well characterized as CD2, CD3, CD56, and TCR γ positive, and CD4, CD5, and CD6 negative [6].

Herein, we report a patient with CD8-positive primary cutaneous gamma/delta T-cell lymphoma. CD8-positivity is uncommon in this entity, having been reported in only a small number of cases [2, 7, 8]. This case highlights the importance of both clinical and pathologic acumen in making this diagnosis and also provides evidence to support heterogeneity within

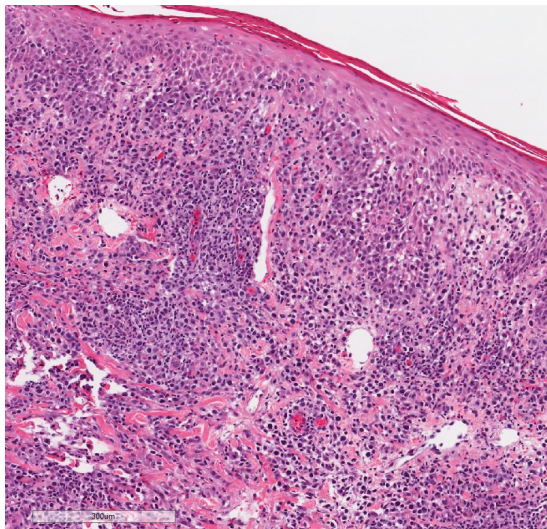


Figure 1. H&E stain demonstrating significant epidermotropism of abnormal population of neoplastic cells. 100%.



Figure 2. Well-circumscribed erythematous plaque with necrotic center and serosanguinous crust on scalp.

this small subset of PC γ δ TCL as our clinical and pathologic understanding of the disease continues to broaden.

Case Synopsis: A 73-year-old man with history of rheumatoid arthritis, previously treated with methotrexate and infliximab, presented to his community dermatologist with a 4 to 5-week history of a growing lesion on his left neck/shoulder. This area had been unresponsive to previous treatments with systemic and topical antibiotics as well as a previous incision and drainage attempt. Physical exam revealed 4x2 cm erythematous, indurated, non-fluctuant plaque studded with firm red-brown papules located on the left anterior clavicular neck. He was otherwise well and reported no constitutional symptoms. A recent WBC count was 7,000 (normal 4,500 – 11,000). A punch biopsy was performed on the skin lesion.

Histopathologic examination revealed ulceration of the epidermis with a diffuse infiltrate of atypical cells involving the dermis and subcutis with marked epidermotropism. Syringotropism, angiotropism, and angiocentricity were also noted. The neoplastic cells demonstrated irregular nuclear contours and mitoses were readily identifiable (**Figure 1**). The neoplastic cells expressed CD3, CD8, CD56, granzyme B, and TIA-1, but were negative for CD2, CD4, CD5, CD7, CD30, CD79a, CD123, and myeloperoxidase. EBV in situ hybridization was negative. The neoplastic cells were positive for TCR gamma and negative for

TCR beta (BF-1) by immunohistochemistry.

After the diagnosis was established, the patient underwent chemotherapy with ifosfamide, carboplatin, and etoposide, and radiation treatment with a total of 15 treatments at total dose of 3000 cGy with 200 cGy per treatment. He achieved complete remission with a negative PET scan. However, two months later, new lesions developed on his eyelid. A biopsy of the right eyelid was histologically similar and consistent with recurrent disease, which was subsequently treated with radiation therapy. The lesion improved but the patient was left with poor vision in this eye. He continued to develop additional new lesions on the right neck, mid-back, and left flank and was then treated with gemcitabine and oxaliplatin combined with localized radiation treatment. In the following few months, he developed new lesions on the left side of the face and scalp (**Figure 2**).

The patient was then treated with romidepsin and brentuximab, but unfortunately continued to develop new lesions as well as growth of existing plaques to tumors (**Figure 3**). Given the rapid progression of the disease, he was started on pentostatin, which resulted in immediate significant improvement with flattening of the tumors and shrinking of the lesions.

As of his most recent clinic visit, 14 months after initial presentation, he has completed 3 treatments of pentostatin with a plan to continue every 6 weeks. After his second treatment of pentostatin,



Figure 3. Status-post romidepsin and brentuximab initiation therapy. Polymorphic lesions including erythematous plaques with necrotic center and serosanguinous crust, erosions, and nodules over the anterior trunk.

bexarotene 150mg daily was added to the treatment regimen. He achieved complete clearance of active skin lesions with clinical remission lasting 6 months (**Figure 4**).

Case Discussion

Cutaneous lymphoid neoplasms are a diverse group of diseases and continued revision of classification with diagnostic and therapeutic implications has been necessary to reflect the growing body of research. PC $\gamma\delta$ TCL is a rare and aggressive lymphoma, which was introduced in the 2008 WHO classification and only recently confirmed in 2016 in a revision of the classification of lymphoid neoplasms [6, 9].

PC $\gamma\delta$ TCL may produce a wide range of clinical manifestations. Occurring primarily in adults without gender predilection, the lesions may be highly variable and range from patches and plaques to deeper subcutaneous nodules progressing to ulceration and necrosis. Extremities are preferentially involved with a relative sparing of the trunk [1]. Systemic symptoms such as fever and hepatosplenomegaly are rare. Given the protean nature of this disease, initial misdiagnosis is not uncommon. Similar clinical



Figure 4. Status-post pentostatin and bexarotene chemotherapy. Complete clearing of active lesions.

characteristics may be seen in nodular panniculitis, lupus erythematosus profundus, systemic vasculitis, and erythema nodosum, to name a few [10].

The histologic appearance of PC $\gamma\delta$ TCL can likewise vary; epidermotropic, subcutaneous, as well as pandermal and panniculitic patterns of involvement have been described. Angiocentricity, syringotropism, and folliculotropism have been reported as prominent features in some cases [4]. Alternatively, a recent case was reported with bland histologic features yet an aggressive clinical course [5]. Furthermore, the disease may display varying histologic patterns at different biopsy sites in the same patient, highlighting the importance of adequate sampling of the lesions [4]. Repeat biopsies are often necessary in order to arrive at the correct diagnosis [11].

PC $\gamma\delta$ TCL consists of an abnormal clonal proliferation of mature, activated gamma delta T-cells expressing the $\gamma\delta$ heterodimer of the TCR, expressed by only 5% of normal circulating T-cells. This percentage may increase to 30% in organs such as the GI tract and the epidermis of the skin, highlighting their predominant role as part of the innate immune system [1, 2]. The clonal population expresses rearrangements of both γ and δ TCR genes and is negative for TCR-BF1 expression. Most of these T-cells are CD4-/CD8-, which aids in distinguishing PC $\gamma\delta$ TCL from other histologically similar cutaneous lymphomas such as mycosis fungoides. A small subset of these

$\gamma\delta$ T-cells, however, expresses CD8 [3]. The classic immunophenotype of PC $\gamma\delta$ TCL includes expression of CD2, CD3, CD56, and TCR γ , whereas CD4, CD5, and CD6, are negative. Expression of $\gamma\delta$ TCR is essential for the diagnosis [6]. Of note, the $\gamma\delta$ TCR phenotype has been rarely reported in a small percentage of other cutaneous lymphomas, and the recent revision to the 2008 WHO classification emphasizes the importance of excluding other cutaneous lymphoproliferative disorders that may also express the $\gamma\delta$ phenotype, notably mycosis fungoides and type D lymphomatoid papulosis (LyP), [1, 9, 12]. Like other types of LyP, type D LyP is clinically characterized as self-healing, waxing and waning, exhibiting papulonodular skin lesions, and having a good prognosis. Type D LyP can simulate CD8+ cytotoxic T-cell lymphoma histologically, though most cases express CD30. The clinical behavior as well as classic CD30-positivity of LyP exclude this entity from our differential diagnosis [13]. Of the two cases of mycosis fungoides that were found to express TCR- γ in the aforementioned study by Rodriguez-Panilla, et al., one was CD4- / CD8- and expressed perforin and the other exhibited large cell transformation with CD30-positivity [12].

Given the CD8-positivity in our case, the differential diagnosis also included primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. This entity expresses the more common $\alpha\beta$ TCR heterodimer, which was found to be negative in our case. Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T cell lymphoma can have a similarly broad range of histologic features ranging from lichenoid pattern to diffuse dermal infiltrates; subcutaneous involvement, however, is typically less prominent [14]. Expression of the $\gamma\delta$ receptor in PC $\gamma\delta$ TCL is the major distinguishing feature between these two entities.

Our case highlights the importance of clinical, histopathologic, and immunophenotypic correlation in making this diagnosis. Molecular studies for clonality can also be useful, if necessary. Our patient's aggressive clinical course, the histologic features, and cytotoxic, $\gamma\delta$ immunophenotype was consistent with a diagnosis of PC $\gamma\delta$ TCL; this case serves as a rare example of CD8-positivity in this entity [7].

The prognosis for PC $\gamma\delta$ TCL is characteristically poor,

with a median survival of 15 months after diagnosis [11]. Treatment options include a combination of radiation, immune therapy, and multiagent chemotherapy, but remission is not typically sustained with these treatment modalities [2]. Stem cell transplantation is becoming an increasingly promising option for patients with cutaneous lymphomas, with a recent series showing increased survival in patients with PC $\gamma\delta$ TCL after both allogeneic and autologous stem cell transplantation [15].

As PC $\gamma\delta$ TCL is a recently confirmed entity by WHO classification, additional study is necessary to further characterize and refine the disease within the larger subset of cutaneous lymphomas. There is a growing body of evidence to suggest that there is marked heterogeneity even within the small group of PC $\gamma\delta$ TCL. A recently published study comparing primarily epidermotropic cases to dermal/subdermal cases of $\gamma\delta$ TCL found that these two diseases show differences in immunophenotype and also differences in overall survival. These outcome differences, corresponding to differences in histologic as well as immunologic expression, suggest subsets that may have different underlying pathophysiology [4].

Conclusion

PC $\gamma\delta$ TCL is a disease that evades simple characterization owing to its clinical and pathologic heterogeneity. More work remains to understand the roles of different populations within the disease. Interestingly, new evidence suggests that CD8-positivity contributes to immune surveillance and quiescence in CTCL [16]. No such studies have been done on this subset of PC $\gamma\delta$ TCL with CD8 positivity as a possible group with altered clinical outcomes, response to treatment, or underlying pathophysiology. Additionally, a recent study showed that, although considered rare in other cutaneous lymphomas, PC $\gamma\delta$ TCL commonly undergoes immunophenotypic shifts in cellular antigens that are not associated with a second neoplasm or change in clonality. This further contributes to the diversity of the disease, even temporally within the same patient's clonal population of tumor cells. Whether these shifts are associated with underlying pathogenesis and progression of the disease remains to be understood [8]. Further work is needed to

understand this subset within this newly recognized disease that has manifested itself as both increasingly heterogeneous and diagnostically evasive.

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