Primary Cutaneous Gamma-Delta T-Cell Lymphoma: Two Cases and a Review of the Literature

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Abstract

Background: Primary cutaneous gamma delta T cell lymphoma (PCGD TCL) is a rare and rapidly progressive cutaneous malignancy that can be diagnostically challenging. Purpose: To improve characterization of the clinical and histologic features of PCGD-TCL. Methods: We present two patients with PCGD TCL and review an additional 97 PCGD TCL cases from the English literature. Results: A 51 year old male with biopsy proven psoriasis and a previously healthy 31 year old male with vitiligo developed PCGD-TCL. Initial biopsy specimens in both patients suggested tumor stage mycosis fungoides (MF), but subsequent histopathology confirmed PCGD TCL. Ninety-seven patients were identified in the literature, mostly males (53%) with a mean age of 55.2 years. Lesions most commonly involved the lower (60%) and upper (30%) extremities and existed a mean of 26 months before diagnosis. The most common immunohistochemical markers were EBV(-), CD3(+), CD4(-), CD5(-), CD7(-), CD8(-), CD30(-), CD56(+), granzyme-B(+), perforin(+), and βF1(-). Radiation and CHOP chemotherapy were the most common interventions and 52% of patients died. Conclusion: PCGD TCL is a devastating disease that can clinically and histologically mimic more common dermatologic conditions, such as psoriasis and MF, and its diagnosis may require multiple biopsies and review by a multi specialty pathology team.

Keywords: Cutaneous T-cell lymphoma, hemophagocytic lymphohistiocytosis, mycosis fungoides, primary cutaneous gamma-delta T-cell lymphoma, psoriasis

Introduction

Cutaneous lymphomas are a diverse group of non-Hodgkin lymphomas.[1] Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) is a rare subtype, which accounts for less than one percent of all cases of cutaneous lymphoma.[1] Its rarity precludes extensive study, and there is currently no standardized treatment protocol. In addition, PCGD-TCL is characterized by heterogeneous presentations, clinical courses, and immunophenotypes, which may present a diagnostic challenge.[2] We present two patients with PCGD-TCL followed by a review of an additional 97 PCGD-TCL cases from the English literature.

Patient one

A 51-year-old male with a several-year history of psoriasis refractory to hydrocortisone and triamcinolone presented to clinic with disease flare. A physical examination revealed psoriasiform plaques of the bilateral upper and lower extremities, bilateral hands, and trunk (15% body surface area) [Figure 1a-c]. The patient was treated with apremilast and clobetasol. Two months later, after discontinuation of apremilast, the patient’s condition worsened, and additional lesions appeared on both arms. A punch biopsy specimen from the right lower flank demonstrated epidermal hyperplasia with suprapapillary thinning, focal diminution of the granular layer, parakeratosis, Munro’s microabscesses, and focal spongiosis, findings consistent with psoriasis [Figure 2a and b]. A complete blood count and a complete metabolic panel

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were unremarkable. An infectious workup was negative for tuberculosis and viral hepatitis.

Despite starting oral methotrexate (10 mg weekly) three months after the initial visit, the patient’s lesions continued to enlarge and became bullae, spreading to the neck, face, and scalp, raising concern for pustular psoriasis. The lesions worsened over the next month despite additional treatment with 100 mg/mL guselkumab, and the patient developed tumor-like nodules [Figure 3a and b]. A review of systems was negative for fevers, night sweats, cough, and recent foreign travel. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed mildly enlarged axillary, common femoral, and inguinal lymph nodes. A repeat punch biopsy of the left lower back demonstrated an atypical epidermal atrophic and dermal lymphoid infiltrate, characteristic of mycosis fungoides (MF) [Figure 4a and b]. Given the patient’s atypical clinical presentation and rapid progression from plaques to tumors, additional dermatopathologic evaluation was pursued. The infiltrate immunophenotype was: T-cell receptor (TCR)-δ(+)/CD2(−)/CD3(+) /CD4(−)/CD5(−)/CD8(−)/CD30(−)/CD56(−)/BF1(−)/TIA-1(+/−)/CD45RA(+).

Epstein–Barr encoding region-1 in situ hybridization was negative and Ki67 (MIB-1) monoclonal antibody markers showed proliferative activity of approximately 80%, characteristic of a high-grade tumor. A diagnosis of PCGD-TCL with cytotoxic activity was confirmed. The patient was started on EPOCH chemotherapy (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin); after four months of chemotherapy, the patient began adjuvant radiation therapy with the goal of remission and eventual stem cell transplant. However, the patient died slightly over 2 years from the time of diagnosis.

**Patient two**

A 31-year-old Caucasian male with a diagnosis of vitiligo presented to his primary care physician with a firm, painful 3 cm × 2 cm lesion over his right thigh. Despite several courses of antibiotics, the lesion enlarged and additional smaller nodules appeared in his right groin. A skin biopsy was suspicious for cutaneous T-cell lymphoma.

Four months later, the patient presented to our institution with a large erythematous plaque accompanied by several punctate ulcerations over the right lateral thigh and smaller plaques on the left thigh and right calf [Figure 5a and b]. He endorsed intermittent fever but denied night sweats, chills, and weight loss. Physical examination was negative for palpable lymphadenopathy. His serum transaminase and lactate dehydrogenase levels were elevated. A biopsy specimen showed a dense infiltrate of atypical lymphocytes in the dermis extending to the subcutaneous fat [Figure 6a and b]. Immunohistochemistry identified atypical T-cells with an elevated CD4:CD8 ratio, CD5(−), and granzyme-B(−), suggestive of tumor-stage MF. Subsequent bone marrow biopsy showed no evidence of T-cell disease. A CT scan revealed inguinal lymphadenopathy and hepatomegaly. He was started on 75 mg daily bexarotene with a plan to increase to 600 mg daily.
Immunohistochemical stains of a repeat biopsy seven weeks later identified CD3(+), granzyme-B(+), CD7(−) T-cells, characteristic of a cytotoxic T-cell phenotype [Figure 7a and b]. The tumor cells were βF1(−), CD56(+) [Figure 7c]. Polymerase chain reaction assay showed gamma rearrangement of the TCR and immunohistochemistry for gamma-delta showed diffuse, strong staining in the atypical lymphocytic infiltrate [Figure 7d]. The patient was diagnosed with PCGD-TCL and was started on daily dose-adjusted EPOCH chemotherapy with the goal of allogeneic bone marrow transplant once disease control was achieved.

Despite two cycles of EPOCH and one cycle of ifosfamide, carboplatin, and etoposide chemotherapy, the patient’s disease continued to progress. He had a partial response after two cycles of CPI-613 with bendamustine, but this was discontinued after he experienced two grand-mal seizures. Six months after his diagnosis, a bone marrow biopsy revealed hemophagocytic lymphohistiocytosis (HLH), with a serum ferritin level greater than 25,000. The patient failed to improve with etoposide, dexamethasone, and alemtuzumab, and a bone marrow transplant became nonviable. He passed away seven months after initial diagnosis.

**METHODS**

A systematic review of the literature was performed in the MEDLINE (PubMed) database using the keywords, “primary cutaneous gamma-delta T-cell lymphoma.” This search identified 68 publications, 63 of which were accessible and encompassed a total of 97 cases of PCGD-TCL. We reviewed demographic data, presenting features, treatment regimens, and clinical responses.

**RESULTS**

Ninety-seven patients, mostly males (52.6%) with a mean age of 55.2 ± 18.4 years (median 57 years; range 1.5–88 years), were identified in the literature. Their presentation characteristics, treatment regimens, and outcomes are summarized in Tables 1 and 2.

**DISCUSSION**

PCGD-TCL is a rare and aggressive T-cell lymphoma caused by clonal expansion of mature cytotoxic gamma-delta T-cells, a peripheral T-cell seen in epithelial and mucosal tissues.[1,3] Gamma-delta T-cells are divided into two subpopulations, Vδ1 and Vδ2, based on the variable region of the delta chain of their TCR.[3] While both functional subsets may give rise to PCGD-TCL, each subtype has its own clinically relevant distinguishing features.[3] Differences in Vδ1 and Vδ2 tropism for skin layers and differential production of cytotoxic cytokines partially explain PCGD-TCL’s heterogeneity, and epidermal-derived lesions carry a better prognosis than dermal or subcutaneously-derived infiltrates.[1,3,4]

PCGD-TCL is more common among middle-aged individuals and may be more likely to affect men than subcutaneous panniculitis-like T-cell lymphoma.[2,5] However, there are reports of the disease occurring in children with variable outcomes.[6-9] It most commonly presents as plaques and ulcerating lesions over the extremities, as seen in our two cases, but may also present as panniculitis, erythroderma, pyoderma, cellulitis, and rarely, Sezary syndrome.[2,10-13] Extracutaneous manifestations, such as bone metastasis and central nervous system involvement, have also been described.[16,17] Unlike other lymphomas, the spleen, bone marrow, and lymph nodes are rarely involved.[11] If splenic involvement is evident, PCGD-TCL can be confused with a similar, but distinct
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While comorbid inflammatory disease has not been consistently described, chronic antigen stimulation and immunosuppression may contribute to its pathogenesis.\[18\] Several patients have developed PCGD-TCL in the setting of systemic inflammatory disease including Behçet’s syndrome, rheumatoid arthritis, psoriasis, and ankylosing spondylitis.\[6,17,29,30\] There are at least two patients whose disease became clinically apparent after beginning biologic therapy, including one of our case presentations and a patient with rheumatoid arthritis.\[29\] It is unclear if longstanding T-cell inflammation or immunomodulation contributed to disease onset in these cases.

According to the World Health Organization and the European Organization for Research and Treatment of Cancer, the cells of PCGD-TCL are classically CD3(+), CD4(−), CD8(−), CD56(+), and EBV(−).\[1\] However, many immunophenotypical variants have been reported.\[1\] Several cases, including both of our patients, were initially diagnosed with MF based on the first biopsy specimen.\[17,31,34\] Other histopathologic features, such as Pautrier microabscesses, may further mislead pathologists.\[35\]

The treatment of PCGD-TCL usually involves lymphotoxic chemotherapy, sometimes with concomitant cutaneous radiation. Depending on the immunophenotype, targeted immunotherapies may present an additional treatment option; for example, brentuximab vedotin, an anti-CD30 antibody, can be used for CD30(+) disease. Depending on the immunophenotype, targeted immunotherapies may present an additional treatment option; for example, brentuximab vedotin, an anti-CD30 antibody, can be used for CD30(+) disease. However, hematopoietic stem cell transplant appears to be the only curative treatment option and may be associated with safety risks.\[36\] At least one patient developed multiple complications after allogenic stem cell transplant: BK virus-associated cystitis, ocular herpes simplex, and bronchiolitis obliterans – before dying from graft-versus-host-disease.\[37\] Another patient developed PCGD-TCL shortly after receiving an allogenic stem cell transplant for MF.\[38\]

**Conclusion**

PCGD-TCL is a rare disease plagued by a limited knowledge fund. Diagnosis can be difficult due to its variable clinical presentation and the histologic similarities it shares with more common cutaneous pathologies. The two cases presented, along with our literature review, serve as a reminder that repeat biopsies may be indicated for cases of dermatoses that exhibit unusual behavior.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Lesion onset to diagnosis (months) (mean)</td>
<td>26±37</td>
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<tr>
<td>Lesion site (%)</td>
<td></td>
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<tr>
<td>Lower extremities</td>
<td>60</td>
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<td>Upper extremities</td>
<td>30</td>
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<tr>
<td>Trunk</td>
<td>21</td>
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<tr>
<td>Diffuse involvement</td>
<td>14</td>
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<tr>
<td>Immuno histochemical markers (%)</td>
<td></td>
</tr>
<tr>
<td>EBV(−)</td>
<td>86</td>
</tr>
<tr>
<td>CD3(+)</td>
<td>99</td>
</tr>
<tr>
<td>CD4(−)</td>
<td>85</td>
</tr>
<tr>
<td>CD7(−)</td>
<td>71</td>
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<tr>
<td>CD8(−)</td>
<td>61</td>
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<td>CD10(−)</td>
<td>76</td>
</tr>
<tr>
<td>CD56(+)</td>
<td>66</td>
</tr>
<tr>
<td>Granulocyte-B(+)</td>
<td>56</td>
</tr>
<tr>
<td>Perforin(+)</td>
<td>85</td>
</tr>
<tr>
<td>βF1(+)</td>
<td>94</td>
</tr>
<tr>
<td>Associated conditions (%)</td>
<td></td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>12</td>
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<td>EBV: Epstein-Barr virus</td>
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**Table 2: Treatment regimens and outcomes of 97 primary cutaneous gamma-delta T-cell lymphoma patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Pretransplant preparative regimens (values &lt;10% were excluded) (%)</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>30</td>
</tr>
<tr>
<td>CHOP</td>
<td>29</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10</td>
</tr>
<tr>
<td>Transplant</td>
<td></td>
</tr>
<tr>
<td>Hematopoietic stem cell transplant</td>
<td>13% (8% allogenic; 2% autologous; 2% unspecified; 1% syngeneic)</td>
</tr>
<tr>
<td>Outcomes (%)</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>37</td>
</tr>
<tr>
<td>Death</td>
<td>52</td>
</tr>
<tr>
<td>Mean survival upon diagnosis (months)</td>
<td>13±13</td>
</tr>
</tbody>
</table>

CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone

lymphoma: hepatosplenic gamma-delta lymphoma.\[19\] Another variant of cutaneous malignancy involving a gamma-delta lineage that can present with ulcerating plaques is extranodal T-cell lymphoma, which may be differentiated from PCGD-TCL by its classical expression of CD8(+) and EBV(+)\[1\]. While PCGD-TCL can present a diagnostic challenge, laboratory tests, such as lactate dehydrogenase levels, may help support a diagnosis of lymphoma.\[19\] The clinical course of PCGD-TCL is typically very aggressive with a five-year survival rate of approximately 10%.\[19\] The development of HLH in the setting of PCGD-TCL indicates a poor prognosis, as seen in our second case presentation and reflected in our literature review.\[13,14,20-26\] Cases of indolent disease progression have occurred, but one patient suffered rapid deterioration and death after a 15-year indolent course; atypical expression of markers, such as βF1(+), CD30(+), and CD4(+), may be indicators of less aggressive disease.\[13,14,20-26,27,28\]
names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

**Conflicts of interest**
There are no conflicts of interest.

**References**


