

Pediatric Cutaneous Gamma-delta T-cell Neoplasm and Mimics: Not Always Aggressive

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Abstract

Pediatric cutaneous T-cell lymphoma with $\gamma\delta$ immunophenotype is extremely rare. Only a few cases of $\gamma\delta$ T-cell neoplasm have been reported in the literature and therefore little is known whether $\gamma\delta$ T-cell neoplasms in children are distinct from their adult counterparts with respect to the clinicopathological presentation, behavior and prognosis. In this study, we demonstrate three unique cases with increased $\gamma\delta$ T-cells in malignant and non-malignant skin conditions of children. All cases showed an indolent clinical course. Full integration of clinical presentation, morphology, immunophenotype, and genetics supports the correct diagnosis and guides the treatment.

Introduction

Normal T-lymphocytes express either $\alpha\beta$ or $\gamma\delta$ T-cell receptors, while $\gamma\delta$ T-cells comprise 0.5%–10% of total T-cells with variable distribution in mucosa, spleen, lymph node and other sites, that play critical roles of innate and adaptive immunity.¹ The physiological development and immunophenotype of $\gamma\delta$ T-cells are different from $\alpha\beta$ T-cells.² For instance, subsets of $\gamma\delta$ T-cells are less dependent on thymic microenvironment and may arise extrathymically.¹⁻³ The $\gamma\delta$ T-cells express CD3, variable CD5, variable CD56 and CD57, while they are often negative for CD4 and CD8.

T-cell lymphomas (TCLs) account for about 12% of the total lymphoid tumors, and comprise over 20 distinct entities in the World Health Organization (WHO) classifications.⁴ TCLs are extremely rare in children. Aside from T-lymphoblastic and anaplastic large cell lymphomas; the majority of TCLs originate from $\alpha\beta$ T-cells and only few arise from $\gamma\delta$ T cells,⁴⁻⁶ including primary cutaneous $\gamma\delta$ T-cell lymphoma (PCGDTCL), hepatosplenic T-cell lymphoma (HSTCL), and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).⁴ Patients with these types of $\gamma\delta$ TCLs appear to have an aggressive clinical course and poor outcome despite aggressive chemotherapy and/or additional treatments.⁴ Occasional $\gamma\delta$ T-cell lymphoma cases are limited to the subcutis and show a less aggressive clinical course.^{3,7-10} Further, some cutaneous and subcutaneous TCLs and non-malignant skin conditions may demonstrate an increase in $\gamma\delta$ T-cells, with uncertain significance.^{2-4,11,12}

Hence, our current knowledge of $\gamma\delta$ TCLs is mostly based on adult patients; and the pathological and clinical studies of pediatric $\gamma\delta$ TCLs are scarce.¹³ Moreover, the spontaneous regression of cutaneous $\gamma\delta$ T-cell clonal proliferation has been reported in inflammatory and in non-neoplastic disorders.¹⁴ In this study, we report the pathological and clinical features of three unusual patients from this unique pediatric multi-disciplinary cutaneous lymphoma clinic.

Case Description

The first patient is a 14-year-old female with a clinical history of tumid lupus (biopsy proven at age 2) on immunomodulator treatment, who presented with a 3-year history of progressive cutaneous plaques, subcutaneous nodules, and ulcerations on the left forearm. Serologic studies were negative for auto-antibodies. PET/CT scans demonstrated avidity of skin lesions and two minimally enlarged axillary lymph nodes without additional lesions. The patient had a history of intermittent fevers, occasional malaise and mild cytopenia, which improved without intervention, and elevated CXCL9 on an inflammatory cytokine workup. The biopsy of one plaque showed features of lobular panniculitis, while another biopsy of an ulcerated skin lesion revealed an epidermal ulceration and subcutaneous lobular panniculitic pattern with marked $\gamma\delta$ T cell infiltrates rimming the adipose tissue, with a high Ki67 proliferation rate. T-cell gene rearrangements were clonal. NGS studies for both germline and somatic pathogenic mutations were negative. The overall findings favored a SPTCL with increased $\gamma\delta$ T-cells (Figure 1). The patient received immunomodulation therapy and with close follow up, disease progression was not observed.

The second patient was diagnosed with stage 1B hypopigmented mycosis fungoides with a $\gamma\delta$ T-cell variant at approximately 5 years old. After seven years of follow up, the patient's skin lesions did not appreciably progress. The third patient is a 6-year-old male who presented with a three-monthly history of extensive hyperpigmented macules on the trunk and extremities and hypopigmented patches on the face. Skin biopsy revealed parakeratosis, psoriasiform epidermal hyperplasia with minimal spongiosis, exuberant lymphocyte exocytosis with epidermotropism, and a perivascular lymphohistiocytic infiltrate in dermis. Immunohistochemical stains revealed an atypical population of CD3+ T-lymphocytes with diminished CD4, CD8, CD5 and CD7 expression within the epidermis. Molecular studies for T-cell gene rearrangements were clonal. A diagnosis of cutaneous T cell lymphoma was suspected. However, additional immunostaining for TCR-delta highlighted that the atypical T-cell population were $\gamma\delta$ T cells in nature. The overall findings favored a diagnosis of $\gamma\delta$ variant of pityriasis lichenoides (Figure 2). The skin lesions were fully resolved after PLC treatment (azithromycin and triamcinolone ointment).

Discussion

Rare cases of primary $\gamma\delta$ cutaneous T-cell lymphoma (CTCL) have been reported in children,⁵ which creates major diagnostic and treatment challenges for pathologists and primary clinicians. Here we describe three unusual pediatric patients with this rare condition and its mimics.

PCGDTCL, a definitive entity in the WHO classification of lymphomas, expresses a mature cytotoxic phenotype with frequent necrosis and/or apoptosis and exhibits diverse histological patterns and clinical symptoms.¹⁵ Because of the poor clinical outcome, early diagnosis and aggressive therapy are indicated in these patients. Most PCGDTCL have pathogenic mutations in the JAK-STAT, MAPK, and MYC signaling pathways.¹⁶ In contrast, subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a clonal expansion of $\alpha\beta$ cytotoxic T-cells involving subcutaneous adipose tissue. Patients typically present with subcutaneous nodules, systemic symptoms, and as many as 20% of cases are associated with an autoimmune condition.¹⁷ SPTCL patients often respond to immunomodulatory therapy. Only 10-20% SPTCL contain somatic mutations in epigenetic genes and rarely in JAK-STAT signaling pathways. Primary cutaneous $\gamma\delta$ T-cell lymphoma is extremely rare in children. Such a diagnosis should always be based on the integration of clinical presentation, morphology, immunophenotype, and genetics. Our first patient demonstrated an indolent clinical course, with negative germline and somatic pathogenic mutations, which argues against an aggressive PCGDTCL, and favor a SPTCL with increased $\gamma\delta$ T-cells. It is therefore critical to avoid aggressive chemotherapy in these patients, and instead, commence initial therapy with an immunomodulator.

Mycosis fungoides (MF), a non-Hodgkin T-cell lymphoma of the skin, is the most common primary cutaneous lymphoma. Rare MF contains an increase in $\gamma\delta$ T-cells, which may represent a subset of the malignant clone or a background reactive population.⁴ These patients may show a variety of types of MF, ranging from folliculotropic to granulomatous, hypopigmented, pigmented purpuric dermatosis-like, large-cell transformation, and classic patch/plaque. Due to the scarce data in the literature, there is no solid evidence that demonstrates a significant difference in prognosis for patients with $\gamma\delta$ type MF versus $\alpha\beta$ type MF.^{16,18} A relatively aggressive disease course for $\gamma\delta$ type MF has been reported in one study,¹⁹ but not all. Our second

patient of $\gamma\delta$ type MF shows an indolent clinical course, similar to the $\alpha\beta$ type of MF.

As observed in our third patient, $\gamma\delta$ T cells can be increased in non-malignant skin lesions, such as pityriasis lichenoides (PL), an inflammatory condition of the skin characterized by waxing and waning eroded and crusted papules.¹² PL chronica (PLC) or et variolaformis acuta (PLEVA) mostly arise from $\alpha\beta$ T cells, while extremely rare lymphomas derive from $\gamma\delta$ T cells.¹² The histopathology of $\gamma\delta$ type PL appears to be not appreciably different from $\alpha\beta$ type PLs. Finally, it is important to note that all three patients show an indolent course.

In summary, our three cases demonstrated increase in $\gamma\delta$ T-cells in malignant and non-malignant skin conditions of children, and all of them showed an indolent clinical course. In borderline case like our first patient, NGS studies may be helpful to establish the diagnosis and avoid aggressive therapies. However, biological and collaborative studies of these unusual and rare disorders are needed in future.

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Figure Legend:

Φιγυρε 1: Α σκιν βιοψψ οφ ΣΠΤ^αΛ ωιτη ινςρεασεδ γδ Τ ρελλλς. A and B, the skin lesions show a spectrum of plaques, subcutaneous nodules and so on. The skin biopsy reveals an ulcerated lesion with extensive dermal and subcutaneous lymphoid infiltrate (C, H&E, 20x). Repeated PCR for T-cell gene rearrangements in multiple skin biopsies confirms a persistent clonal gene rearrangement (D). On high power, the H&E sections show a adipose rimming by atypical lymphocytes (E, H&E 200x and F, H&E, 400x). The atypical lymphocytes are predominantly CD3+ T cells (G, 200X), CD8+ (H, 200x) with high Ki67 proliferation rate (I, 200x). TCR delta stains a marked increase of atypical T lymphocytes (K, 200x), although TCR BF1 also highlights substantial T lymphocytes (L, 200X). CD79a, CD123 and EBER-ISH are mostly negative (not shown).

Φιγυρε 2: Α σκιν βιοψψ οφ γδ αριαντ οφ ΠΑ^α. The H&E sections reveals parakeratosis, psoriasiform epidermal hyperplasia with minimal spongiosis but exuberant lymphocyte exocytosis multifocally tagging along the dermoepidermal junction and forming small clusters (A, H&E, 200x; B, H&E, 400X) within the epidermis. The dermis features a mildly dense perivascular lymphohistiocytic infiltrate. Immunohistochemical stains reveal a population of CD3+ T lymphocytes (C, 200X) with very rare CD20+ B lymphocytes (not shown). CD5 (D, 200X) and CD7 (not shown) expressions are diminished compared to epidermal CD3 expression. CD4 (E, 200x) and CD8 (F, 200X) expression are decreased within the epidermis. TCR-Delta highlights an increase in γδ T cells (G, 200x). CD30 (H, 200x) is largely negative. Neither fungal microorganisms nor basement membrane changes are seen with interpretation of PAS histochemical stain (not shown). PCR for T-cell gene rearrangements were positive.

Figure 1

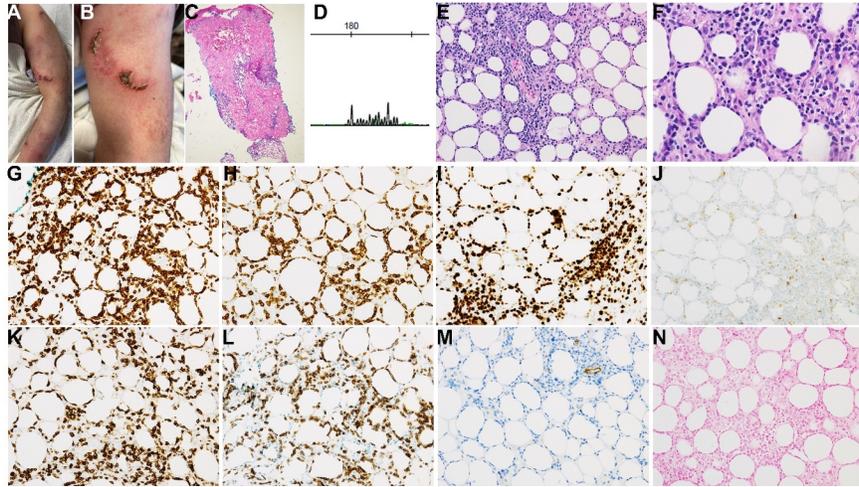


Figure 2

