Title

Concurrent Subcutaneous Panniculitis-like T-Cell Lymphoma and B-Cell Acute Lymphoblastic Leukemia in 2 Pediatric Patients.

Journal

Journal of pediatric hematology/oncology, 43(6)

ISSN

1077-4114

Authors

Smith, Geoffrey A
Levinson, Anya L
Galvin, Robert T
et al.

Publication Date

2021-08-01

DOI

10.1097/mph.0000000000001921

Peer reviewed

HHS Public Access

Author manuscript

J Pediatr Hematol Oncol. Author manuscript; available in PMC 2022 August 31.

Published in final edited form as:

J Pediatr Hematol Oncol. 2021 August 01; 43(6): e791–e794. doi:10.1097/MPH.0000000000001921.

Concurrent Subcutaneous Panniculitis-like T-cell Lymphoma and B-cell Acute Lymphoblastic leukemia in two pediatric patients

Geoffrey A. Smith, MD, PhD[a,†], **Anya L. Levinson, MD**[a], **Robert T. Galvin, MD**[b], **Leah E. Lalor, MD**[c,‡], **Timothy McCalmont, MD**[c,d], **Linlin Wang, MD, PhD**[e], **Michael C. Geis, MD**[f], **Karah Odegaard, MD**[f], **Meghan Hupp, MD**[g], **Sheilagh Maguiness, MD**[h], **Lucie M. Turcotte, MD, MPH**[i], **Kelly M. Cordoro, MD**[c], **Michelle L. Hermiston, MD, PhD**[a]

[a]Division of Hematology/Oncology, University of California San Francisco Benioff Children's Hospital, San Francisco, CA.

[b]Department of Pediatrics, University of Minnesota, Minneapolis, MN.

[c]Department of Dermatology, University of California San Francisco, San Francisco, CA.

[d]Department of Pathology, University of California San Francisco, San Francisco, CA.

[e]Department of Laboratory Medicine, University of California San Francisco, San Francisco, CA.

[f]Department of Pathology, Sanford Health Pathology Clinic, Sioux Falls, SD.

[g]Department of Pathology, University of Minnesota, Minneapolis, MN.

[h]Department of Dermatology, University of Minnesota, Minneapolis, MN.

[i]Division of Hematology/Oncology, University of Minnesota, Minneapolis, MN.

Abstract

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a cutaneous lymphoma characterized by CD8+ T-cell infiltrate in the subcutis that is rare in children. Acute lymphoblastic lymphoma (ALL) is the most common pediatric malignancy and often presents with fevers and pancytopenia. Herein, we report two pediatric patients presenting with SPTCL and B-cell ALL, distinct hematologic malignancies arising from different lymphoid lineages, with no identifiable germline cancer predisposition.

Introduction

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare cutaneous non-Hodgkin lymphoma characterized by CD8+ T-cell infiltrates surrounding adipocytes in the subcutis. Patients typically present with variably sized subcutaneous nodules, often accompanied by B symptoms, anemia and thrombocytopenia.[1] Fewer than 50 cases of pediatric SPTCL have been published,[2–4] underscoring its relative rarity, although one case series suggests that up to 20% of cases occur in children.[1] SPTCL outcomes are generally favorable, with

†Present address: Department of Medicine, Boston Children's Hospital, Boston, MA.
‡Present address: Department of Dermatology, Medical College of Wisconsin, Milwaukee, WI.

5-year overall survival of 82%, in contrast to the similar but distinct primary cutaneous γδ T-cell lymphoma (PCGD-TCL, 5 year-OS 11%).[1] Hemophagocytic lymphohistiocytosis (HLH) occurs in 15–20% of SPTCL cases and can alter otherwise favorable outcomes.[1] Treatment of pediatric SPTCL lacks a standard of care, with treatment ranging from watchful waiting[4] to CHOP[3] to hematopoietic stem cell transplantation. In contrast, acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, representing 26% of all cancer diagnoses,[5] and typically has excellent outcomes with several years of conventional chemotherapy.[6] Cutaneous lesions rarely occur in ALL, in fewer than 2% of cases.[7] Here, we report two young children from different institutions who presented with concurrent SPTCL and B-cell ALL without an identifiable link between the two entities.

Case One

A previously healthy four-year-old female presented to dermatology with a one-month history of poorly defined, firm, 5mm subcutaneous nodules on her back without trauma. Parents noted the nodules had recently receded significantly, thus they were initially observed. She returned two months later with several new tender subcutaneous nodules associated with low-grade fever, prompting diagnostic skin biopsy (Figure 1A-B). Histopathologic review revealed a dense, atypical, subcutaneous CD8+ lymphocytic infiltrate showing ‘rimming’ around lipocytes, with an elevated Ki-67 proliferation index in the same distribution, consistent with SPTCL (Figure 1B). Further evaluation revealed pancytopenia (hemoglobin 9.8 g/dL, platelets 68 × 109/L, ANC 360 cells/μL) and an elevated ferritin at 2,440 ug/L, suspicious for marrow infiltration or SPTCL-associated HLH.

Bone marrow biopsy was performed to evaluate pancytopenia, which showed lymphoblasts expressing CD19, CD79, PAX5 and TDT, consistent with B-cell ALL (Figure 1C). Given the disparate findings in the skin and marrow, another skin biopsy was obtained, with confirmatory findings. An extended staining panel showed an extensive cytotoxic T-cell (CD2+CD3+CD4-CD7+CD8+TIA1+) infiltrate that had lost expression of CD5, and PCR of the T-cell receptor gamma chain (TCRG) locus identified a clonal population, consistent with SPCTL. Increased γδ T cells comprised part of the atypical population, but the lack of CD56 staining and sparing of the dermis and epidermis favored SPTCL over PCGD-TCL. There were only rare PAX5+CD79+ cells and these lacked TDT expression, indicating a distinct malignant process from the B-cell ALL.

Given the unexpected development of both SPTCL and B-cell ALL, DNA from cheek-swab, skin and bone marrow biopsies was submitted for targeted sequencing of 500 genes frequently mutated in cancer. No mutations were detected in the cheek swab or the lesional skin biopsy. The B-cell ALL sample was positive for a likely pathogenic KRAS p.A146V mutation[8] and two variants of unknown significance (internal tandem duplication of ETV6 exons 3–5 and two mutations in SNCAIP). She began standard-risk treatment for B-cell ALL according to the Children’s Oncology Group (COG) protocol AALL0932, and is currently in maintenance therapy without any evidence of disease recurrence and no recurrence of the skin lesions (Figure 1D).

Case Two

A previously healthy 3-year-old male presented with fevers and pancytopenia. Bone marrow aspirate and biopsy were hypocellular with trilineage hematopoiesis and no dysplasia. Hemoglobin and platelet counts completely recovered within weeks of presentation while leukopenia, neutropenia and fevers did not. Over the next three months, the patient developed transaminitis (peak ALT and AST of 1,176 and 1,008, respectively) and skin nodules on the trunk and extremities resembling erythema nodosum (Figure 2A). Skin biopsy showed atypical CD8+ cytotoxic T-cells within the subcutis with elevated Ki-67 and positive TIA-1, perforin, and β-F1 staining, consistent with SPTCL (Figure 2B). PET-CT showed widespread hypermetabolic subcutaneous activity in the legs, trunk and skull and diffuse marrow hyperplasia. At this point, repeat bone marrow evaluation was consistent with *MLL*-rearranged B-ALL (Figure 2C). His skin biopsy was then stained with TDT, CD34, PAX-5, CD79a, and CD20 with negative results, and outside pathology review confirmed the skin lesion diagnosis of SPTCL. The patient initiated therapy according to the very high risk arm of COG protocol AALL1131 because of the MLL gene rearrangement and is currently doing well in the maintenance phase of treatment with resolution of his skin disease (Figure 2D).

Discussion

While therapy-related secondary malignancies are well documented, the concurrent presentation of two distinct primary malignancies is rare in children.[9] Even among the most common pediatric cancers, leukemia and CNS tumors, there are only five reports of concurrent neoplasms in patients without a known cancer predisposition syndrome.[9–13] SPTCL is exceptionally rare in pediatrics, accounting for less than 1% of all non-Hodgkin lymphomas, or fewer than one in ten million children.[5] Given the improbability of a simultaneous presentation of B-ALL and SPTCL in a child, it is unsurprising that no such cases have been previously documented.

In both cases described here, immunohistochemical stains of the skin biopsies were specifically performed in search of alternative explanations for the skin lesions, such as a cutaneous manifestation of B-cell ALL[7] or a reactive process to the leukemia. In both cases, few B cells were seen in the subcutis, and those that were present had a distinct immunophenotype from the B-lymphoblasts in the bone marrow, confirming that the skin pathology was a distinct entity. While the CTL population could have plausibly represented a reactive response to the leukemia, there was a lack of skin-localized lymphoblasts required to trigger such a response; furthermore, the TCR clonality and loss of T-cell marker CD5 strongly favored a malignant T-cell process.[14]

The simultaneous occurrence of two unrelated hematopoietic malignancies raised the possibility of a germline cancer predisposition syndrome, perhaps involving immune dysregulation. Alternatively, the malignancies could have developed from a common mutated hematopoietic stem cell, as reported in the adult literature for two cases of mixed myeloid/lymphoid neoplasms with common PDGFRA and PDGFRB rearrangements.[15,16] However, in next generation sequencing of case 1, no germline mutations were detected in

p53, BRCA2, BLM, NBN, ATM, or in other known cancer predisposition genes recognized to increase pediatric leukemia risk.[17] Furthermore, there were no mutations common to both malignancies on a selected panel of genes implicated in cancer.

Concurrent malignancies could also arise from impaired immune surveillance secondary to the initial hematopoietic malignancy. For instance, mycosis fungoides has been associated with secondary malignancies, including B-cell lymphomas. Miyatake, et al. hypothesize that the malignant T-cells promote immunodeficiency, and this environment may subsequently allow malignant clonal expansion.[18] Patients with primary immunodeficiencies have significantly increased rates of B and T-ALL,[19,20] which suggests a possible role for immune surveillance in controlling malignant precursors. In our cases, immune dysregulation from the preceding SPTCL may have allowed the developing B-ALL to escape surveillance.

These cases illustrate a rare phenomenon for which a unifying mechanism is elusive. Whether these cases represent the unrelated, spontaneous onset of two distinct tumors, secondary development of a malignancy in the context of reduced immune-surveillance and a permissive environment, an epiphenomenon, or other as yet unknown pathway is unknown. There is no clear standard of care for pediatric-onset SPTCL, which can have an indolent course;[4] tailoring therapy to the potentially fatal B-ALL resulted in optimal responses in both cases. Pediatric patients presenting with concurrent malignancies should undergo screening for cancer predisposition syndromes, as this would have implications for the individual and family.

Acknowledgements

At the University of California San Francisco (UCSF), we thank Kristin Shimano for her critical role in the early management of this case, Kristie White for helpful discussion and review of the hematopathology, and Elaine Jaffe and Stefania Pittaluga for independent review of the pathology. At the University of Minnesota, we thank Dr. Laura Pincus at UCSF dermatopathology for her independent review of the pathology.

References

1. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111(2):838–845. doi:10.1182/blood-2007-04-087288. [PubMed: 17934071]
2. Hu ZL, Sang H, Deng L, Li Z. Subcutaneous Panniculitis-Like T-Cell Lymphoma in Children: A Review of the Literature. Pediatric Dermatology 2015;32(4):526–532. doi:10.1111/pde.12452. [PubMed: 25727090]
3. Huppmann AR, Xi L, Raffeld M, Pittaluga S, Jaffe ES. Subcutaneous panniculitis-like T-cell lymphoma in the pediatric age group: A lymphoma of low malignant potential. Pediatr Blood Cancer 2013;60(7):1165–1170. doi:10.1002/pbc.24462. [PubMed: 23382035]
4. Johnston EE, LeBlanc RE, Kim J, et al. Subcutaneous panniculitis-like T-cell lymphoma: Pediatric case series demonstrating heterogeneous presentation and option for watchful waiting. Pediatr Blood Cancer 2015;62(11):2025–2028. doi:10.1002/pbc.25626. [PubMed: 26146844]
5. SEER cancer Statistics Review, 1975-2015. https://seer.cancer.gov/csr/1975_2015/. Published April 2018. Accessed August 5, 2018.
6. Rabin KR, Gramatges MM, Margolin JF, Poplack DG. Acute Lymphoblastic Leukemia. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology 7 ed. Philadelphia; 2016:463–497.

7. Millot F, Robert A, Bertrand Y, et al. Cutaneous Involvement in Children With Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma. Pediatrics 1997;100(1):60–64. doi:10.1542/peds.100.1.60. [PubMed: 9200360]
8. Oshima K, Khiabanian H, da Silva-Almeida AC, et al. Mutational landscape, clonal evolution patterns, and role of RAS mutations in relapsed acute lymphoblastic leukemia. Proc Natl Acad Sci USA 2016;113(40):11306–11311. doi:10.1073/pnas.1608420113. [PubMed: 27655895]
9. Regelson W, Bross IDJ, Hananian J, Nigogosyan G. Incidence of second primary tumors in children with cancer and leukemia. A seven-year survey of 150 consecutive autopsied cases. Cancer 1965;18(1):58–72. doi:10.1002/1097-0142(196501)18:1<58::AID-CNCR2820180110>3.0.CO;2-R. [PubMed: 14260851]
10. Anoop P, Hargrave D, Zacharoulis S, Saran F. Diagnostic and Therapeutic Challenges Owing to Concurrent Pontine Glioma and Acute Lymphoblastic Leukemia. Journal of Pediatric Hematology/oncology 2008;30(6):454–457. doi:10.1097/MPH.0b013e318161aa4e. [PubMed: 18525463]
11. Kim AL, Fernandez CV, Greer WL, Hogg D, Lassam NJ, Resch L. Concurrent acute lymphoblastic leukemia and juvenile pilocytic astrocytoma in a pediatric patient. Journal of Pediatric Hematology/oncology 2000;22(5):451–453. [PubMed: 11037859]
12. Panagopoulou P, Hatzipantelis ES, Sidi V, Papakonstantinou E, Anastasiou A, Koliouskas DE. A Child With Concurrent Acute Lymphoblastic Leukemia and a Brain Tumor. Journal of Pediatric Hematology/oncology 2014;36(8):659–660. doi:10.1097/MPH.0b013e318286d518. [PubMed: 23588327]
13. Kurosawa H, Matsunaga T, Shimura N, et al. Successfully Treated Acute Lymphoblastic Leukemia Associated With Craniopharyngioma. Journal of Pediatric Hematology/oncology 2007;29(6):416–419. doi:10.1097/MPH.0b013e318063ef39. [PubMed: 17551406]
14. Gorczyca W, Weisberger J, Liu Z, et al. An approach to diagnosis of T-cell lymphoproliferative disorders by flow cytometry. Cytometry 2002;50(3):177–190. doi:10.1002/cyto.10003. [PubMed: 12116341]
15. Gonsalves WI, He R, Pardanani A, et al. Chronic Eosinophilic Leukemia—Not Otherwise Specified (NOS) in the Background of a Large Cell Lymphoma. Case Reports in Hematology 2013;2013(6):1–4. doi:10.1155/2013/458303.
16. Pourabdollah M, Gupta M, Schimmer A, Chang H. Synchronous T lymphoblastic lymphoma and myeloid neoplasm with PDGFRA rearrangement. International Journal of Laboratory Hematology 2017;39(1):e28–e32. doi:10.1111/ijlh.12596. [PubMed: 28013529]
17. Seif AE. Pediatric leukemia predisposition syndromes: clues to understanding leukemogenesis. Cancer Genetics 2011;204(5):227–244. doi:10.1016/j.cancergen.2011.04.005. [PubMed: 21665176]
18. Miyatake J, Inoue H, Serizawa K, et al. Synchronous Occurrence of Mycosis Fungoides, Diffuse Large B Cell Lymphoma and Acute Myeloid Leukemia. Intern Med 2018;57(10):1445–1453. doi:10.2169/internalmedicine.9668-17. [PubMed: 29321428]
19. Suarez F, Mahlaoui N, Canioni D, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. J Clin Oncol 2015;33(2):202–208. doi:10.1200/JCO.2014.56.5101. [PubMed: 25488969]
20. Vajdic CM, Mao L, van Leeuwen MT, Kirkpatrick P, Grulich AE, Riminton S. Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? Blood 2010;116(8):1228–1234. doi:10.1182/blood-2010-03-272351. [PubMed: 20466855]

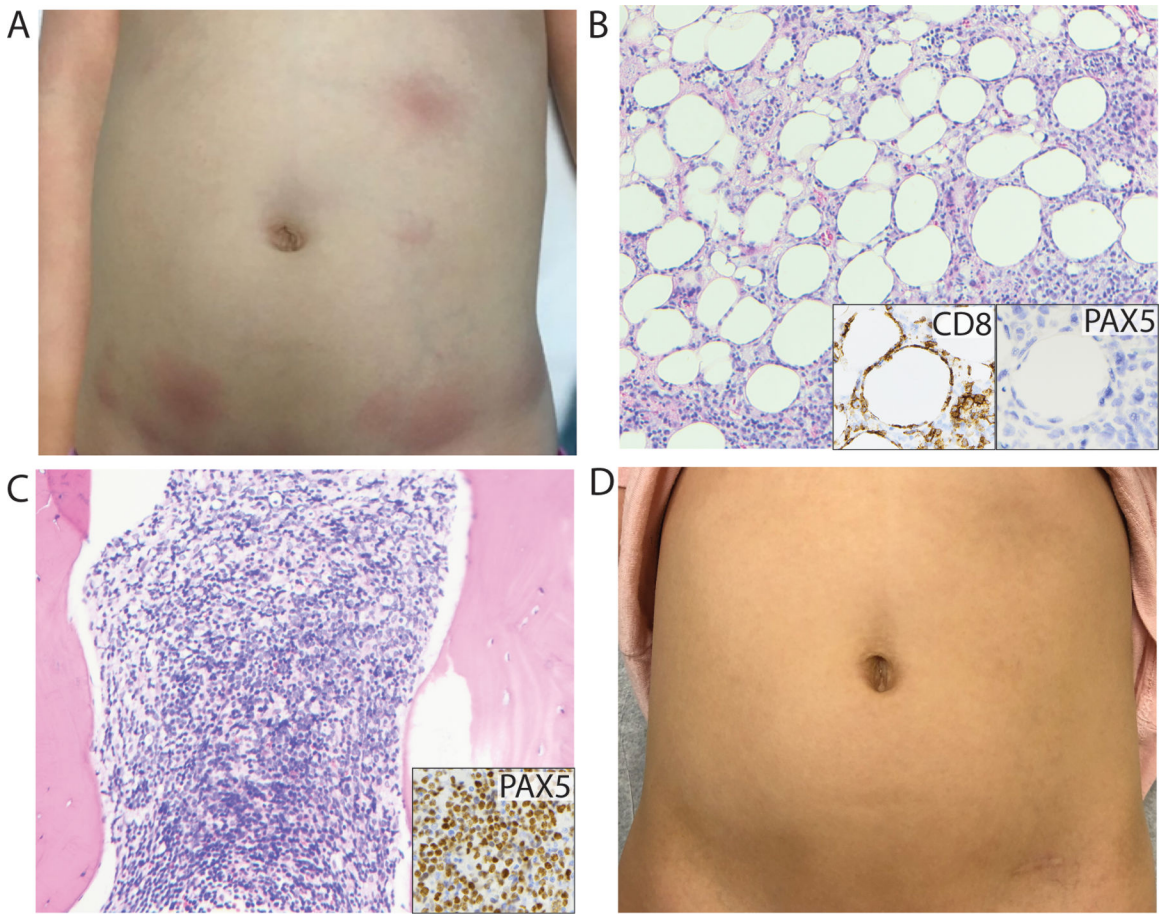

Figure 1:

A. Abdominal lesions at presentation. B. Subcutis hematoxylin and eosin (H&E) stain (10x) CD8 immunohistochemistry (IHC) (left inset, 40x) and PAX5 IHC (right inset, 40x). C. Bone marrow core H&E (10x) and PAX5 IHC (inset 40x). D. Abdominal lesions after ALL therapy.

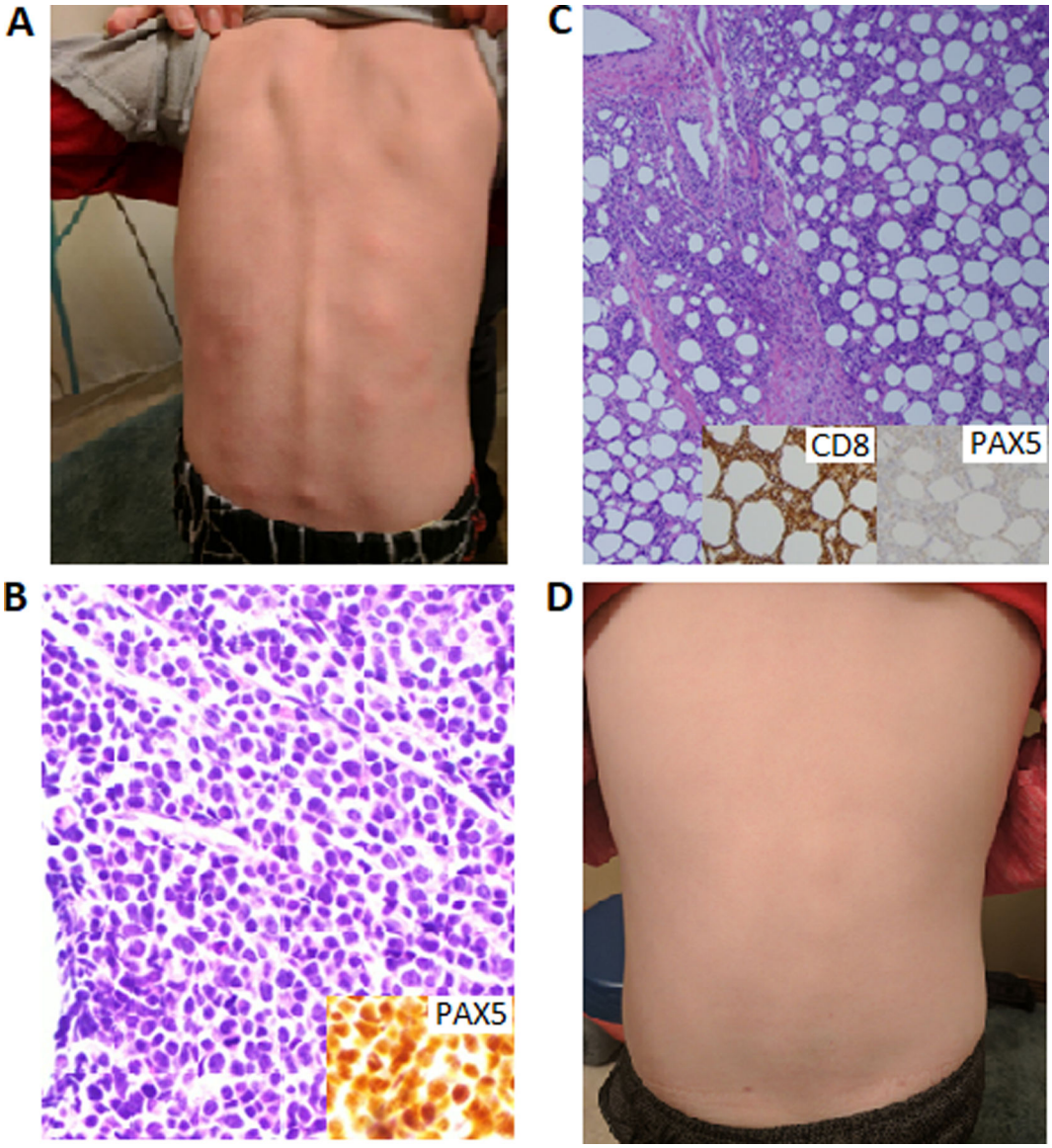

Figure 2:

A. Truncal lesions. B. Subcutis hematoxylin and eosin (H&E) stain (10x) CD8 immunohistochemistry (IHC) (left inset, 40x) and PAX5 IHC (right inset, 40x). C. Bone marrow core H&E (40x) and PAX5 IHC (inset 100x). D. Truncal lesions after ALL therapy.