DOI: http://dx.doi.org/10.3315/jdcr.2015.1191

Journal of Dermatological Case Reports

Primary cutaneous γ/δ T-cell lymphoma. An atypical case with bone marrow granulomas

Guy Shalom[1], *Ronit Gurion*[3], *Daniel Benharroch*[2]

1. Department of Dermatology and Venereology, Soroka Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel;
2. Department of Pathology, Soroka Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel;
3. Institute of Hematology, Davidoff Center, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel.

Corresponding author:

Guy Shalom, MD, MHA

Department of Dermatology and Venereology

Soroka Medical Center

Beer Sheva, P.O.B. 151, 84101, Israel

E-mail: *Guyshallom1234@hotmail.com*

Key words:

bone, cutaneous gamma/delta T-cell lymphoma, lymphoma, subcutaneous panniculitis-like T-cell lymphoma, peripheral T-cell lymphoma, ulcer

Abstract

Background: Primary cutaneous γ/δ T-cell lymphoma is a rare variant of peripheral T-cell lymphoma which has been only recently set apart from subcutaneous panniculitis-like T-cell lymphoma and is known for its aggressive nature.

Main observation: We hereby report a case of primary cutaneous γ/δ T-cell lymphoma in a 35-year-old man with bone marrow granulomas, an unexpected feature in this lymphoma. The patient was treated with combination chemotherapy. Partial response was obtained, followed by relapse. Allogeneic stem cell transplantation was then carried out, and full remission was achieved.

Conclusion: Bone marrow granulomas can be an accompanying feature in primary cutaneous γ/δ T-cell lymphoma. (*J Dermatol Case Rep*. 2015; 9(1): 15-18)

Introduction

Primary cutaneous γ/δ T-cell lymphoma, formerly part of subcutaneous panniculitis-like T-cell lymphoma (SPTCL), is now considered a distinct type of T-cell lymphoma with an aggressive clinical behavior.[1] Subcutaneous panniculitis-like T-cell lymphoma was first described in 1991 as a lymphoma involving the subcutaneous tissues, including the septa and sparing epidermis and dermis. It is composed of atypical lymphoid cells of varying cell range that express cytotoxic proteins.[2] In the last decade, genotypic analysis studies depict two subtypes of SPTCL: 1) the more frequent α/β T-cell phenotype SPTCL and 2) the rare phenotype γ/δ, each showing a different clinical course.[3-5]

The rapidly progressive cutaneous γ/δ T-cell lymphoma shows a fatal outcome despite systemic chemotherapy, compared with the clinical course of SPTCL which is considered to be more indolent. As a specific modality of treatment has not been determined to date for primary cutaneous γ/δ T-cell

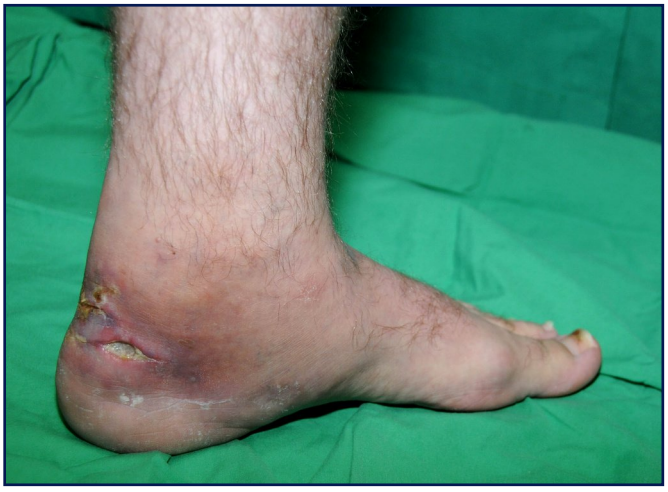

Figure 1

Ulcer 2X3 centimeter in diameter, covered with a thin layer of fibrin, left ankle.

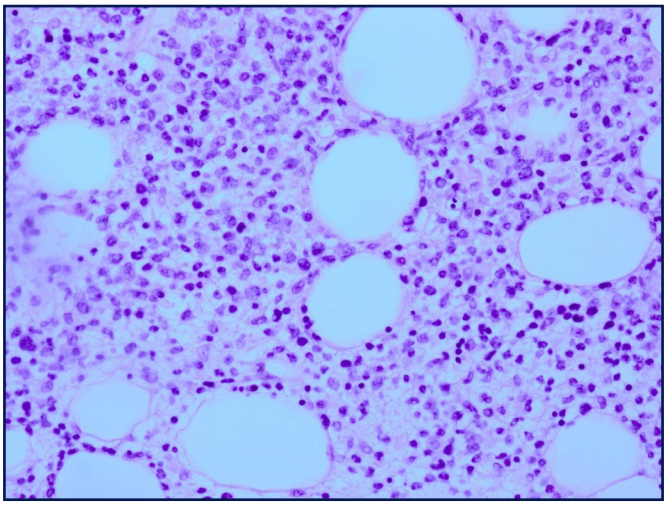

Figure 2

Skin biopsy photomicrograph showing evidence of panniculitis. The infiltrate is composed of medium-sized lymphoid cells, some delimiting the lipocytes (H&E, magnification X360).

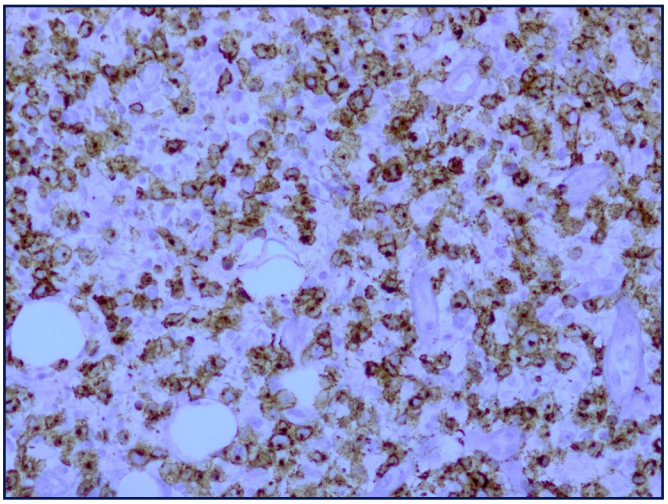

Figure 3

Skin biopsy, panniculitis. Immunohistochemistry for CD2 (H&E, magnification X 360).

lymphoma, the recommended treatment for SPTCL, a combination chemotherapy, anthracycline-based (such as CHOP protocols: cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone or CHOP-like regimens), has been used tentatively also for primary cutaneous γ/δ T-cell lymphoma.

We present a case of primary cutaneous γ/δ T-cell lymphoma with unusual features but an excellent response to allogeneic stem cell transplantation.

Case Report

A 35-year-old Caucasian male presented with a 4-month history of subcutaneous erythematous nodules, on both calfs and on the right arm associated with an ulcer of six weeks duration on the left ankle. Fever of 38.8ºC and night sweats were noted. The patient denied recent insect bites.

The lesions, 22 in number, consisted of erythematous to violaceous non tender nodules, 2-5 cm in diameter, slightly scaly. In addition an ulcer, 2x3 cm in diameter, was noticed on the left ankle (Fig. 1). The spleen tip was palpated, but no enlargement of the liver was found. The patient was otherwise well.

Complete blood cell count showed pancytopenia. Liver function tests reached three times the upper limit of normal. Lactate dehydrogenase concentration was 1250 u/L. Titers for hepatitis B and C, human immunodeficiency virus, Epstein Barr virus and cytomegalovirus were negative. Serological tests for Q-fever, Bartonella henselae, monocytic ehrlichiosis and Brucella infection were all negative.

Abdominal-thoracic computed tomography imaging showed a splenic span of 19 cm. Retroperitoneal and left inguinal lymphadenopathy of up to 1.3 cm were also noted.

A 5 mm punch biopsy from the skin of the right calf demonstrated panniculitis, perivascular and periadnexal inflammation. The tissue was tested for the presence of leishmania major and tropica, cutaneous tuberculosis and non-

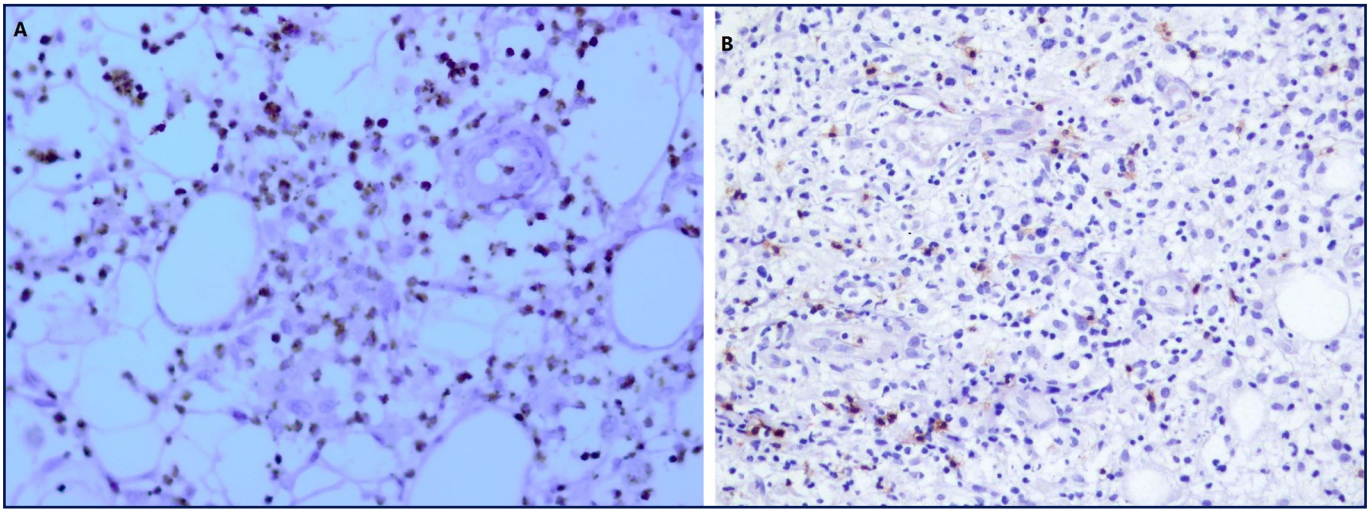

Figure 4

Skin biopsy with panniculitis. A: Perforin-positive tumor cells are evident. B: BetaF1-negative tumor cells are evident. (IHC, using DAB, magnification X360).

tuberculous mycobacterial infections and for deep mycotic infections — all were negative by culture and by polymerase chain reaction.

A punch biopsy from a left calf lesion showed sparing of the overlying epidermis. The upper dermis was involved by atypical lymphoid cells and by hemophagocytosis. In the subcutaneous fatty tissue, a heavier infiltrate composed of medium-sized lymphocytes with irregular nuclei, histiocytes and a few large lymphoid cells were found (Fig. 2). Immunohistochemistry demonstrated the following phenotype: the medium-sized lymphocytes were CD2+ (Fig. 3), CD3+, CD4-, CD5+/-, CD7- and Ki-67+ (70%). The large lymphoid cells stained CD30+, CD5+/-, CD8-, CD20-, CD56+ and CD57-. The lymphocytes were positive for the cytotoxic proteins T-cell intracellular antigen-1 (TIA1), perforin (Fig. 4A), granzyme B and betaF1 negative (Fig. 4B). A bone marrow biopsy demonstrated several non-necrotizing, sarcoid-like granulomas with irregular borders and no giant cells. Additionally, the tissue was involved by a remarkable hemophagocytosis. A T-cell γ receptor gene rearrangement, performed on a skin biopsy, defined a population of monoclonal T-cells.

Positron emission tomography /computed tomography (PET/CT) imaging demonstrated highly enhanced absorption of Fludeoxyglucose 18 in all of the cutaneous lesions and slightly to moderately enhanced absorption in the left inguinal, obturator and iliac lymph nodes. Based on the above morphology, immunophenotype and the genotypic study, a diagnosis of primary cutaneous γ/δ T-cell lymphoma with secondary hemophagocytic syndrome was made.[3,4,7]

The patient was treated with six cycles of the CHOEP regimen (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) with disappearance of all lesions both clinically and on PET/CT. Because of the aggressive nature of his lymphoma, the patient was considered a candidate for allogeneic stem cell transplantation. Upon admission to the stem cell transplant department, the disease relapsed. The patient was started on salvage combination chemotherapy with ICE (Ifosfomide, Carboplatinum and Etoposide). Remission was obtained and allogeneic stem cell transplantation from a matched siblinig was performed successfully. Remission has persisted for the last 18 months with no graft vs. host disease.

Discussion

In 1994, γ/δ type subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was first reported, characterized by an unusually rapid fatal course.[6] Like SPTCL, primary cutaneous γ/δ T-cell lymphoma, as it was named, affects predominantly young adults.[2,7] A wide spectrum of clinical involvement comprises splenomegaly, pancytopenia, elevated LDH and high blood levels of liver enzymes. Hemophagocytosis may occur in both subtypes of this lymphoma,[8] yet much more frequent in primary cutaneous γ/δ T-cell lymphoma than in SPTCL. Both subtypes express cytotoxic proteins.[9]

Primary cutaneous γ/δ T-cell lymphoma is rare, preferentially affecting the skin of the extremities, may present with epidermotropic lesions or deep dermal and subcutaneous tumors. Occasionally, more than one pattern of involvement is seen.[1] Primary cutaneous γ/δ T-cell lymphoma is typically CD4-, CD8-, and often co-expresses CD56+, while SPTCL is more often CD8+1. Primary cutaneous γ/δ T-cell lymphoma shows a very poor outcome regardless of the presence of a hemophagocytic syndrome or the type of treatment.[10] Recent evidence established that SPTCL and primary cutaneous γ/δ T-cell lymphomas represent two distinct clinicopathological entities.[4,5]

We suggest that the lymph nodes were enlarged due to involvement by the lymphoma, by hemophagocytosis, by non-specific reactive changes related with the ulcerated lesions, or by granulomatous changes, as described in the bone marrow biopsy. The non-necrotizing, sarcoid-like granulomas found in the bone marrow, are as a rule associated with infection which was excluded. Granulomas may, however, be reactive to a neighboring malignancy. A granulomatous reaction has not been described in primary cutaneous γ/δ T-cell lymphoma, to our knowledge. Nevertheless, Ruiz-Arguelles, years ago, mentioned the possibility that the presence of granuloma in lymphoma could be a sign of good prognosis. That could be a possible explanation for the good results in the present case.

The clinical, morphological, immunophenotypic and molecular findings presented by this patient are consistent with the diagnosis of primary cutaneous γ/δ T-cell lymphoma, in spite of the atypical features mentioned above.

Treatment protocols for primary cutaneous γ/δ T-cell lymphoma are not well established yet, due to its rarity. Willemze *et al*[4] identified twenty patients with this condition. Despite the appropriate therapy, 15 of 20 patients died of the hemophagocytic syndrome and/or of progressive lymphoma. One was still alive with progressive disease, and four patients were in complete remission 4-108 months after diagnosis. Three out of the four patients were treated with autologous stem cell transplantation. Another patient, who had not responded to CHOP, reached a complete remission following allogeneic stem cell transplantation. We adopted this modality in the present patient, following his relapse. Allogeneic stem cell transplantation is not the standard treatment for γ/δ T-cell lymphoma, yet the present case demonstrates an apparent success following it, with an 18 months period remission after the initial diagnosis.

Conclusions

In conclusion, we have described a case of cutaneous γ/δ T-cell lymphoma with clinical features that were suggestive for a different, more aggressive disease than SPTCL. Bone marrow biopsy demonstrated non-specific granulomas. The patient was treated several combination chemotherapy and allogeneic stem cell transplantation and currently he is in complete remission.

References

1. Gluzman DF. WHO classification of lymphoid malignancies. *Exp Oncol*. 2012; 34: 377-378. PMID: 23303001.
2. Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcome, treatment, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. *Cancer*. 2004; 15; 101: 1404-1413. PMID: 15368328.
3. Salhany KE, Macon WR, Choi JK, Elenitsas R, Lessin SR, Felgar RE, Wilson DM, Przybylski GK, Lister J, Wasik MA, Swerdlow SH. Subcutaneous Panniculitis-like T-Cell Lymphoma: Clinicopathologic, Immunophenotypic, and Genotypic Analysis of Alpha/Beta and Gamma/Delta Subtypes. *Am J Surg Pathol*. 1998; 22: 881-893. PMID: 9669350.
4. Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C, Canninga-van Dijk MR, Carlotti A, Geerts ML, Hahtola S, Hummel M, Jeskanen L, Kempf W, Massone C, Ortiz-Romero PL, Paulli M, Petrella T, Ranki A, Peralto JL, Robson A, Senff NJ, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ; EORTC Cutaneous Lymphoma Group. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood*. 2008; 15; 111: 838-845. PMID: 17934071.
5. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, Ralfkiaer E, Chimenti S, Diaz-Perez JL, Duncan LM, Grange F, Harris NL, Kempf W, Kerl H, Kurrer M, Knobler R, Pimpinelli N, Sander C, Santucci M, Sterry W, Vermeer MH, Wechsler J, Whittaker S, Meijer CJ. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005; 105: 3768-3785. PMID: 15692063.
6. Avinoach I, Halevy S, Argov S, Sacks M. Gamma/delta T-cell lymphoma involving the subcutaneous tissue and associated with a hemophagocytic syndrome. *Am J Dermatopathol*. 1994; 16: 426-433. PMID: 7978074.
7. Toro JR, Beaty M, Sorbara L, Turner ML, White J, Kingma DW, Raffeld M, Jaffe ES. Gamma/delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. *Arch Dermatol*. 2000; 136: 1024-1032. PMID: 10926739.
8. Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES. T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. *Am J Surg Pathol*. 1991; 15: 17-27. PMID: 1985499.
9. Kumar S, Krenacs L, Medeiros J, Elenitoba-Johnson KS, Greiner TC, Sorbara L, Kingma DW, Raffeld M, Jaffe ES. Subcutaneous panniculitic T-cell lymphoma is a tumor of cytotoxic T lymphocytes. *Hum Pathol*. 1998; 29: 397-403. PMID: 9563791.
10. Caudron A, Bouaziz JD, Battistella M, Sibon D, Lok C, Leclech C, Ortonne N, Molinier-Frenkel V, Bagot M. Two atypical cases of cutaneous gamma/delta T-cell lymphomas. *Dermatology*. 2011; 222: 297-303. PMID: 21606639.