Case Study

CD20-positive primary cutaneous extranodal NK/T-cell lymphoma

Xiangdong Xu[1,3], Laura Romero[2,3], Young Kim[4], and X. Frank Zhao[1,3,*]

Departments of [1]Pathology and [2]Dermatology, University of California San Diego; [3]VA San Diego Healthcare System, San Diego, CA; [4]Department of Pathology, City of Hope, Duarte, CA.

Abstract: Cutaneous extranodal NK/T-cell lymphoma, nasal type, and primary cutaneous γ/δ T-cell lymphoma (PCGD-TCL) are rare cutaneous lymphoid neoplasms with overlapping features. Although EBV positivity favors the former, EBV+ PCGD-TCL has recently been reported. They also share cytotoxic markers and a poor prognosis. Here we report an unusual case of cutaneous NK/T-cell lymphoma with overlapping features of PCGD-TCL in a 55-year-old man who also developed hemophagocytic lymphohistiocytosis. Although it presents the typical pathological and immunophenotypic features of a cutaneous NK/T-cell lymphoma and PCGD-TCL, it aberrantly expresses CD20, giving an impression of mixed populations of T cells and B cells that are commonly seen in reactive conditions. This rare case represents a diagnostic pitfall and intends to raise more awareness among both pathologists and dermatologists. The CD20 positivity may also provide a target for rituximab therapy.

Keywords: Cutaneous NK/T-cell lymphoma; primary cutaneous γ/δ T-cell lymphoma; hemophagocytic lymphohistiocytosis; CD20, rituximab

Introduction

CD20 is encoded by the *MS4A1* gene, a member of the membrane spanning 4A gene family. It is commonly expressed on the surface of mature B lymphocytes and serves as an important marker for lineage determination, although CD20 expression has also been observed in a small population of normal T cells [1]. Aberrant expression of CD20 was reported in cases of T-cell lymphomas [2] and T-cell leukemias [3]. However, aberrant CD20 expression has only rarely been reported in NK/T-cell lymphoma, nasal type, and not yet in primary cutaneous γ/δ T-cell lymphoma (PCGD-TCL). Here we report a CD20+ lymphoma with overlapping features of cutaneous NK/T-cell lymphoma, nasal type and PCGD-TCL in a patient who also developed hemophagocytic lymphohistiocytosis (HLH).

*Correspondence: X. Frank Zhao, MD PhD, 650 E Indian School Road, Main Bldg., Rm. 2131, Phoenix, AZ 85012. Office: 602-277-5551, x6346; Fax: 602-222-2669; Email: Xianfeng.Zhao@va.gov

Case Report

The patient was a 55-year-old man with a past medical history of type 2 Diabetes Mellitus who presented to VA San Diego Medical Center with weight loss, weakness, peripheral neuropathy and ulcerated skin rash. His symptoms started three months ago with left hand weakness, left foot drop and a localized rash on the feet. Pain, weakness and rash progressed

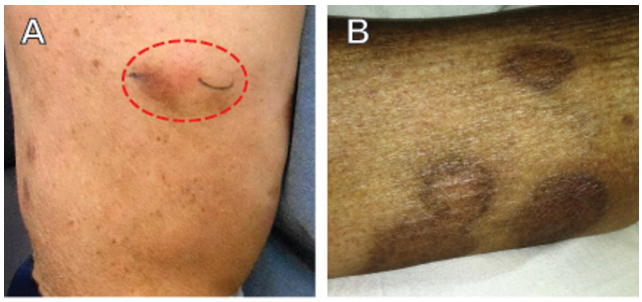

Figure 1: Skin lesions before and after treatment. A) Skin nodule (dashed circle) on the right upper arm before chemotherapy. B) Improvement of the skin lesions on the right arm after two cycles of chemotherapy (photos taken with the patient's informed consent).

at the time of presentation. On exam, the patient demonstrated annular crusted red plaques on the extremities, trunk, penis, and hard palate. He also had tender hands and feet that demonstrated paresthesia and burning pain triggered by movement.

On admission, he had mild anemia with the following complete blood count: white blood cells (WBCs) 4.7 X 10^9/L, hemoglobin (Hgb) 10.2 g/dL, mean corpuscular volume (MCV) 91.2 fL, platelets 184 X 10^9/L. Extensive workup showed cryoglobulinemia, negative ANCA and ANA serology, and sural nerve vasculitis. Skin biopsy of an ulcerated plaque showed a lichenoid, dermal and subcutaneous mixed infiltrate with necrotic and focal acantholytic keratinocytes in the epidermis. Vasculitis and neuritis were present, but seemed secondary. Special stains were negative for microorganisms and immunostains revealed a mixed infiltrate of lymphocytes and histiocytes (not shown). The differential diagnosis included erythema multiforme-like drug eruption, paraneoplastic pemphigus and Rowells syndrome. Direct immunofluorescence (IF) detected C3 and indirect IF was negative for paraneoplastic pemphigus. The patient was discharged on treatment for vasculitis including high dose prednisone and cyclophosphamide as well as gabapentin.

Approximately two weeks later, the patient was readmitted with an MRSA-positive abscess on the back, fever and severe anemia. His abscess was surgically debrided and he was placed on intravenous ceftarolone. Further work up at this time revealed pancytopenia (WBCs of 4.1 X 10^9/L, Hgb of 7.8 g/dL, and platelets of 52 X 10^9/L). His other abnormal laboratory test results included: fibrinogen 154 mg/dL; triglyceride 400 mg/dL; ferritin >13,000 ng/mL; soluble CD25 >90,000 U/mL. Serology for EBV was positive for viral capsid antigen and nuclear antigen. PCR for EBV revealed 69,600 copies/mL. These clinical and laboratory findings met the diagnostic criteria of HLH [4]. Bone marrow biopsy and aspirate were performed. Of note, the patient's skin rash had improved modestly since treatment for his vasculitis, but now he noted nodules on his upper extremities [Figure 1A]. One of the skin nodules was biopsied.

The skin biopsy revealed dense lymphocytic infiltrate mainly involving the deep dermis and the subcutis with focal epidermotropism [Figure 2A]. The infiltrate was composed of medium to large atypical cells with coarse chromatin, inconspicuous nucleoli, and irregular nuclear contours [Figure 2B]. The atypical cells encircled adnexal structures in the deep dermis and also surrounded subcutaneous adipocytes, rendering a "panniculitis-like" pattern [Figure 2C]. Mitotic figures were present. Necrosis, angioinvasion, or hemophagocytosis was not identified.

Immunohistochemistry showed the neoplastic cells were positive for CD3 [Figure 2D] and other pan T-cell markers (CD2, partial CD5, CD7), cytotoxic markers (TIA-1, perforin, granzyme B) and CD56. CD4 was weakly positive in a subset of the neoplastic cells [Figure 2E]. Stains for T-cell receptor (TCR) γ, CD8 and βF1 were negative in those cells [Figure 2F & 2H]. Interestingly, the neoplastic cells were strongly positive for CD20 [Figure 2G], while other B-cell markers (CD19, Pax5 and CD79a) were negative. Stain for EBV LMP was negative, but in situ hybridization for EBV encoded RNA (EBER) was strongly positive in the neoplastic T cells [Figure 2I].

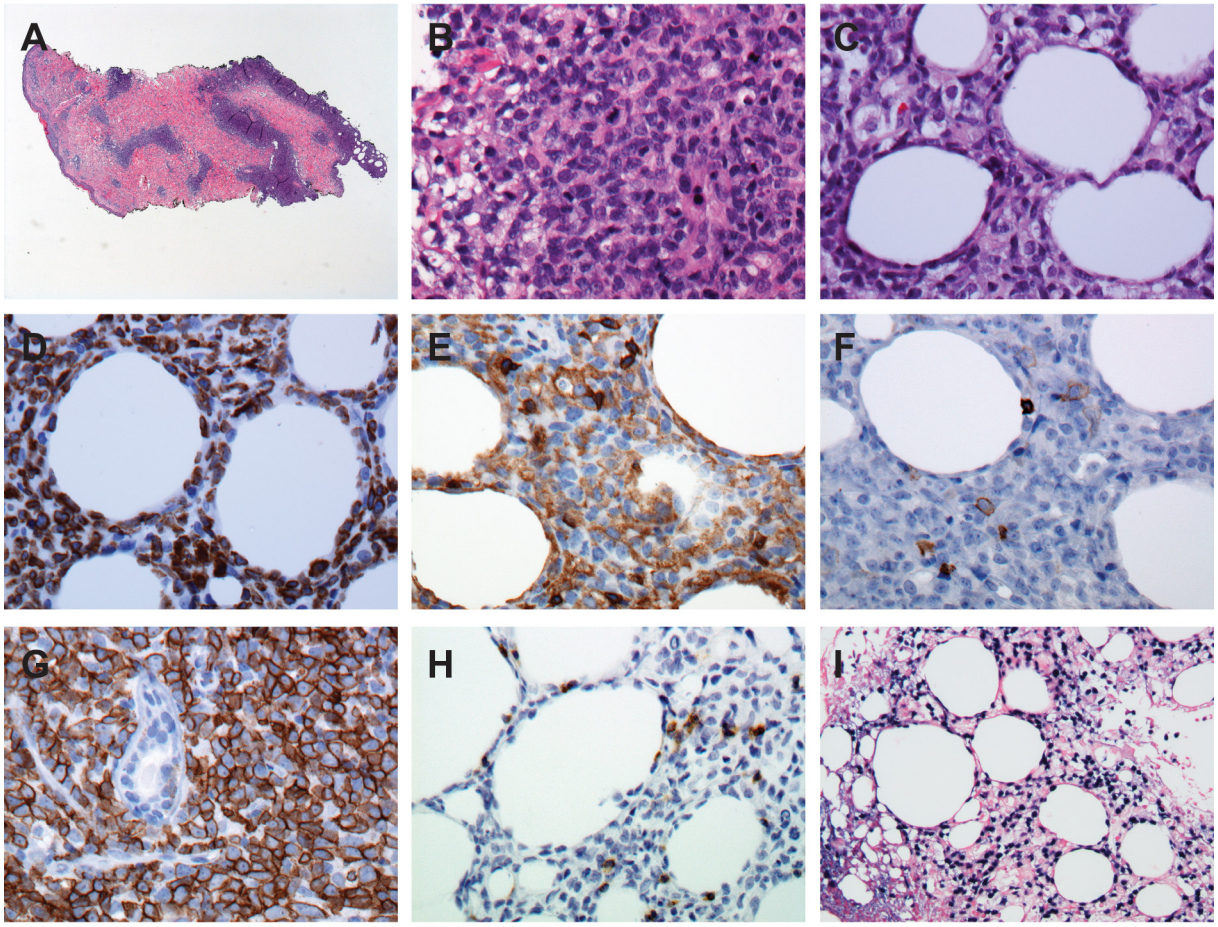

Figure 2: Primary cutaneous extranodal NK/T-cell lymphoma. A) Low magnification shows dense infiltrates mainly involving the deep dermis and the subcutis (original magnification 20x). B) High magnification reveals medium-to-large sized atypical lymphoid cells with irregular nuclear contour, coarse chromatin and small nucleoli. Mitotic figures are present. C) Rimming neoplastic cells of individual fat space are positive for CD3 (D), CD4 (weak) (E), and negative for CD8 (F) and βF1 (H). The neoplastic cells aberrantly express CD20 (G) and are positive for EBV infection by EBER (I). (B-I: original magnification 400x).

No fresh tissue was available for flow cytometric analysis or karyotyping. Molecular study performed on paraffin sections failed to detect *TCRG* or *IGH* gene rearrangement.

The concurrent bone marrow biopsy showed EBER+ lymphocytes with hemophagocytosis (not shown).

The patient was treated with 2 cycles of HiDAC and etoposide. Two weeks after the start of treatment, his soluble CD25 dropped to normal level. His skin eruption improved significantly with resolution of all but one of the subcutaneous nodules [Figure 1B]. Neuritis improvement was minimal. A follow up bone marrow biopsy showed no evidence of lymphoma or hemophagocytosis. Myelopoiesis is markedly decreased with neutropenia. The patient was given neulasta for his neutropenia and intrathecal methotrexate for possible CNS involvement by lymphoma. After 2 cycles of chemotherapy, the patient was discharged home with scheduled clinical follow up. Rituximab was being considered but never given for his cutaneous lymphoma. He

underwent allogeneic bone marrow transplantation in May 2014 and expired six weeks later.

Discussion

We present a rare case of cutaneous CD20-positive lymphoma with overlapping features of extranodal NK/T-cell lymphoma, nasal type, and PCGD-TCL. CD20 expression in a subset of T cells may give a false impression of a "mixed" population of B and T lymphocytes, particularly when the lymphocytic infiltrates are less dense and a limited panel of immunohistochemical stains is performed: this may be falsely interpreted as a reactive dermatitis (as occurred in the 1st skin biopsy of this patient). The current case will help pathologists to recognize this diagnostic pitfall.

On the other hand, aberrant CD20 expression in this aggressive T-cell lymphoma provides an additional therapeutic target for rituximab, which has been reported in six cases of CD20+ T-cell lymphomas [2, 5–7], and one indolent NK/T-cell lymphoma [8]. The six cases of T-cell lymphoma were diagnosed as peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS). Three of those (Case #4, #5 of Rahemtullah *et al*., and the case of Hirata *et al*.) showed decreased CD20 expression in lymphoma cells after rituximab therapy [2, 6]. However, there was no sufficient information to conclude the effects of rituximab on overall survival in those cases.

The EBV positivity and the lack of TCRγ in the neoplastic cells favor the diagnosis of primary cutaneous extranodal NK/T-cell lymphoma, nasal type, although the clinical and histologic presentations are also compatible with PCGD-TCL; the presentation with crusted plaques and subcutaneous nodules and the histologic pattern of epidermal interface involvement with dense panniculitis mimicking lupus profundus are all characteristic. Yu *et al*. recently reported a cutaneous EBV+ γ/δ T-cell lymphoma [9], and more interestingly, NK/T-cell lymphomas shares strikingly similar molecular signatures with γ/δ T-cell lymphoma as well [10], suggesting that these two entities overlap and separation of these two entities may sometimes be difficult.

HLH caused by disturbed and uncontrolled inflammatory responses is associated with congenital or acquired defective NK/T-cell functions [11]. Mortality rate is approximately 95% if untreated, although rare cases demonstrated an indolent clinical course with response to systemic steroids [12]. Acquired HLH is known to be associated with benign conditions, such as EBV infection [13], as well as T-cell and NK-cell malignancies, including cutaneous NK/T-cell lymphoma, nasal type and PCGD-TCL [12, 14]. Our patient has both EBV infection and cutaneous extranodal NK/T-cell lymphoma, both of which could have contributed to his HLH.

In summary, we have reported an unusual case of cutaneous extranodal NK/T-cell lymphoma, nasal type, with overlapping features of PCGD-TCL and aberrant CD20 expression, which may present a diagnostic pitfall, as well as a therapeutic target for this aggressive lymphoma.

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