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Case Report

A Case Report of CD56-Positive Aggressive Lymphoma Involving Skin and Subcutaneous Tissue

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Abstract

We report the clinical and pathologic features of a CD56-positive aggressive lymphoma occurring in the skin and subcutaneous tissue of a 44-year-old female. The disease started with skin pigmentation of the left flank, pancytopenia and a high serum LDH level. A skin and subcutaneous biopsy revealed diffuse lymphoblastic-like lymphoma of mainly medium-sized cells with a small area of necrosis. Lymphoma cells showed cytoplasmic azurophilic granules. These cells were positive for CD2, CD56 and HLA-DR but negative for CD3 on flow cytometry, positive for CD2, CD7 and CD56 on frozen sections, and positive for cytoplasmic CD3 and Epstein-Barr virus EBER RNA on paraffin sections. Despite extensive chemotherapy, the patient had a downhill course and died 111 days after admission.

Key words: CD56-positive lymphoma, skin and subcutaneous tissue, Epstein-Barr virus

Introduction

It has been noted that CD56 (NKH 1), a natural killer (NK) cell-associated antigen, is often expressed in sinonasal lymphomas including polymorphic reticulosis[1,2]. However, CD56-positive lymphomas occurring outside the sinonasal and upper aerodigestive tract are very rare[3-6].

We report herein a case of CD56-positive aggressive lymphoma occurring in the skin and subcutaneous tissue of a 44-year-old woman.

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Case Report

The patient, a 44-year-old female, had been well until November 1992, when she noticed pigmentation in the skin of the left flank. She had past history of chronic pyelonephritis at age 40. Her family history was unremarkable. In January 1993, periphiral edema developed in the feet and spread over the thighs. Intermittent fever as high as 39°C developed. The patient consulted a physician who discovered pancytopenia and an elevated LDH level. She was admitted to Tenri Hospital, Nara, on May 1, 1993.

Examination on admission revealed high fever (39°C), anemia, erythema with pigmentation in the trunk (Fig. 1) and extremities, peripheral edema, and

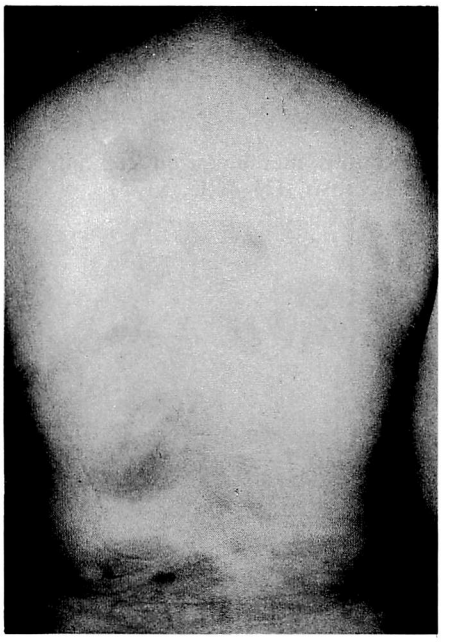

Fig. 1. Erythema with pigmentation in the back.

tenderness in the legs. A small bean-sized lymph node was palpable in the right inguinal region. The liver was not felt. The spleen extended 2 cm below the left costal margin. On laboratory data, pancytopenia and elevated GOT and LDH levels were noted. (RBC 347 x $10^4/\mu l$, Hb 8.1g/dl, Hct 25.2%, PLT 11.1 x $10^4/\mu l$, WBC 1,800/μl, LDH 1,448 IU/L, GOT 63 IU/L). Anti-HTLV-1 antibody was negative. A biopsy was taken from the cutaneous-subcutaneous tissue in the right shoulder region, and was diagnosed as CD56-positive aggressive lymphoma. Chemotherapy was started on June 1, 1993 with VEPA-B(ADM, VCR, CPM, PDN) which was not effective. Then, on June 29, it was switched to FEPP-A (ADM, VP-16, VDS, PDN, PCZ), which worked well. The skin lesions disappeared and the LDH level decreased. This regimen had to be discontinued, however, due to severe bone marrow suppression. Then, skin lesions recurred. Acute renal failure appeared on July 24. On July 28, CRP and LDH levels increased abruptly. Repeated chemotherapy was not effective. Pancytopenia, renal failure and bleeding from the gastrointestinal tract appeared. The patient eventually died on August 19, the 111th hospital day. Autopsy was not permitted.

Pathology

The biopsy specimen measured 1.2 x 0.5 cm. Section showed extensive infiltration of atypical lymphoid cells in the dermis and subcutaneous adipose tissue. These were composed mainly of monotonous medium-sized cells with frequent mitotic figures (Figs. 2 and 3). The histology mimicked a high-grade lymphoma such as lymphoblastic lymphoma of the T-cell type. The tumor cells infiltrated around the skin appendages and blood vessels in the dernis. Necrosis was not a main feature but a small ischemic necrosis was seen in one area (Fig. 2). Giemsa stained imprint of the tissue showed lymphoid cells with oval or irregular nuclei and abundant cytoplasm containing azurophilic granules. Electron microscopic analysis showed atypical lymphocytes of 6 to 10 μm in diameter with dense core granules similar to those of large granular lymphocytes (Fig. 4). According to flow cytometric analysis, the tumor cells were positive for CD2, CD56 and HLA-DR, and negative for most of T-cell markers like CD3, CD4, CD5 and CD8 (Table 1). Immunohistochemical analysis on frozen sections (Table 1) showed positivity for CD2, CD7 and CD56 (Fig. 5), but CD1, CD4, CD5

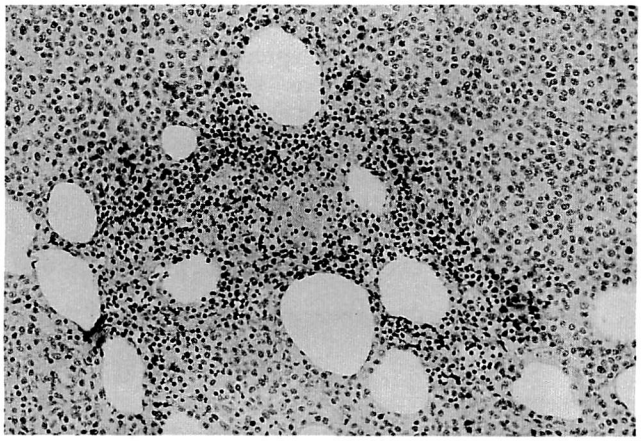

Fig. 2. Monotonous medium-sized cell infiltration with focal necrosis. (H & E, x175)

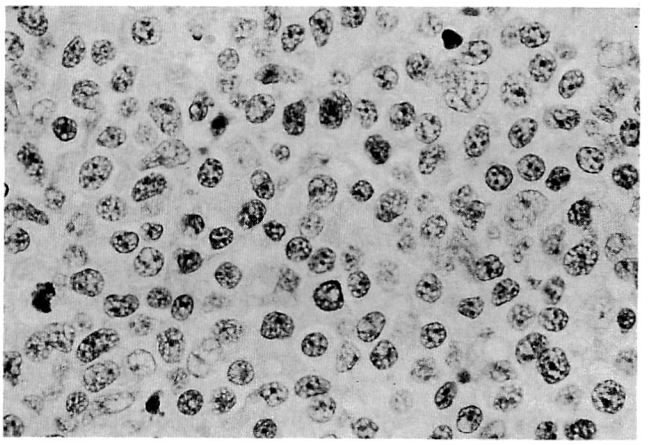

Fig. 3. Lymphoma cells in high power. (H & E, x700)

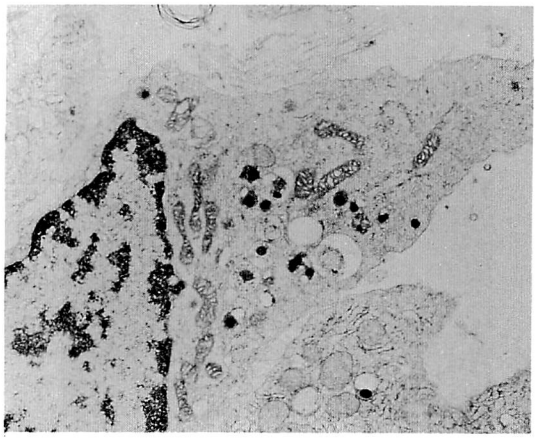

Fig. 4. Ultrastructure of lymphoma cells with cytoplasmic granules. (Electron microscopy, x5000)

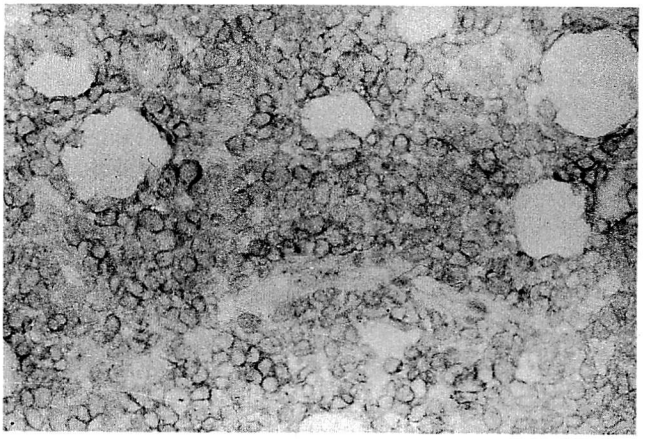

Fig. 5. CD56 positivity in lymphoma cells. (ABC method, frozen section, x350)

Table 1. Immunophenotyping of the lymphoma cells

	Cell suspension (Flow cytometry)	Frozen section	Paraffin section
CD 1		(−)	
CD 2	96%+	(+)	
CD 3	14%−	(−)	(+)*
CD 4	8%−	(−)	
CD 5		(−)	
CD 7		(+)	
CD 8	8%−	(−)	
CD13	6%−		
CD14	10%−		
CD15			(−)
CD16	2%−		
CD19	3%−		
CD20			(−)
CD30			(−)
CD33	6%−		
CD34	1%−		
CD36	4%−		
CD43			(±)
CD45			(±)
CD45RA	4%−		
CD45RO			(±)
CD56	80%+	(+)	
CD57	8%−	(−)	
HLA-DR	98%+		

*:Cytoplasmic CD 3.

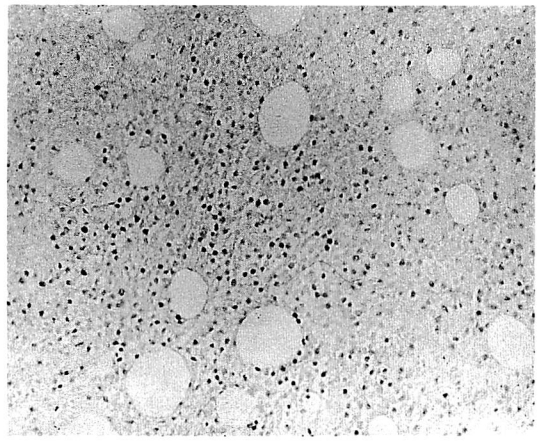

Fig. 6. EBER RNA positivity in nuclei of lymphoma cells. (In situ hybridization, x175)

and CD8 were negative. Immunohistochemistry and in situ hybridization on paraffin sections showed positivity for cytoplasmic CD3 and Epstein-Barr virus EBER oligonucleotide (Fig. 6), respectively. Genotypic studies revealed a germline configuration in J_H and TCR genes. From these findings, we conclude that this tumor was a CD56-positive aggressive lymphoma featuring large granular lymphocytes.

Discussion

NK cell marker(CD56)-positive aggressive lymphoma has recently been described mostly in the sinonasal and upper aerodigestive tract,[1,2] but rarely in other sites such as skin and subcutaneous tissue, intestines, spleen, lymph node, bone marrow and so on.[1,3-6] Histologically, it is a diffuse lymphoma often with an angiocentric growth pattern and ischemic necrosis. Cytologically, these neoplastic cells are mainly comprised of large cells, but, there are some instances of medium-sized cells, with azurophilic graunles in the cytoplasm. Neoplastic cells in these tumors were usually positive for CD2, CD56 and HLA-DR, but negative for CD3 and B-cell markers. Expression of CD4, CD7, CD8, CD11, CD16, CD57 and other markers was variable. In terms of markers, CD56-positive aggressive lymphomas are divided into CD3-negative and CD3-positive groups. The former group may be called CD56-positive cell lymphoma and the latter CD56-positive NK cell-like T-cell lymphoma. Regardless of differences in expression of these markers, the clinical course of CD56-positive lymphomas is very aggressive.

In the present case, the tumor was composed mainly of medium-sized lymphoblastic cells with frequent mitoses and intracytoplasmic azurophilic granules. Although cytoplasmic CD3 was positive on paraffin sections, surface CD3 was negative and TCR genes showed a germline configuration. This type of discrepancy in CD3 expression is also found in NK cells, since polyclonal CD3 stain may detect cytoplasmic CD3-ε chain which is found in NK cells.[7] The present case also showed EBER oligonucleotide of Epstein-Barr virus, which is consistent with the observations by Chan et al. of EBER positivity in non-nasal/nasopharyngeal CD3 negative and CD56 positive lymphomas.[8]

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