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CASE REPORT

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Blastic NK-cell lymphoma/leukemia with T-cell receptor γ rearrangement

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Abstract A 79-year-old Japanese man was admitted to our hospital with dyspnea in June 1999. Physical examination revealed general exanthema, hepatosplenomegaly, and lymphadenopathy. Increased numbers of abnormal cells were observed in peripheral blood; these cells were of lymphoblastic morphology with high nuclear/cytoplasm ratios and few azurophilic granules. Immunophenotypic analysis revealed positivity for CD2, CD4, CD56, and HLA-DR, and negativity for CD3, CD13, CD16, CD33, CD34, and T cell receptor (TCR). On genotypic analysis, TCRγ chain was rearranged, but neither the TCRβ chain nor TCRδ chain. Despite an initial good response to chemotherapy the disease relapsed in the early stage, and the patient died 6 months after diagnosis.

Keywords Blastic NK-cell lymphoma/leukemia · CD4 · CD56 · T-cell receptorγ rearrangement

Introduction

Since it is difficult to distinguish between natural killer cell (NK)-cells and T-cells morphologically, immunophenotypic and genotypic analyses are performed to distinguish them. Recently, surface antigen analysis using monoclonal antibodies has made it easy to diagnose NK cell neoplasms. True NK-cells are positive for CD16 and/or CD56, negative for surface CD3 and T-cell receptor TCR, and do not exhibit TCR gene rearrangements [1]. Blastic NK cell leukemia/lymphomas, which appear to be of NK precursor cell origin, were described by Nakamura et al. [2] in 1995. They are characterized by unusual skin involvement, blastic morphology, surface $CD3^-$ and $CD56^+$ phenotype without B-cell and myeloid cell markers, and absence of TCR gene rearrangements. We report here a case of blastic NK-cell lymphoma/leukemia with TCRγ gene rearrangement.

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Case report

In early June 1999, a 79-year-old Japanese man was admitted to Osaka City General hospital with dyspnea. Physical examination revealed unusual skin plaques (Fig. 1), hepatosplenomegaly, and lymphadenopathy. Hematological examination revealed increased

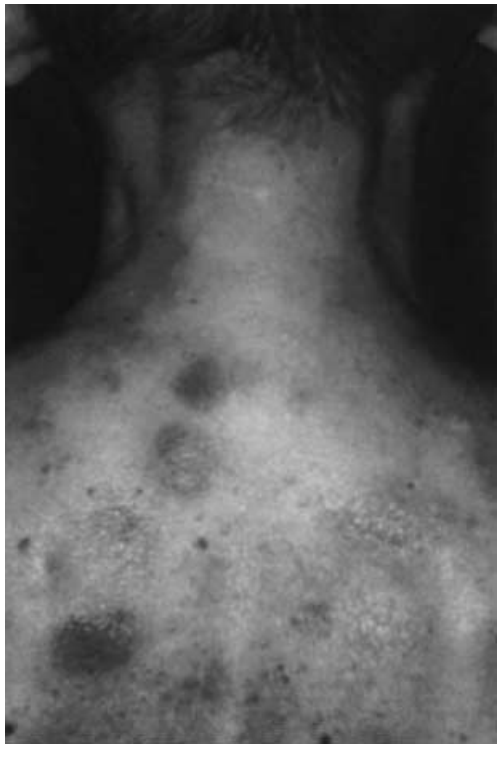

Fig. 1 Photographic findings for skin plaque

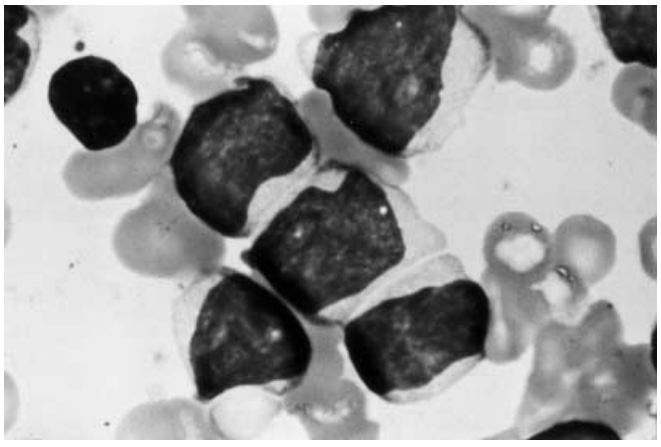

Fig. 2 Light microscopic findings for the blast cells of bone marrow aspirate. May-Giemsa staining, ×400

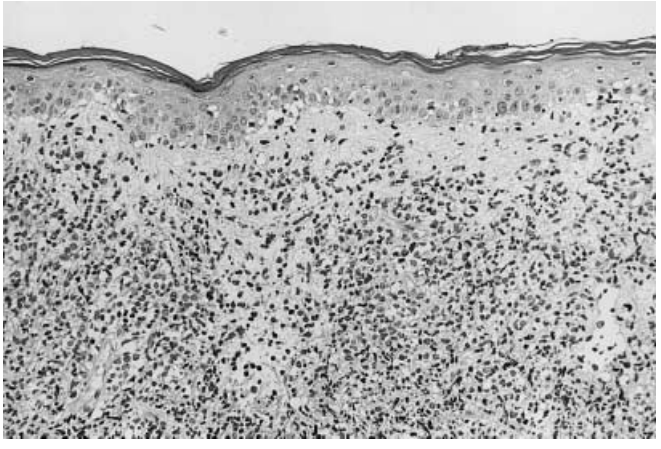

Fig. 3 Light microscopic findings for the blast cells of skin biopsy. Hematoxylin-eosin staining, ×400

numbers of abnormal cells in peripheral blood, anemia, and thrombocytopenia. The abnormal cells were of lymphoblastic morphology with high nuclear/cytoplasm (N/C) ratios and few azurophilic granules in the cytoplasm. Blood biochemistry examination revealed a high serum lactate dehydrogenase level (671 IU/l). Serological examination revealed a CRP of 1.38 mg/dl and an elevated soluble interleukin-2 receptor level of 3030 U/ml, and negativity for human T-lymphotropic virus 1. Coagulation study results were normal. On bone marrow aspiration, tumor cells with high N/C ratios and few azurophilic granules accounted for 98.5% of cells (Fig. 2). Tumor cells were negative for myeloperoxidase, and they appeared to be lymphoblasts. Lymph node and skin biopsy (Fig. 3) revealed clear infiltration of tumor cells. Immunophenotypic analysis revealed positivity for CD2, CD4, CD56, and HLA-DR, and negativity for surface CD3, CD13, CD16, CD33, CD34, and TCR. On paraffin immunohistochemistry, responses to tumor cells were positive for cytoplasmic CD3, granzyme B and TIA-1, but less than 20% positive for terminal deoxynucleotidyl transferase (TdT). Epstein-Barr viral RNA as measured by in situ hybridization and Epstein-Barr viral DNA as measured by Southern blotting analysis were negative in tumor cells. Chromosomal analysis revealed a normal male karyotype. Genotype analysis revealed a germline configuration of the immunoglobulin heavy chain (IgH) gene, TCRβ gene, and TCRδ gene, but a rearranged TCRγ gene chain (Fig. 4). Computed tomography revealed hepatosplenomegaly and lymphadenopathy in both inguinal regions. Blastic NK/T-cell lymphoma/leukemia was diagnosed, because this case was very similar to blastic NK-cell lymphoma/leukemia as previously described [2, 3, 4, 5, 6, 7, 8, 9] but exhibited TCRγ chain rearrangement.

On 19 June, remission induction chemotherapy with vincristine and prednisolone was performed, and complete remission was achieved. Consolidation maintenance therapy with oral administration of sobusoxane, vincristine plus prednisolone, and etoposide was performed on an outpatient basis. In October 1999, the patient was readmitted to the hospital because of dyspnea. Hematological examination revealed leukoblastosis, anemia, and thrombocytopenia. Relapse was diagnosed, and he was treated with combination chemotherapy. After chemotherapy bacterial pneumonia developed. On 20 December 1999, he died of respiratory failure 6 months after initial diagnosis.

Discussion

Blastic NK-cell leukemia/lymphomas are rare hematological malignancies, which may be of NK progenitor cell origin [2, 3, 4, 5, 6, 7, 8, 9]. They are characterized by occurrence in relatively elderly patients and nodal and extranodal involvement, for example, in skin and bone marrow, but rarely the mediastinum. Morphologically, the tumor cells display a lymphoblastic morphology with high N/C ratio and generally few azurophilic granules in cytoplasm. Immunophenotypically, surface antigens of tumor cells are positive for CD4 and CD56

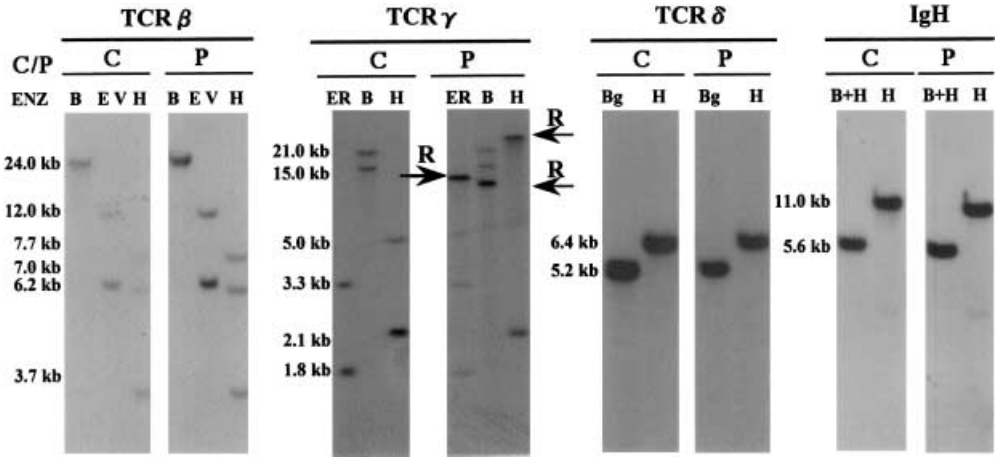

Fig. 4 Southern blot analysis of DNA extracted from tumor cells. A rearranged band was observed only with TCRγ probe, and not TCRβ, TCRδ, or immunoglobulin heavy-chain gene probes. *ENZ* Restriction enzyme; *TCR* T-cell receptor; *IgH* immunoglobulin heavy chain; *C* control; *P* patient; B *Bam*HI; *EV Eco*RV; *ER Eco*RI; H *Hin*dIII; Bg *Bg*III; *R* rearranged band

and negative for CD3, B-cell, and myeloid cell markers. No Epstein-Barr viral genome or transcripts are detected in blastic NK-cell lymphoma/leukemias. Genotypically, there are no detectable rearrangements of TCR genes or immunoglobulin heavy chain genes. Chemotherapeutic regimens for lymphoid malignancy are more effective than for myeloid malignancy. The prognosis of this disease is very poor, with a mean survival period less than 2 years (mean 22.2, range 13.3–31.1) [8].

Immunophenotypically and clinically, our case was very similar to blastic NK-cell lymphoma/leukemia as described in previous reports [2, 3, 4, 5, 6, 7, 8, 9], but cannot be considered a true NK neoplasm because the tumor cells exhibited TCRγ chain rearrangement. To date, only one case has been reported to exhibit a surface antigen pattern similar to blastic NK-cell lymphoma/leukemia and rearrangement of the TCR gene, as observed in the present case [3]. Since it is difficult to distinguish between NK cells and T-cells morphologically, immunophenotypic and genotypic analysis are performed to distinguish them. True NK-cells are positive for CD16 and/or CD56, and negative for surface CD3 and TCR, and do not exhibit TCR gene rearrangements [1]. The blasts of typical T-cell lymphoblastic lymphoma/leukemia are usually positive for TdT, but mature NK cells usually do not bear TdT. The level of expression of TdT in blastic NK cell lymphoma/leukemia was lower than that in typical T-cell lymphoblastic lymphoma/leukemia, and also below the cutoff level of 20% [8]. Although rearrangement of TCR genes implies T-cell lineage, the blasts in a case described by Pirruccello et al. [3] and our case were negative or less than 20% positive for TdT and negative for immunoglobulin. Furthermore, TCR gene rearrangements frequently occur across lineages in acute leukemia [10]. These findings, together with the phenotype and morphology of the tumor cells, suggest that the tumor cells in the present case were of NK cell lineage, but not those of a true NK-cell neoplasm. In 1999 Petrella et al. [11] reported seven cases of peculiar cutaneous tumors, "agranular $CD4^+$ $CD56^+$ hematodermic neoplasms." They were positive for CD4 and CD56, and also for CD45, CD43, and HLA-DR, and negative for all T-cell and B-cell markers. Myelomonocytic markers were negative except for CD68. Polymerase chain reaction studies did not detect any B or T clonal rearrangement. Our case differs from the cases of $CD4^+$ $CD56^+$ hematodermic neoplasms reported by Petrella et al. because the latter cases were negative for CD2, cyCD3, TdT, TIA-1, and granzyme B, and our patient exhibited TCRγ chain rearrangement.

The blasts in the case of Pirruccello et al. [3] and our case appeared to be of NK precursor origin morphologically, immunophenotypically and clinically, but of T-cell lineage genotypically. Recent studies suggest that NK cells and T-cells share a common developmental pathway [12, 13], and Lanier et al. suggested the existence of a common T-cell–NK-cell progenitor that is distinct from totipotent hematopoietic or lymphoid progenitors [13]. However, the differentiation of NK cells and T-cells has not been clarified. The tumor cells in the case of Pirruccello et al. [3] and our case may be considered a manifestation of tumorigenesis of NK and/or T progenitor-cells. The case reported here appears to be very similar to blastic NK-cell lymphoma/leukemia morphologically, immunophenotypically, and clinically, but included TCR gene rearrangement. We therefore propose calling these cases "blastic NK/T-cell lymphoma/leukemia."

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