Primary Bone Marrow T-cell Anaplastic Large Cell Lymphoma with Triple M Gradient

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We present a case of a 60-year-old male patient with primary bone marrow anaplastic large cell lymphoma. He was admitted to the hospital with the symptoms of anemia and fever. There was no evidence of lymphadenopathy or splenomegaly. Immunoelectrophoresis showed the presence of a triple M gradient (double IgM and an IgG), with the IgG and one of the IgM paraproteins functioning as a cryoglobulin. The patient had no hepatitis C virus infection. Bone marrow biopsy showed massive CD30-positive, ALK-negative large lymphoid cell infiltration of T-cell origin with anaplastic morphology. PCR analysis of lymphoid cells separated from the bone marrow demonstrated the presence of a B/T hybrid genotype disorder with no evidence of the t(2;5), nor t(1;2) translocations. The patient entered a period of remission following CHOP chemotherapy. The patient subsequently died of sepsis as a consequence of serious humoral immunodeficiency.

Key words: anaplastic large cell lymphoma, T-cell receptor gene rearrangement, immunoglobulin heavy chain rearrangement, M gradient, bone marrow

Introduction

Anaplastic large cell lymphoma (ALCL) is a small, heterogeneous group of high-grade non Hodgkin’s lymphomas, accounting for about 2-5% of all non Hodgkin’s lymphomas. Recently three main subtypes of ALCL have been identified: primary systemic ALK-positive ALCL, primary systemic ALK-negative ALCL and primary cutaneous ALCL. The most important histological signs of the lymph node in ALCL are the paracortical tumor cell involvement, intrasinusoidal invasion and cohesive propagation of large, bizarre tumor cells with characteristic nucleoli. Primary systemic ALCL (both ALK-positive and ALK-negative) generally involves extranodal sites in 50-60% of cases while bone marrow involvement is observed in only about 0-17% of all ALCLs. Thus, while primary bone marrow lymphoma is an infrequent event, the additional presence of the auto-immune phenomena, M gradient, as presented in this case study, is an extremely rare event in ALCL.

Case report

A 60-year-old male patient was admitted to our hospital with the symptoms of anemia: retrosternal pain, dizziness, fatigue and weight loss. He had pancytopenia: severe normocytic, normochromic anemia (hgb:86 g/l), a white blood cell count of 1.5 G/l, with a platelet count of 105 G/l. The lactate dehydrogenase level was normal, but the β2-microglobulin level was elevated (3.212 mg/l). Immunoelectrophoresis showed the presence of a triple M gradient (two IgM and one IgG paraprotein: 6.4
g/l, 3.7 g/l and 23.5 g/l, respectively). The IgG and one of IgM paraproteins formed an immune complex, which functioned as a cryoprotein in the medium containing heparin. There was no evidence of infection with hepatitis C virus (HCV) or of HBsAg. Bone marrow biopsy showed heterogeneous cell population (Fig. 1a): epitheloid cells gave a granulomatous appearance intermixed with small and medium-sized T lymphocytes (CD3 positivity), plasma cells and scattered large, atypical cells with oval-irregular nuclei, broad cytoplasm. The phenotype of atypical cells was CD30+ (Fig. 1b), CD45+/−, CD3+/−, CD15−, CD20−, CD79a−, CD4−, CD8−, Tia-1+/−, ALK1−. Because the phenotype of the large cells was not completely the same as that of the small and medium-sized T lymphocytes, the final diagnosis was anaplastic large cell lymphoma with partial T-phenotype. Cytogenetic examination showed a normal male karyotype. Computed tomographic scan showed no lymphadenopathy, and only a mild hepatosplenomegaly (there was a heavy alcoholism in the patient’s past history). The tumor was classified as Ann-Arbor stage IV/Bes, the International Prognostic Index was 3. TCR beta- and gamma gene and IgH gene rearrangement polymerase chain reaction revealed a B/T hybrid genotype (Fig. 2) of separated neoplastic cells from the bone marrow. Following standard treatment with CHOP chemotherapy, there was no residual CD30-positive lymphoid involvement in a second bone marrow biopsy. Flow cytometry studies demonstrated the presence of normal bone marrow cells with no evidence of multidrug resistance (MDR) since P-glycoprotein expression was low on CD7-positive cells (10%). The calcein-MDR test also showed poor functional MDR activity. Seven months later he was admitted with fever, fatigue, repeated upper respiratory Candida albicans infection and severe extrapyramidal symptoms. Red blood cell transfusion, antifungal drugs, central nervous system circulation supporting therapy was administered. In spite of this his general condition deteriorated rapidly, and one month later he died of Enterococcus sepsis while still in complete remission from ALCL.

Figure 1. (a) Bone marrow infiltration of a heterogeneous cell population. Large, bizarre tumor cells with surrounding small or medium-sized T lymphocytes and plasma cells (HE staining, x200). (b) CD30-positive large cells in the bone marrow (x200).

Figure 2. IgH gene rearrangement (FR2a/JH) PCR results (a), T-cell receptor gamma gene rearrangement PCR results (b) and t(2;5)(p23;q35) RT-PCR results (c). Vertical arrows show the present case: sharp band at about 230-240 bp representing rearranged IgH gene (a), sharp band at 230 bp representing rearranged TCR gamma gene (b) and smear representing no nucleophosmin/ALK translocation (c). B: blank, P: positive, N: negative, M: molecular marker, bp: base pairs.