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Case Report

Histiocytic Sarcoma with Simultaneous Gene Rearrangements of both the Clonal Immunoglobulin Heavy Chain and the T-cell Receptor

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Abstract

A 77-year-old man was admitted with thrombocytopenia and splenic tumors. Severe thrombocytopenia continued even after high-dose methylprednisolone and intravenous gamma-globulin treatment. Bone marrow (BM) aspiration revealed atypical macrophages and gene rearrangements of both the IgH and TCR. Chemo/radiotherapies were ineffective, then he died from the disease progression. The autopsy revealed proliferation of large neoplastic cells in the spleen, liver and BM. The cells were positive for histiocytic markers, and negative for B-cell and T-cell markers. He was diagnosed with histiocytic sarcoma (HS). This is the first report of sporadic HS with gene rearrangements of both the IgH and TCR.

Keywords: Histiocytic Sarcoma; Gene Rearrangements; Immunoglobulin Heavy Chain; T-Cell Receptor; Poor Prognosis

Introduction

Histiocytic sarcoma (HS), which represents less than 0.5% of non-Hodgkin's lymphoma cases, is a rare hematopoietic neoplasm that mainly occurs in the lymph nodes, spleen, skin, and gastrointestinal tract. It is characterized by the malignant proliferation of cells that have the morphologic and immunophenotypic features of mature tissue histiocytes [1-3].

HS shows aggressive behavior and is associated with a poor prognosis [1-4]. Its pathogenesis is not fully understood [1-4]. Recently, some investigators demonstrated a detectable clonal immunoglobulin heavy chain (IgH) gene rearrangement in the tumor cells of patients with HS [5-7]. Moreover, Feldman et al [7] reported a case of HS after acute lymphoblastic leukemia that showed gene rearrangements of both the IgH and T-cell receptor (TCR). These findings may be key issues for elucidating the pathogenesis of HS.

We herein report the first case of sporadic splenic HS with simultaneous clonal gene rearrangements of both the IgH and TCR of bone barrow cells (BMCs) in the clinical course. The patient's HS was treatment-refractory and showed aggressive behavior. It was very interesting to consider the origin

of this patient's tumor cells.

Case Report

A 77-year old man with no notable medical history was referred to our hospital for thrombocytopenia. A physical examination revealed petechiae and purpura on the distal lower extremities. The results of a blood test performed on admission were as follows: white blood cells (WBC), 4.2 ×10^9/L, (without an abnormal differential); red blood cells, 364 × 10^9/L; hemoglobin (Hb), 12.1 g/dL; hematocrit, 35.9%; mean corpuscular volume, 98.8 fl; mean corpuscular hemoglobin, 33.2 pg; mean corpuscular hemoglobin concentration, 33.6%; and platelets (PLT), 11 × 10^9/L. The patient's prothrombin time, activated partial thromboplastin time, and fibrinogen level were normal. His biochemical profile revealed the following values: serum total protein, 4.9 g/dL; albumin (Alb), 2.7 g/dL; total bilirubin, 1.0 mg/dL; aspartate aminotransferase, 27 IU/L; alanine aminotransferase, 20 IU/L; lactate dehydrogenase, 245 IU/L; creatinine, 0.85 mg/dL; C-reactive protein, 0.43 mg/dL; sodium, 141 mEq/L; potassium, 3.6 mEq/L; chloride, 108 mEq/L; IgG, 798 mg/dL (normal range: 893-1838 mg/dL); IgA, 216 mg/dL (normal range: 102-396 mg/dL); IgM, 28 mg/dL (normal range: 30-195 mg/dL); soluble interleukin-2 receptor (sIL2R), 1370 U/mL. Serum immunoelectrophoresis showed no M-component. The patient's blood glucose level and thyroid function were normal. The levels of anti-Helicobacter pylori (HP) and platelet-associated IgG were both elevated (23 U/mL and 95 ng/10^7 cells, respectively). BM aspiration showed normal cellularity with an elevated megakaryocyte level (69/μL) without dysplasia or tumor cells, and showed a normal karyotype. The gene rearrangements of IgH or TCR were not checked at that point. A computed tomography (CT) scan (Figure 1A, B) showed splenomegaly with poorly enhanced multiple low-density nodules. Gadolinium-enhanced dynamic MRI (Figure 1C, D) showed multiple poorly enhanced splenic lesions in comparison to the parenchyma in the arterial phase. Fluorodeoxyglucose (FDG) positron emission tomography (Figure 1E, F) revealed no obvious lesions with FDG-uptake other than those in the spleen. Taken together, a diagnosis of immune thrombocytopenic purpura (ITP) accompanied by a splenic tumor was suspected. The patient was treated with high-dose methylprednisolone (1 g/day) for 3 days and lansoprazole, clarithromycin, and amoxicillin hydrate to eliminate the HP and allow for splenectomy for the purpose of therapeutic diagnosis. A high dose of gamma-globulin was intravenously administered; however, his PLT remained low (0.9 × 10^9/L), and the splenectomy was abandoned. The patient's pancytopenia showed continued progression; thus, BM aspiration and biopsy were performed, which revealed several atypical macrophages (Figure 2A, B), and clonal gene rearrangements of both the IgH and TCR β of BMCs were detected by a polymerase chain reaction (PCR) (Figure 3). We assumed that the patient had some kind of lymphoma or histiocytic neoplasm; therefore, R-THP-COP (rituximab, pirarubicin, cyclophosphamide, vincristine, and prednisolone) treatment was started as an induction therapy 2 months after his first admission. After the second cycle of R-THP-COP, the chemotherapy was discontinued due to a bacterial infection and because the size of his splenic tumor had not changed. Eight months after the first admission, he was admitted due to the progression of hypoalbuminemia, and pancytopenia (WBC, 1.6 × 10^9/L; Hb, 8.6 g/dl; PLT, 11 × 10^9/L), massive fluid retention, and peripheral edema. The serum sIL2R level was prominently elevated (7350 U/mL). BM aspiration showed a hypocellular marrow (nuclear cell count: 3.0 × 10^4/ μL) with a decreased megakaryocyte count (13/ μL). Once again, we did not observe dysplasia or tumor cells. A CT scan showed massive pleural effusions and ascites and the enlargement of the splenic tumors. The general fluid retention was not improved by the use of either anti-diuretics or Alb. Splenic radiotherapy (50 gray/25 fractions) was selected after the progression of the patient's splenic tumors was confirmed. Although FDG uptake was not detected in the spleen after the irradiation, a new lesion showing FDG uptake appeared in the liver. The patient's general condition deteriorated because of hepatic failure and pancytopenia, and he died from the progression of the disease 11 months after his first admission.

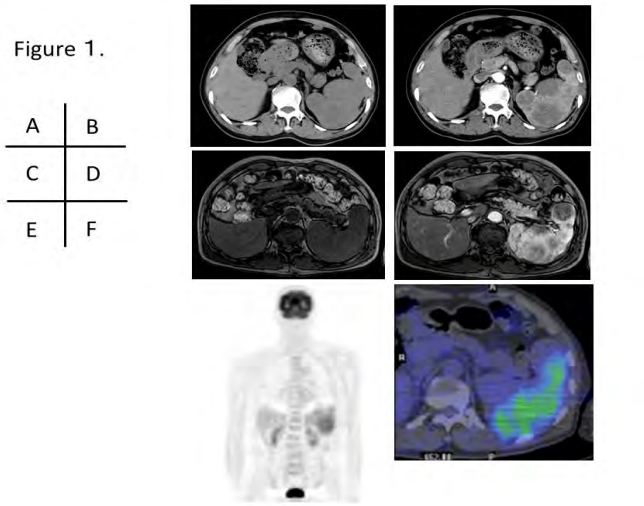

Figure 1. A CT scan (A: plain, B: enhanced) showed splenomegaly with multiple poorly enhanced low-density nodules. Gadolinium-enhanced dynamic MRI (C: plain, D: hepatic arterial phase imaging) showed multiple poorly enhanced splenic lesions in comparison with the parenchyma in the arterial phase. Fluorodeoxyglucose (FDG) positron emission tomography (E, F) revealed no lesions with obvious FDG uptake other than the spleen.

The autopsy findings showed diffuse non-cohesive pleomorphic proliferation of the large neoplastic cells in the spleen, liver, and BM with massive necrosis. The neoplastic cell was characterized by large, round to oval nuclei with rich chromatin and abundant foamy cytoplasm on hematoxylin-eosin staining (Figure 4A, B, C). An immunohistochemical analysis revealed that the neoplastic cells were positive for HLA-DR, CD45 and

histiocytic markers such as CD68 (Figure 4D, E), CD163 (Figure 4F, 4G), and lysozyme, but negative for EMA, HMB-45, S100, cyclin D1, CD3, CD4, CD10, CD15, CD20, CD30, CD31, and CD79a. Tumor cell infiltration was seen in the hepatic sinusoid (Figure 4B, 4G). There was no involvement of the tumor cells in other organs. Based on these findings, the patient was diagnosed with HS of the spleen, liver, and BM. The cause of death was assumed to be hepatic failure caused by the massive hepatic involvement of the tumor cells. To investigate whether the tumor cells performed the essential functions of B-cells, an immunohistochemical analysis of PAX5, (which is the specific B-cell transcription factor and which is known to be essential for maintaining the identity and function during late B lymphopoiesis [8]), was performed. The tumor cells in the spleen and in the BM were negative for PAX5 (data not shown), suggesting that they did not have a mature B-cell function.

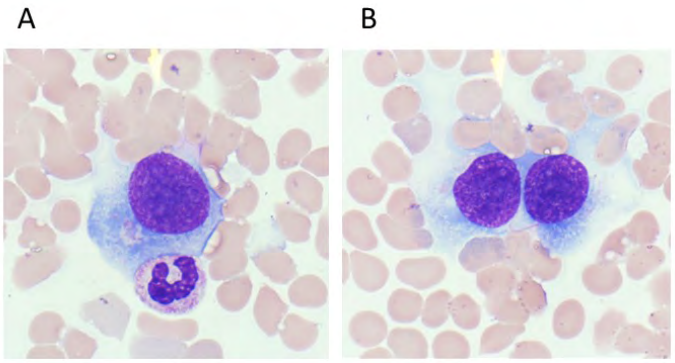

Figure 2. The May-Giemsa stain of the second bone marrow aspiration revealed atypical macrophages with immature features such as basophilic cytoplasms and obvious nucleoli (A, B) or the polynuclear (B).

Figure 3.

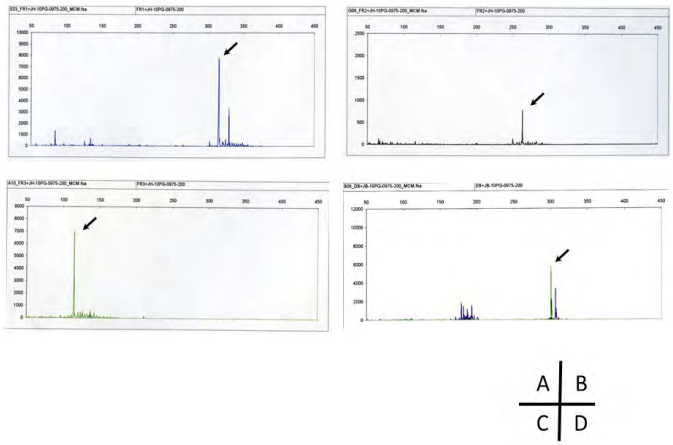

Figure 3. Molecular studies show clonal immunoglobulin heavy chain (IgH) and T-cell receptor (TCR) β gene rearrangements. The arrows indicate peaks representing the rearrangement products from FR1 (A), FR2 (B), and FR3 (C) all of IgH, and Dβ/Jβ (D) of TCR β. The detection of positive peaks of FR1, FR2, FR3, and Dβ/Jβ was expected between the regions of 310-360, 250-295, 100-170, and 170-210 or 285-325 bp, respectively. These assays are commercially available and were performed in the Mitsubishi Chemical Medience Corporation (Tokyo Japan) according to the manufacturer's protocol [22].

Figure 4.

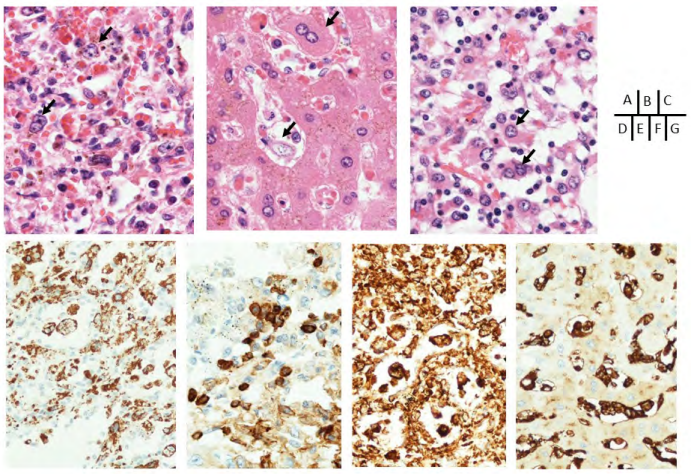

Figure 4. The histological findings at autopsy (A, B, and C: hematoxylin-eosin staining) reveal diffuse non-cohesive pleomorphic proliferation of the large neoplastic cells in the spleen (A: 400×), liver (B: 400×), bone marrow (C: 400×) with necrosis. The neoplastic cells are characterized by large, round to oval nuclei with prominent chromatin and abundant foamy cytoplasm. Arrows show the neoplastic cells. The immunohistochemical findings at autopsy reveal that the neoplastic cells are positive for histiocytic markers, such as CD68 (D: spleen, E: bone marrow) and CD163 (F: spleen, G: liver). The tumor cells are diffusely involved in the hepatic sinusoid (G).

Discussion

Only two HS cases (including the one discussed above) have been reported with gene rearrangements of both IgH and TCR (Table 1). Both cases involved male patients who showed splenomegaly and thrombocytopenia. Neither case showed the expression of the B- or T-cell related markers. Case No. 1 [7] showed a TCR γ rearrangement, and case No. 2 (the present case) showed a TCR β rearrangement. Both cases were resistant to treatment and the patient in the present case died after only 11 months. In case no. 1, the patient developed HS after acute lymphoblastic leukemia and underwent allogeneic stem cell transplantation. Thus, to our knowledge, the present case is the first reported case of sporadic HS with simultaneous genetic rearrangements of both the IgH and TCR.

Case No. [references]	Age/ Sex	Tumor sites involved	Initial symptoms	Hematological malignancies preceding HS	Cell surface marker		Rearrangement		Treatment	Outcome	Survival (Mo)
					Positive	Negative	Ig	TCR			
1 [7]	14/ M	Spleen, right renal, 12th rib, pelvic bone	Anemia, thrombocytopenia, splenomegaly	Pre-B cell lymphoblastic lymphoma	CD68, S100, lysozyme	CD1a, CD3, CD10, CD15, CD20, CD21, CD79a, TdT, HMB-45, S-100, cyclin D1, MPO	H	TCRγ	Additional CT → non-CR → allogeneic SCT	Alive	31+
2 [our case]	77/ M	Spleen, bone marrow, liver	Splenomegaly, thrombocytopenia, hypoalbminemia, hypogammaglobulinemia	No (Sporadic HS)	CD68, CD163, lysozyme, HLA-DR, CD45	CD3, CD4, CD10, CD15, CD20, CD30, CD31, CD79a, HMB-45, S-100, cyclin D1,	H	TCRβ	mPSL pulse, HP elimination, IVIG, R-THP-COP, splenic RT (PD)	Deceased	11

Table 1. The clinical characteristics of two histiocytic sarcoma cases with gene rearrangements of both the immunoglobulin heavy chain and the T-cell receptor. No., number; HS, histiocytic sarcoma; Ig, immunoglobulin; H, heavy chain; TCR, T-cell receptor; Mo, months; M, male; MPO, myeloperoxidase; CT, chemotherapy; SCT, stem cell transplantation; mPSL, methylprednisolone; HP, *Helicobacter pylori*; IVIG, intravenous gamma globulin; R-THP-COP, rituximab, pirarubicin, vincristine, prednisolone; RT, radiotherapy; CR, complete response; PD, progressive disease.

It is difficult to explain why simultaneous gene rearrangements of both IgH and TCR were detected in our case. Several investigators [9-13] have reported that HS cases with IgH rearrangement occurred subsequent to or concurrently with B- or T-cell lymphomas. Sporadic HS cases with IgH rearrangement have also been reported [5,6]. Chen et al. [6] demonstrated that 6 of 14 cases (43%) of sporadic HS had clonal IgH rearrangement and that the tumor cells in all of 6 cases with IgH rearrangement were found to be negative for CD20 and PAX5 by immunohistochemical analysis. However, the authors did not mention whether they checked the tumor cells for a clonal TCR rearrangement. An analysis of lymphoid neoplasms demonstrated that B-cells in which the PAX5 is inactivated by methylation can differentiate into macrophages or other counterpart cells and that the inactivated PAX5 can be involved in neoplastic pathogenesis [14,15]. As in the previous report, the tumor cells in our patient were found to be negative for PAX5 by immunostaining; however, the cells displayed TCR rearrangement. Therefore, the origin of the tumor cells in our patient may be the common progenitors of B- and T-cells or more immature progenitors rather than the B-cells or B-cell progenitors.

Another possible explanation is the transdifferentiation from neoplastic cells with lymphoid characteristics to cells with histiocytic characteristics [16]. Some types of tumor cells show transdifferentiation or lineage plasticity [17,18]. Of course, we cannot completely deny the possibility of TCR rearrangement being a false positive because we could not performed gene rearrangement studies on the tumor material obtained at autopsy. Although further investigations are needed to confirm the fact of the gene rearrangements of both the IgH and TCR in HS, it is interesting to consider the origin of the tumor cells in the patient of the present case.

Splenic HS is extremely rare. Patients with splenic HS are reported to present with potentially lethal conditions with unique initial symptoms including thrombocytopenia, anemia, hypogammaglobulinemia, hypoalbuminemia, and splenic tumors [4,19-21]. However, the definitive diagnosis is often delayed and difficult. One of the reasons is that clinicians may not fully recognize the existence of this disease due to its rarity. The second reason is that it is difficult to perform splenectomy for a definitive diagnosis because the disease is associated with a low platelet count. Clinicians should recognize the aggressive nature of HS when they encounter patients with such unique initial symptoms and should try to make a definitive diagnosis

before the progression of the patient's condition.

Conflict of Interest

The authors declare that they have no conflict of interest.

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