Relapse of Acute Myeloid Leukemia Mimicking Autoimmune Pancreatitis after Bone Marrow Transplantation

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Abstract

We herein present the case of a 30-year-old man who developed recurrent pancreatitis and chronic graft-versus-host disease following unrelated bone marrow transplantation for acute myeloid leukemia (AML) with t(16;21)(p11;q22). Autoimmune pancreatitis was initially suspected due to the radiological findings and lack of response to gabexate mesilate and antibiotics. An examination of specimens successfully obtained via endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) demonstrated invasion of AML cells in the pancreatic tissue. EUS-FNA is a less invasive method and a particularly useful diagnostic tool in severely ill patients.

Key words: acute myeloid leukemia, t(16;21)(p11;q22), extramedullary relapse, pancreas, chronic GVHD

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Introduction

Although much progress has been achieved in the treatment of acute myeloid leukemia (AML), extramedullary relapse is problematic, even after hematopoietic cell transplantation (HSCT). Genetic abnormalities of leukemic cells and the extent of graft-versus-leukemia effects are associated with extramedullary tumor formation. AML cells can form both solitary lesions and diffuse infiltrates in various organs that defy attempts at making a definitive diagnosis, particularly in cases of deep-seated organs, such as the pancreas. The difficulty in establishing an early diagnosis contributes to delays in treatment and a poor prognosis.

We herein present a case of AML with t(16;21)(p11;q22) involving pancreatic tumor formation mimicking autoimmune pancreatitis (AIP) after unrelated bone marrow transplantation. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) revealed AML cell infiltration in the pancreas three months before the spread of systemic dissemination. We herein describe the usefulness of EUS-FNA and the unique clinical manifestations observed in this patient.

Case Report

After his regular medical checkup, the patient was referred to our hospital in May 2010 with suspected acute leukemia. A complete blood count showed a white blood cell count of 5,900 cells/μL (myeloblasts: 72% and neutrophils: 13%), a hemoglobin level of 11.7 g/dL and a platelet count of 71,000/μL. The bone marrow was filled with myeloperoxidase (MPO)-positive leukemic blasts, which corresponded to a diagnosis of AML not otherwise specified (AML with maturation, M2) according to the 2008 WHO classification. FLT3 ITD was negative. A chromosome analysis revealed abnormalities, including t(16;21)
Figure 1. An abdominal enhanced CT scan showed diffuse enlargement of the pancreas with delayed enhancement and a capsule-like-rim’ (arrows).

(p11.2;q22) (46,XY,del(6)(q?) t(16;21)(p11.2;q22), add (21) (q22) [6]/46, XY [14]). The leukemic cells were positive for CD13, CD33, CD56 and CD34 according to a flow cytometric analysis. There were no extramedullary lesions. Induction treatment with idarubicin and cytarabine was unsuccessful, and high-dose cytarabine and mitoxantrone (HAM regimen) was thus administered, after which the first remission was achieved.

In December 2010, following consolidation with high-dose cytarabine, HSCT was performed from an HLA allele-matched unrelated female bone marrow donor. The conditioning regimen included cyclophosphamide (60 mg/kg for two days) and total body irradiation (12 Gy). The graft-versus-host disease (GVHD) prophylaxis regimen included tacrolimus and methotrexate. Stage 1 acute GVHD of the skin occurred on day 45, then spontaneously subsided. In May 2011, the patient developed severe chronic GVHD (NIH global severity score: lungs=0, skin=1, throat=3, eye=2, gut=3 and liver=2). Treatment with prednisolone (1 mg/kg) improved these symptoms and was continued until May 2012. The tacrolimus was stopped in April 2012.

In July 2012, the patient developed mild acute pancreatitis. A CT scan revealed mild swelling of the pancreatic body, and treatment with gabexate mesilate and antibiotics ameliorated the symptoms. However, in September 2012, the patient again complained of a high fever, jaundice and severe back pain. The laboratory data showed marked elevation of the serum amylase and direct bilirubin levels, as is often the case with type 2 AIP. To reach a definitive diagnosis, we performed EUS-FNA with the patient’s consent. Although the patient was very ill at this stage, he tolerated the procedure well. A biopsy showed that the pancreatic tissue had been destroyed and replaced by mononuclear cell infiltration (May-Giemsa stain ×10 Fig. 3a and ×40 Fig. 3b). The invasive cells were unexpectedly positive for MPO, CD34 and MIB-1 (Immunostaining ×40 Fig. 3c-e, respectively) and negative for CD3, CD20 and CD138 (Immunostaining ×40 Fig. 3f-h, respectively). No granulocytic epithelial lesions (GELs), a typical feature of type 2 AIP, were observed. A diagnosis of relapsed AML involving the pancreas was thus immunohistologically confirmed. We were unable to obtain enough tissue material for flow cytometric or chromosome analyses using FNA. The patient refused further chemotherapy and requested palliation. To reduce the obstructive jaundice, an endoscopic biliary stent was inserted, which relieved the related symptoms.

In December 2012, leukemic cells appeared in the peripheral blood, with blast cells showing additional chromosomal abnormalities (46,XY,t(16;21)(p11.2;q22), der(16)t(1;16) (q21;q22) [1], 46,idem,del(6)(q?),+16,der(16)t(1;16) [7], 46,XY [3]). Pleural effusion and ascites developed, followed by mechanical ileus due to gastrointestinal invasion by leukemic cells. Opioids were administered for visceral pain, and the patient died of multiorgan dysfunction in February 2013.

Discussion

Fewer than 20 cases of pancreatic AML have previously been reported (2). This condition usually occurs concur-

Figure 2. Endoscopic retrograde cholangiopancreatography showed irregular narrowing of the main pancreatic duct (>1/3 of the total length) without marked upstream dilatation (arrows).

(Fig. 2). These are characteristic radiological findings of AIP. At that time, the patient’s chronic GVHD was classified as mild (throat: 1 and eye: 1) on topical steroid monotherapy. Gabexate mesilate and antibiotics were ineffective, and the patient’s general condition deteriorated. Considering the presence of chronic GVHD and the rarity of pancreatic relapse in patients with AML, acute pancreatitis related to GVHD or type 2 AIP according to the international consensus diagnostic criteria (1) was initially suspected. The serum IgG4 level was not elevated (26 mg/dL; normal <135 mg/dL), as is often the case with type 2 AIP. To reach a definitive diagnosis, we performed EUS-FNA with the patient’s consent. Although the patient was very ill at this stage, he tolerated the procedure well. A biopsy showed that the pancreatic tissue had been destroyed and replaced by mononuclear cell infiltration (May-Giemsa stain ×10 Fig. 3a and ×40 Fig. 3b). The invasive cells were unexpectedly positive for MPO, CD34 and MIB-1 (Immunostaining ×40 Fig. 3c-e, respectively) and negative for CD3, CD20 and CD138 (Immunostaining ×40 Fig. 3f-h, respectively). No granulocytic epithelial lesions (GELs), a typical feature of type 2 AIP, were observed. A diagnosis of relapsed AML involving the pancreas was thus immunohistologically confirmed. We were unable to obtain enough tissue material for flow cytometric or chromosome analyses using FNA. The patient refused further chemotherapy and requested palliation. To reduce the obstructive jaundice, an endoscopic biliary stent was inserted, which relieved the related symptoms.

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Fewer than 20 cases of pancreatic AML have previously been reported (2). This condition usually occurs concur-
Figure 3. Biopsy specimen obtained via endoscopic ultrasound-guided fine needle aspiration. The pancreatic tissue was destroyed and replaced by mononuclear cell infiltration (AB). The invasive cells were positive for CD34, MPO and MIB-1 (C, D and E, respectively) and negative for CD3, CD20 and CD138 (F, G and H, respectively). May-Giemsa stain ×10 (A), ×40 (B) and immunostain ×40 (C-H).

rently with the involvement of the bone marrow and/or peripheral blood. Making a diagnosis is challenging when the pancreatic lesion is solitary. Surgical resection is often performed due to suspected pancreatic carcinoma in such cases. Two case reports have been published regarding relapse involving the pancreas after HSCT, one of a patient with AML with t(8;21) (3), the other of a patient with AML with t(16;21)(p11;q22) (4). In the latter case, which was very similar to the present case, the patient was tentatively diagnosed with AIP and treated with corticosteroids and gabexate mesilate, which temporarily improved the symptoms; however, multiple tumors systematically appeared within three months when relapsed AML was diagnosed. In the present case, EUS-FNA successfully demonstrated the presence of AML cells in the pancreas three months before the occurrence of leukemic dissemination. EUS-FNA has been found to be a safe procedure that contributes to the antemortem histological detection of AML relapse in deep-seated organs.

The recurrent pancreatitis observed in our patient may be a clue to the early diagnosis of leukemic invasion of the pancreas. Nevertheless, making an accurate diagnosis was difficult because acute pancreatitis occurs during the course of HSCT. In one report, 21% of the patients showed elevated levels of serum pancreatic amylase following HSCT and 5% were symptomatic (5). The incidence of pancreatitis is closely associated with that of GVHD and possibly viral infection (6). Pancreatitis caused by calcineurin inhibitors has also been reported (7), although our patient was not administered tacrolimus at onset. The patient had symptoms of
chronic GVHD, which often resemble those of autoimmune diseases. Therefore, a diagnosis of AIP was initially suspected in our patient due to the radiological findings, absence of a response to gabexate mesilate and antibiotics and presence of chronic GVHD. AIP is an autoimmune disorder and is now recognized to be an IgG4-related disease (8, 9). Due to the dramatic response to corticosteroid therapy, making an appropriate diagnosis is important. The typical radiological findings of AIP include diffuse enlargement of the pancreas, as observed in the present case. In regard to diagnostic criteria, the role of histological findings is as crucial as that of radiological imaging and measurements of the serum IgG4 levels, where EUS-FNA plays a pivotal role. EUS-FNA is now established as an accurate and safe technique for obtaining a diagnosis of pancreatic tumors (10). The AML cells in the present patient invaded the pancreatic tissue, similar to the lymphocytes of AIP, which may explain the similar radiological findings.

Cytogenetic and molecular genetic changes have been shown to be involved in the prognosis of AML (11). Due to the poor prognosis of AML with t(16;21)(p11;q22) reported in the literature, the patient underwent HSCT at the first complete remission seven months after the initial diagnosis. Nevertheless, the leukemia relapsed 19 months after HSCT, and he died 33 months after diagnosis. Even with the administration of very intensive therapy, such as HSCT, almost all published cases involved relapse, and the median survival duration is reportedly only a little over one year (12). Extra-medullary lesions are often associated with chromosomal abnormalities and the CD56 expression. Reported AML patients with t(16;21)(p11;q22) developed relapse in sites such as the breast, central nervous system and pancreas. Blast cells are frequently found to be CD56-positive, and some patients exhibit hemophagocytosis of leukemic cells (13, 14), which may be related to the poor prognosis. The genes involved in t(16;21)(p11;q22) are ERG on chromosome 21 and TLS/FUS on chromosome 16, and the FUS/ERG fusion gene plays a pivotal role in promoting leukemogenesis (15, 16). High levels of the ERG expression have also been shown to be an independent risk factor in cytogenetically normal AML patients (17). Conducting an RT-PCR analysis for FUS/ERG may have contributed to the early detection of minimal residual disease (MRD) and systemic relapse, although we did not have such data on this patient. In addition, RT-PCR could have detected MRD in either the pancreatic juice or tissue obtained via FNA, even if we did not obtain enough tissue material for flow cytometric and chromosome analyses.

In summary, we herein reported a rare case of AML involving t(16;21)(p11;q22) that relapsed after HSCT and mimicked autoimmune pancreatitis. Although the use of diagnostic approaches such as surgical biopsies of pancreatic masses may be difficult following HSCT, EUS-FNA is a much less invasive method and a particularly useful diagnostic tool in severely ill patients. Physicians should also be aware of the unique clinical manifestations of AML with t(16;21)(p11;q22), which has a tendency to relapse in extra-medullary sites. At present, an effective cure for these patients remains elusive, even with HSCT. Further increasing understanding of the pathophysiology involved may enable the development of a new therapeutic approach for treating this extremely aggressive type of AML.

The authors state that they have no Conflict of Interest (COI).

References