Abstract

A 25-year-old Japanese man was diagnosed with steroid-resistant Adult Still’s Disease (ASD) in August 2000. No evidence of chronic myelogenous leukemia (CML) had been found during admissions in 2000 and 2001. In August 2002, he was diagnosed with CML with a peripheral white blood count of 69,940/μl and positivity for Philadelphia chromosome and BCR/ABL fusion gene on bone marrow aspiration. No case of CML was reported to develop from ASD. Because a diagnosis of ASD is based on the exclusion of other diseases, we must be cognizant of the possibility of the development of concurrent diseases.

(Key words: chronic myelogenous leukemia, adult Still’s disease, cyclophosphamide, cyclosporine)

Introduction

Adult Still’s disease (ASD) is a cryptogenic disease characterized by hyperthermia, arthralgia, pharynx pain, and a fixed form eruption called salmon eruption, as first reported in 1971 (1). Although the exact mechanism remains unknown, cytokines, such as interleukin-6, interleukin-18, tumor necrosis factor — α, and interferon γ have been reported to affect the pathogenesis and activity (2, 3). The clinical course of ASD can be divided into three main patterns, a self-limited pattern with complete resolution, a polycyclic or intermittent course, and a chronic course characterized by persistently active disease. Cases with steroid resistance are well known to be difficult to treat, but immunosuppressants such as cyclosporine and methotrexate have been shown to be effective (4, 5).

The genetic hallmark of chronic myeloid leukemia (CML) is the Philadelphia (Ph) chromosome, which occurs in at least 90% of the patients. The reciprocal translocation between chromosomes 9 and 22 places the 5’ regulatory domains of the breakpoint cluster region (BCR) gene from chromosome 22 in juxtaposition with the 3’ tyrosine kinase domains of the abelson murine leukemia virus (ABL) gene from chromosome 9. This unique BCR/ABL gene fusion leads to the expression of chimeric bcr-abl messenger RNA and the production of functional BCR-ABL fusion protein (6). The detection of BCR-ABL molecular disease is strongly associated with the onset and relapse (7).

We report a rare Japanese case of CML diagnosed two years after the onset of ASD.

Case Report

A 25-year-old Japanese man was admitted to our hospital with a body temperature of 39°C and pharynx pain in August 2000 (Fig. 1). ASD was diagnosed because all the exclusion criteria were satisfied and the three major criteria (fever of at least 39°C and arthralgia lasting one week or longer, characteristic rash, leukocytosis (10,000/μl or greater) with 80% or more granulocytes), and all minor criteria were met (2). Although the disease was steroid-resistant and serious, remission was attained by a combination of methylprednisolone pulse therapy plus cyclophosphamide and cyclosporine. After discharge, the disease was well controlled by oral administration of prednisolone and cyclosporine, but the patient was again admitted to our hospital because of an ASD relapse in May 2001 and for bacterial pneumonia in March 2002, although the continuance of leukocytosis was observed. Hepatosplenomegaly was not found during these ad-
missions. No apparent evidence of CML was found in the repeated bone marrow aspiration tests during these admissions: Ph chromosome was negative, hyperplasia of element of the granulocyte series was not found, and the neutrophil alkaline phosphatase score was within normal range. Therefore, the continuance of leukocytosis was thought to be related to an ASD.

In July 2002, because of a body temperature of 38°C, pharynx pain, white blood count (WBC) 84,610/µl, and C-reactive protein (CRP) of 23.1 mg/dl, the patient again entered our hospital. He was treated with antibiotics for suspected bacterial diseases of unknown origin. The symptoms improved and he was discharged. However, a slight fever and a feeling of general malaise with an abnormally increased WBC and a remarkable leukocyte shift to the left persisted. When his body temperature reached 39°C, he was hospitalized again on August 26, 2002. On admission, a slight sore throat was noted, but no pyrexic eruption was seen. The superficial lymph nodes were not palpable. Because of an abnormal increase in the WBC (69,940/µl) and an increase of CRP (14.8 mg/dl), we suspected an infectious disease. Peripheral blood tests showed a remarkable leukocyte shift (neutrophils 70.3%, lymphocytes 3.8%, eosinophils 7%, basophils 1.7%, metamyelocytes 5.4%, myelocytes 14.4%, promyelocytes 0.4%, myeloblasts 0.4%) and an increase of platelets. We also found hepatosplenomegaly on abdominal ultrasonography, swelling of the thymus on chest computed tomography, and an accumulation to the liver and the spleen were found on gallium scintigraphy. In the bone marrow aspiration, we found remarkable hyperplasia and granulocytes of each mature stage, without an increase of myeloblasts. The neutrophil alkaline phosphatase score was 390 (99%) and the Ph chromosome positive rate was 100%. By fluorescent in situ hybridization method, the BCR/ABL fusion gene was 92.5%, and we therefore diagnosed CML.

On PCR analysis of the two bone marrow specimens taken in August 2000 and June 2001 (Table 1), no abnormal genes were found in the first specimen, but in the molecular analysis of the specimen from June 2001, 1,300 copies/


μgRNA of major-BCR/ABL were detectable by polymerase chain reaction. The stage classification was chronic. After the diagnosis, treatment with imatinib mesylate was instituted, and the patient achieved a hematologic remission.

**Discussion**

The present patient was diagnosed with CML after a combination treatment with prednisolone and cyclosporine 25 months after the onset of ASD. The CML is thought to have developed at least ten months after the diagnosis by BCR/ABL fusion gene analysis, despite no morphological evidence of CML. This case presents the following issues: is the primary diagnosis of ASD correct, is there any relationship between the ASD and CML, and did the cyclosporine may have an influence on the onset of CML.

ASD is characterized by three major manifestations: fever, rash, and joint symptoms (1). The Yamaguchi criteria for ASD classification are widely used for diagnosis criteria, with 96.2% sensitivity and 92.1% specificity (8). This case satisfied all the exclusion criteria and three major criteria (fever of at least 39°C lasting one week or longer, characteristic rash, leukocytosis (10,000/μl or greater) with 80% or more granulocytes) and all minor criteria were met at the first admission (2). A retrospective analysis showing that BCR/ABL fusion gene was not detectable by nested PCR in bone marrow cells eliminated the possibility that CML was present at the time of ASD onset.

It has been reported that autoimmune disease intrinsically increases the risk of neoplasms such as lymphoma (9), and it is possible that ASD may be an intrinsic risk factor for CML. However, no relationship between ASD and CML has been reported.

Some cases in which cyclosporine were effective in the treatment of refractory and steroid-resistant ASD have been reported (5). The present patient had received prednisolone and cyclosporine as a maintenance treatment for about 2 years. Although cyclosporine does not have an apparently direct carcinogenic or mutagenic effect (10), the use of the drug has been associated with an increased risk of malignancies (11). Recently, there has been increasing evidence that the development of cancer is of concern, at least when cyclosporine is administered at a low dose for intermittent periods and without the concomitant use of other immunosuppressive drugs (12, 13). Except for a recurrence in a bone marrow transplantation patient, only two cases in which leukemia developed after treatment with cyclosporine have been reported (14, 15). In both cases, acute myeloid leukemia (AML) developed within one year of treatment with cyclosporine (one case was a blast crisis after the onset of myelodysplastic syndromes). In the present case, the BCR/ABL fusion gene characteristic of CML developed after 10 months of treatment with cyclosporine and before any morphological abnormality appeared, suggesting that hematopoietic system malignancy might develop soon after cyclosporine treatment. Only rarely have cases been reported.
in which treatment-related CML developed after high-dose chemotherapy, radiation and autologous peripheral blood stem cell transplantation (16). Vincristine, adriamycin, cyclophosphamide, actinomycin-D, carboplatin, etoposide, ifosfamide and local irradiation for the treatment of Ewing’s sarcoma developed secondary CML (16). However, these secondary CML patients were often negative for the BCR/ABL gene, and there are no reports of the use of only immunosuppressive drugs, including cyclosporine and cyclophosphamide, causing secondary CML. Although cyclosporine must continue to be used for intractable ASD, strict follow-up of the patient must be done because of the possible carcinogenic effect.

In conclusion, because ASD is of unknown etiology and diagnosed by exclusion, it is necessary to follow ASD patients carefully to monitor the possibility of other, concurrent diseases.

References