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Case Report
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Chylothorax Under Dasatinib in a Child with Chronic Myeloid Leukemia

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Abstract

A 12-year-old girl was admitted to our hospital for hepatosplenomegaly. She was diagnosed with chronic myeloid leukemia more than 8 years ago. Imatinib was administered orally for 5 years; however, an increase was noted in BCR-ABL1 fusion gene levels and the treatment drug was changed to dasatinib. The BCR-ABL1 fusion gene levels gradually decreased and stabilized; therefore, dasatinib treatment was continued. After 3 years on oral dasatinib therapy, she developed hepatosplenomegaly and chylothorax. After repeated examinations to rule out other causes, dasatinib was discontinued and replaced with nilotinib. Thereafter, the pleural effusion completely resolved, the liver and spleen size normalized and the primary disease was controlled and stabilized.

Keywords: Chronic myeloid leukemia; Dasatinib; Chylothorax; Children

Background

Tyrosine Kinase Inhibitors (TKIs) are the cornerstone drugs for the treatment of Chronic Myeloid Leukemia (CML) and BCR-ABL1 [+] Acute B Lymphocytic Leukemia (B-ALL). Dasatinib, a BCR-ABL1 inhibitor with an IC50 of <1 nmol/L, was approved by the Food and Drug Administration in 2006 and is a potent second-generation TKI for CML and first-line treatment for BCR-ABL1 [+] B-ALL [1]. Dasatinib can effectively inhibit gene mutations, except those in T315I and F317V [2]. Common adverse reactions during dasatinib treatment include fluid retention, rash and diarrhea and pleural effusion, with the latter accounting for 15% to 35% of cases [3,4]. Most cases of pleural effusion are classified as exudate, and chylothorax is extremely rare [5]. To date, only 10 cases of dasatinib-associated chylothorax have been reported, with the majority being adult casas, except for one case in a child after hematopoietic stem cell transplantation [6]. Herein, we report a pediatric case of CML to improve the understanding and management of the adverse effects of dasatinib.

Case Presentation

A 12-year-old girl was admitted to our hospital because of 1 year of gradual abdominal distention, which was noted on ultrasound as hepatosplenomegaly. She had shortness of breath on exertion but no chest tightness.

Eight years ago, she was diagnosed with Chronic Myeloid Leukemia (CML), manifesting as intermittent cough for 10 days and abnormal routine blood test results. At that time, she had no bleeding or ecchymosis; no superficial lymph nodes; had normal physical examination findings in the heart, lung and nervous system and had abdominal distention. The lower margin of the liver was 2 cm below the costal margin, and the spleen was 2 cm below the costal margin, with soft and sharp edges. Routine blood tests revealed the following: White blood cell count of 238.6 × 10^9/L; hemoglobin level of 110 g/L and platelet count of 671 × 10^9/L. Complete bone marrow MICM typing test revealed chromosome 46, XX, t(9; 22)(q34; q11) and fusion gene BCR/ABL1 + P210. The patient was treated with oral imatinib from June 2013, and fusion gene quantification (IS) fluctuated by around 0.1% (Table 1). Five years later, imatinib was gradually increased from 100 mg/day to 250 mg/day due to the increase of fusion gene (IS) to 0.248%, but there was no significant improvement, and then dasatinib was replaced by 40 mg/day. Within 3 years thereafter, the patient had no obvious adverse reactions, her general condition was good and fusion gene quantification gradually decreased to 0.04%.

One year ago, the patient was found to have slightly distended abdomen, and abdominal ultrasound indicated no obvious abnormalities. Reexamination at 3 and 6 months later showed no significant changes in distended abdomen and no obvious discomfort. This is a routine visit. Physical examination upon her present admission revealed the following: Temperature of 36.7°C, heart rate

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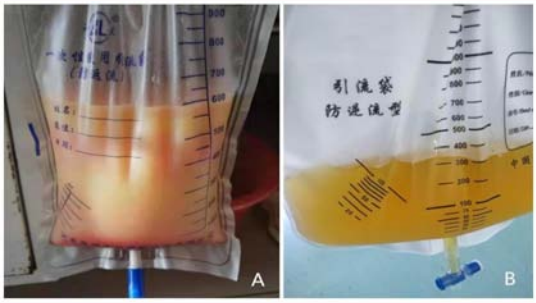

Figure 1: Pleural drainage (A) and Pleural effusion (B) after fasting.

of 92 beats/min, respiratory rate of 20 breaths/min, weight of 26 kg and height of 130 cm. She spoke clearly; cooperated during physical examination; had paler eyelids; had no jaundice, rashes, bleeding spots or petechiae; had pharyngeal congestion; had second-degree bilateral tonsillar enlargement; had clear breath sounds on the left lung, dullness to percussion and decreased breath sounds on the right lower lung field, no dry or wet rales and no obvious three concave sign and had no obvious abnormality on cardiac examination. Physical examination of the abdomen showed distention. The lower margin of the liver was 10 cm below the costal margin and 7 cm below the xiphoid process and the lower margin of the spleen was 2 cm below the costal margin. Abdominal mobility dullness was positive, but there was no direct or rebound tenderness. There was no swelling in both lower extremities. She could freely move her limbs, have normal muscle strength and muscle tone and had no obvious abnormality on neurologic examination.

Chest Computed Tomography (CT) revealed substantial pleural effusion and atelectasis on the right. Abdominal CT revealed enlarged liver and spleen; transient uneven perfusion of the liver parenchyma in the arterial phase; partial intestinal wall thickening and swelling in the abdominal cavity, especially the duodenum and colon; multiple small lymph nodes around the arteries in the mesenteric space; local gallbladder inflammation and oedema of the gallbladder wall; small amount of ascites and multiple exudates from the mesentery and a large amount of pleural effusion on the right. Closed pleural drainage was performed, and a chylous pleural effusion was collected (Figure 1). Pleural fluid analysis revealed the following: Total cell count of $5{,}960 \times 10^6$/L, white blood cell count of 1800×10^6/L, monocyte ratio of 80%, lactate dehydrogenase level of 145 U/L, total protein level of 48.8 g/L, adenosine deaminase level of 16 U/L, glucose level of 5.43 mmol/L and triglyceride level of 9.3 mmol/L. No bacteria, fungi or acid-fast bacilli were observed under the microscope. Pleural fluid culture was negative. The histopathology of pleural fluid showed that there were more fine brittle lymphocytes, mesenchymal cells and monocytes. Immunohistochemical results calretinin (SAN+), CD15(-), CD20(+), CD3(+), CK20(-), CK7(-), Desmin (SAN+), EMA(-), LCA(+), MPO(-). After limiting water intake, intravenous nutrition and diuresis, the pleural effusion gradually cleared on chest radiograph (Figure 1), but the drainage volume did not change significantly.

The series of examinations performed to further clarify the cause of chylothorax revealed no obvious abnormalities on bone marrow aspiration; blood biochemistry, hepatitis screening, ceruloplasmin and immunoglobulin level assessments; ultrasound of the lower extremity vein, hepatic vein, portal vein, jugular vein, heart and central lymphatics; lymphography and thoracic duct imaging. Pulmonary artery pressure was also in the normal range. Considering its adverse effects, dasatinib was discontinued and replaced with nilotinib. The patient developed a minor rash on the face but the pleural effusion and hepatosplenomegaly gradually resolved. After 5 months, repeat chest CT revealed complete absorption of the pleural effusion (Figure 2), and the quantitative level of the BCR-ABL1 fusion gene remained low and in a safe range (Table 1). After 7 months, repeat abdominal ultrasound revealed normal liver and spleen size, and the patient had been in a good condition and living a normal life in campus.

Discussion

Chylothorax is a relatively rare cause of pleural effusion in children and, if left untreated, is associated with high morbidity and mortality. The pleural fluid is usually milky in appearance, with a triglyceride level of >1.24 mmol/L (>110 mg/dL) or the presence of chylomicrons [7,8]. Lymphatic flow can be obstructed because of several etiologies, such as traumatic thoracic duct injury, which may include surgery and subclavian catheterization in pediatric cases. Intrathoracic malignancy, such as lymphoma [9], is the most common cause (60% to 70%) of chylothorax in pediatric cases; other causes include neuroblastoma, teratoma and Wilms tumor. Non-traumatic causes can also obstruct the ducts and lead to chylothorax; these include sarcoidosis, retrosternal goiter, amyloidosis, superior vena cava thrombosis, benign tumors, congenital ductal abnormalities and lymphatic disease. In addition, thoracic duct injury or catheter occlusion after subclavian catheterization may lead to iatrogenic blood flow obstruction secondary to central venous catheter-related thrombosis [10].

The pulmonary adverse events caused by TKIs have been well described in medical literature. Specifically, pleural effusion is a known consequence of TKI therapy. In two major long-term follow-up studies on dasatinib (i.e. DASISION and CA180-034),

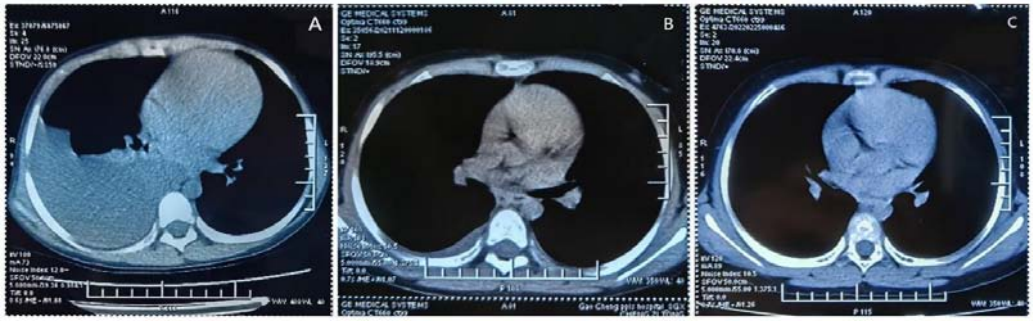

Figure 2: Lung imaging findings at the initial stage of the child's visit (A), re-examination on 20.11.2021 (B) and re-examination on 25.2.2022 (C).

Table 1: Quantitative monitoring of BCR-ABL fusion genes in children.

Inspection date	Specimen type	IS	TKI treatment duration (months)
26-02-2022	Peripheral blood	0.020%	105.57
04-12-2021	Peripheral blood	0.066%	102.77
27-08-2021	Bone marrow fluid	0.015%	99.47
18-08-2021	Peripheral blood	0.040%	99.17
22-04-2021	Peripheral blood	0.039%	95.23
29-09-2020	Peripheral blood	0.032%	88.4
26-11-2019	Peripheral blood	0.032%	78.13
10-08-2019	Peripheral blood	0.067%	74.53
21-12-2018	Peripheral blood	0.100%	66.8
29-08-2018	Bone marrow fluid	0.248%	63
03-07-2018	Peripheral blood	0.213%	61.1
14-11-2017	Peripheral blood	0.065%	53.4
20-07-2017	Peripheral blood	0.147%	49.5
19-04-2017	Peripheral blood	0.099%	46.43
20-12-2016	Peripheral blood	0.103%	42.43

approximately 30% of patients developed exudative pleural effusion anytime from the first year of treatment to up to 6 years of follow-up [11,12]. However, chylothorax cases are rare, especially in children. The pathophysiology of dasatinib-related chylothorax is not fully elucidated. A possible mechanism is the inhibition of PDGFR-β, which regulates angiogenesis, lymphangiogenesis and proliferation of vascular smooth muscle cells, thereby leading to infiltration of lymph into the pleural space [13]. Another possible mechanism is the inhibition of Src kinase, which is well expressed on hematopoietic cells in lung tissue and mediates vascular permeability and stability of the pleural epithelium. At present, new studies have proposed that Tie-2 and cAMP may be involved in hyperpermeability induced by Dasatinib treatment, and the close correlation between Tie-2 and pulmonary hypertension also explains Dasatinib-induced pulmonary hypertension. However, although it has been experimentally confirmed that dasatinib-induced pleural effusion can be prevented by activating cAMP, it may also affect the therapeutic efficacy of Dasatinib and other TKIs [14,15].

Dasatinib-induced pleural effusion can be managed with various clinical therapies, including temporary interruption of therapy, diuretics and/or low-dose steroids and thoracentesis [16]. Symptoms usually resolve after drug discontinuation, but approximately 70% of patients experience recurrent pleural effusion after resumption of dasatinib. In addition, the occurrence of pleural effusion was found to be inversely related with the dose of dasatinib [4,17].

Unfortunately, we have not ascertained the pathogenesis of hepatosplenomegaly in children and did not find any report on dasatinib-induced hepatosplenomegaly. However, the hepatosplenomegaly of the patient in the present case significantly improved after adjustment of the oral medication. We will further explore the pathogenesis and related mechanisms in future follow-up.

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