Case Report

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Discontinuation of imatinib mesylate could improve renal impairment in chronic myeloid leukemia

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Abstract: We aim to report a CML case that had fluid retention and serum creatinine increase under long-term imatinib mesylate (IM) treatment. A 68-year-old woman was diagnosed with chronic myeloid leukemia, and IM was started in 2002 with a dose of 400 mg/day. She had achieved complete hematological, molecular and cytogenetic remission under IM treatment. In September 2015, her creatinine level was 1.7 mg/dl. In May 2016, she was admitted to our hospital with dyspnea. Hypervolemia secondary to fluid retention was detected in our patient. Her laboratory tests results showed hemoglobin 9.7 gr/dl, white blood cell 7.6x10^3/µl, platelet 157x10^3/µl, creatinine 3.2 mg/dl, blood urea nitrogen (BUN) 88 mg/dl. In her X-ray chest film, bilateral pleural effusion was detected. The effusion was detected as transuda. The other reasons of pleural effusion were excluded and the development of pleural effusion was considered secondary to IM. IM was also considered responsible for the acute rise of serum creatinine levels of our patient. Therefore for these two reasons IM was stopped. After the discontinuation of IM, her creatinine levels decreased to 1.6 mg/dl and her pleural effusions disappeared. IM treatment was considered as the reason of serum creatinine elevation since serum creatinine levels decreased after the discontinuation of IM. All of the side-effects disappeared after discontinuation of IM.

Keywords: Matinib mesylate; Renal impairment

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1 Introduction

Imatinib mesylate (IM) was the first tyrosine kinase inhibitor (TKI) which was introduced in chronic myeloid leukemia (CML) treatment [1]. IM targets c-kit, a key molecular abnormality in CML and gastrointestinal stromal tumors. TKIs are generally very well tolerated; most side effects are mild and the majority of cases can continue therapy without interruption [2]. The course of the disease had significantly improved with IM, however there are some side-effects related with long-term IM treatment. Many drugs can damage kidney function in acute and chronic myeloid leukemia [3]. Systemic, cardiovascular, pulmonary and other complications such as rhabdomyolysis may be encountered in CML patients who were given TKI treatment [4]. An increase in serum creatinine levels may be seen during IM treatment [5]. IM-associated fluid retention has also been defined in the literature [6]. Herein, we aim to report a CML case who had fluid retention and serum creatinine increase under long-term IM treatment. Acute and chronic kidney injuries have been rarely reported in cases that were treated with prolonged period IM for CML.

2 Case report

A 68 year old woman first time applied to hospital with fatigue and weight loss in 2002. She had no previous diseases. Her physical examination was normal. Laboratory tests results showed white blood cell 32.6x10^3/µl, hemoglobin 10.1 gr/dl, platelet 340x10^3/µl, AST 35 U/l, ALT 25 U/l, creatinine 1.1 mg/dl, blood urea nitrogen (BUN) 15 mg/dl. Leukoeryroblastosis was observed in her peripheral blood smear. Therefore, bone marrow aspiration and biopsy with cytogenetic analysis were performed. Bone marrow examination favored chronic myeloid leukemia (CML) with blasts fewer than 5% and cytogenetic analysis had revealed t(9:22) Philadelphia chromosome. Our

patient was considered as a chronic stage CML patient so IM was started in 2002 with a dose of 400 mg/day. She had achieved complete hematological, molecular and cytogenetic remission under IM treatment. In 2006, her laboratory tests results showed hemoglobin 11.4 gr/dl, white blood cell 4.6x10^3/µl, platelet 213x10^3/µl, creatinine 1.0 mg/dl, BUN 14 mg/dl, AST 21 U/l, ALT 19 U/l. Her urinary investigation was totally normal. She was diagnosed with essential hypertension in 2008 and ACE-inhibitor was given. Her arterial blood pressure was around 120/80 mmHg. In 2008 her laboratory tests results showed hemoglobin 10.4 gr/dl, white blood cell 7.8x10^3/µl, platelet 248 x10^3/µl, creatinine 1.1 mg/dl, BUN 18 mg/dl, AST 27 U/l, ALT 27 U/l. In 2009 her creatinine level increased to 1.3 mg/dl and she was diagnosed with chronic kidney disease. In 2010, her total cholesterol level was 273 mg/dl and her LDL cholesterol level was 176 mg/dl. Therefore she was diagnosed with primary hyperlipidemia, and simvastatin treatment was started. In 2014, her bone marrow investigation was normal. In September 2015, her creatinine level was 1.7 mg/dl. In May 2016, she applied to our hospital with dyspnea. She was using daily IM pills regularly since 2002, for approximately 14 years. Hypervolemia secondary to fluid retention was detected in our patient. Her laboratory tests results showed hemoglobin 9.7 gr/dl, white blood cell 7.6x10^3/µl, platelet 157x10^3/µl, creatinine 3.2 mg/dl, BUN 88 mg/dl, AST 30 U/l, ALT 18 U/l. In her X-ray chest film, bilateral pleural effusion was detected (Figure 1). Thoracentesis was performed in order to drain the effusion. The effusion was detected as transuda. The other reasons of pleural effusion were excluded and the development of pleural effusion was considered secondary to IM. IM was also considered responsible for the acute rise of serum creatinine levels of our patient. Therefore for these two reasons IM was stopped and she was given no tyrosine kinase treatments. However she was closely monitored with laboratory tests. After the discontinuation of IM, her creatinine levels decreased to 1.6 mg/dl and her pleural effusions disappeared. She was discharged from hospital and she is still under close observation in our clinic.

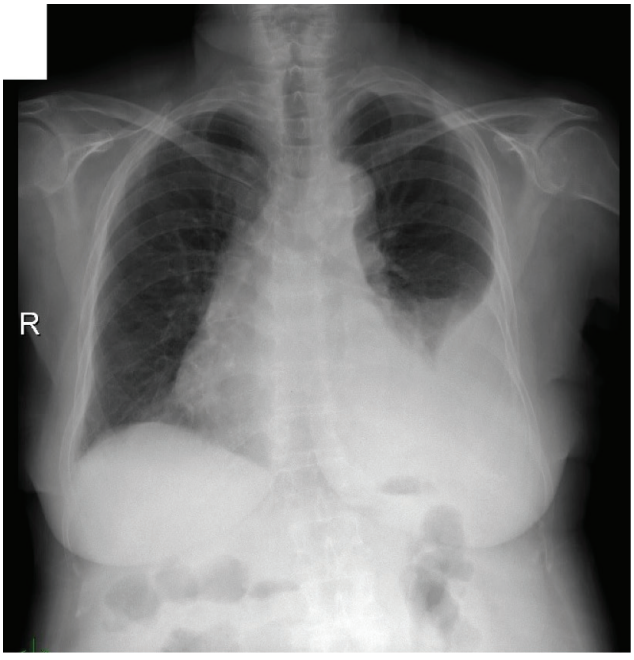

Figure 1: Bilateral pleural effusion under IM treatment

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from patient included in this study.

3 Discussion

IM is the first TKI introduced in CML treatment [1]. Renal failure is an extremely rare adverse event of IM [7]. In the literature it was shown that long-term follow-up of cases who were initially given IM suggests that approximately 60 percent will remain on IM at five years. While many will have persistent low-grade side effects (fatigue, arthralgias, and diarrhea), new toxicities have not emerged with longer follow-up [8]. Similarly our patient were under IM treatment for 14 years without encountering disease relapse or

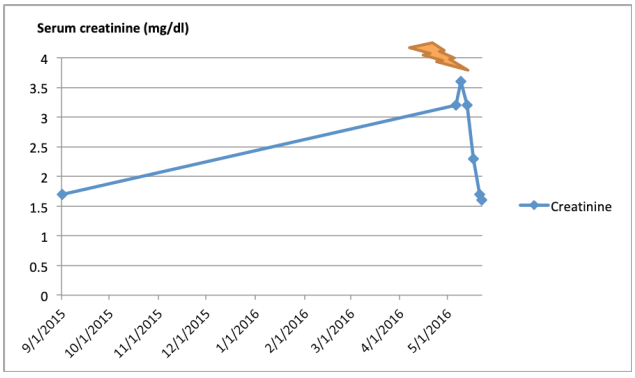

Figure 2: Serum creatinine levels of the patient
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intolerance. Pleural effusions were mostly seen with dasatinib, however it can also occur under IM treatment [9]. It is also well-known that fluid retention may occur with IM treatment [6]. Likewise, IM related fluid retention and pleural effusion had occurred in our patient. Moreover IM treatment can be the reason of serum creatinine elevation by inhibiting tubular secretion of creatinine in a reversible fashion [5]. Acute and chronic kidney injury has been rarely reported in cases that were treated with prolonged period IM for CML [10-12]. In the literature the mean reduction in creatinine clearance was estimated as 2.77 mL/min/1.73 m2 per year [10]. The potential mechanisms of kidney injury by IM include tumor lysis syndrome, acute tubular injury, rhabdomyolysis and inhibition of tubular secretion of creatinine may also be a contributing factor to an observed rise in serum creatinine [13-16]. Also leukemic infiltration into the kidney should be always kept in mind when a patient with CML encounters renal function loss [17]. Similarly, although our patient has a history of hypertension, IM treatment was considered as the reason of serum creatinine elevation since serum creatinine levels decreased after the discontinuation of IM (Figure 2). As a result our patient had encountered several side effects of IM treatment at the same time, which were fluid retention, pleural effusion and serum creatinine elevation. All of the side-effects disappeared after discontinuation of IM. To conclude, IM treatment may result in several reversible side effects such as fluid retention, pleural effusion and serum creatinine elevation and those adverse effects are manageable if patients were managed carefully.

Conflict of interest statement: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/ or affiliations relevant to the subject matter or materials included.

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