Am J Blood Res 2021;11(6):600-604
www.AJBlood.us /ISSN:2160-1992/AJBR0136388

Case Report

Imatinib-induced retroperitoneal fibrosis in a child with chronic myeloid leukemia: a case report

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Received June 15, 2021; Accepted November 17, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: A 12 year old boy with chronic myeloid leukemia (CML) presenting with bilateral pitting pedal edema and abdominal distension after about 41 months of imatinib therapy and was diagnosed to have retroperitoneal fibrosis (RPF) based on imaging and biopsy findings. He was found to have bilateral hydroureteronephrosis needing double-J stenting to the more severely affected right ureter. Imatinib was briefly interrupted and restarted later due to rising transcript levels and unavailability of other alternatives at that time which was later substituted by dasatinib once generic versions became available. Child remains asymptomatic after 18 months of DJ stenting. RPF is a rare complication of imatinib this being the second case reported in the literature.

Keywords: Imatinib, pediatric CML, retroperitoneal fibrosis

Introduction

The advent of tyrosine kinase inhibitors (TKIs) like imatinib has revolutionised the treatment of chronic myeloid leukemia (CML), leading to long-term disease free remissions without allogeneic stem cell transplantation. Pediatric use of imatinib was approved in 2003 by the US-FDA, many children and young adults have since been treated for various indications including CML, Philadelphia positive ALL etc. [1]. CML is a clonal disorder occurring as a result of reciprocal translocation between the genes on chromosome 9 and 22. The translocation results in a fused BCR-ABL oncoprotein with increased tyrosine kinase activity. Imatinib selectively inhibits BCR-ABL tyrosine kinase resulting in sustained and prolonged molecular responses. Although imatinib is a well-tolerated drug in the pediatric population it has been associated with various adverse effects like edema, nausea, vomiting, myalgia, rash, hemorrhage, cytopenia, most of which are mild (less than grade 2) and reversible and not commonly needing dose reduction or treatment interruption. Long term toxicities like growth retardation and bone health is of great concern especially in children [2]. Very little is known about the uncommon side effects of imatinib in children, a drug predominantly used in CML, a rare pediatric malignancy. We present one such rare toxicity, imatinib associated retroperitoneal fibrosis which we came across in a 12 year old boy, following long term use of TKIs [3, 4]. Written informed consent was obtained from the patient regarding anonymised use of the medical details, pathological and radiological images for academic use including publication in medical journals.

Case

A 12 year old boy presented with fever and left sided abdominal pain for 1 month. On examination, he had mild pallor and splenomegaly. His complete blood count (CBC) revealed hemoglobin 9.1 g/dL, total leucocyte count 267000/mm^3, platelets 844000/mm^3 with peripheral blood smear showing 2% blasts and shift to left with myeloid precursors. Bone marrow aspirate was compatible with CML in chronic phase (CML-CP) morphologically and cytogenetically. He was started on hydroxyurea (50 mg/kg/day) and imatinib at 340 mg/m^2/day (400 mg once

daily). Hydroxyurea was later stopped when total leucocyte counts fell below 10,000/mm^3.

He attained complete hematological response (CHR), complete cytogenetic response (CCyR) and major molecular response (MMR) at 3, 5 and 12 months, respectively. He had optimal response to therapy and was followed with BCR-ABL1 Real-time Quantitative Polymerase Chain Reaction (RQ-PCR) transcripts in peripheral blood. He developed skin hypopigmentation, vitamin D insufficiency and myalgia while on imatinib attributable to known imatinib-related toxicities and was managed accordingly.

After 41 months from initiation of imatinib, he presented with mild abdominal pain and increasing bilateral lower limb swelling for a duration of 2 months. On examination bilateral pitting pedal edema was noted. He also had mild abdominal wall edema along with dilated superficial veins. His CBC, renal and liver function tests were within normal limits though the erythrocyte sedimentation rate (ESR) was elevated at 87 mm/hr. Ultrasound of abdomen showed bilateral hydronephrosis (Right > left) and a fibrotic mass in the retroperitoneum.

Differentials considered were disease progression (new onset extramedullary myeloid tumour), infections like tuberculosis (TB) or retroperitoneal fibrosis (RPF). Contrast enhanced CT abdomen revealed ill-defined poorly enhancing soft tissue with the bulk of the tissue in retroperitoneal region, encasing aorta, iliac vessels, ureters and luminal narrowing of infrarenal IVC and renal veins. It was also encasing SMA and both the renal arteries (**Figure 1A** and **1B**). Bilateral hydronephrosis (right > left), with right kidney showing post obstructive changes were also noted. CT-guided biopsy of the retroperitoneal mass was non-diagnostic and revealed only cores of skeletal muscle and fibro-collagenous tissue. However, TB and malignancy/disease progression were ruled out.

Imatinib induced retroperitoneal fibrosis was suspected and imatinib was stopped. He was started on hydroxyurea as an interim therapy. He was managed conservatively with right sided double J stenting (**Figure 1C-E**). He improved symptomatically with the above measures. He was monitored with ESR, CRP and periodic imaging. Repeat CT of the abdomen after 8 weeks revealed decrease in the extent and bulk of the retroperitoneal tissue. Removal of the double J stent is planned if he continues to remain asymptomatic.

His RQ-PCR for BCR-ABL transcripts post 8 weeks of interruption of TKI was rising (0.013 to 0.13%). Due to financial constraints for long-term switch to a 2nd or 3rd generation TKI, imatinib was restarted after 11 weeks of interruption following extensive counseling regarding the chances of recurrence of RPF. His RQ-PCR repeated after 6 months of imatinib showed 1 log reduction (0.05%). Presently, he is asymptomatic for 18 months after double J stenting and in major molecular remission (MMR), on track for stem cell transplant and planned for interim second generation TKI in case of recurrence of RPF. After about 12 months of restarting, imatinib was replaced by dasatinib, once the generic formulations became available at a lower cost.

Discussion

Long term use of imatinib though well tolerated can lead to a series of off-target adverse effects which need routine monitoring and follow up. Fluid retention, gastrointestinal symptoms, joint pain, muscle cramps, skin rash are the common adverse events that resolve over time or after a brief drug holiday. Uncommon, delayed adverse events associated with use of imatinib, reported mainly in adults are mild to moderate liver dysfunction, cardiac adverse events like congestive heart failure, acute renal failure, partial Fanconi syndrome, imatinib induced porphyria, dermatologic adverse events like maculopapular exanthema, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, purpuric vasculitis, etc. [5]. Our patient developed RPF, which is an extremely rare complication of long-term use of imatinib and happens to be the second case of imatinib induced RPF reported in literature (and the first in English language). Our unit is one of the largest pediatric cancer units in the country seeing about 8-10 new patients with pediatric CML annually and currently more than 160 patients on TKI for pediatric CML are following up with us, which is probably one of the largest single-centre cohort of pediatric CML in our country and the region. Long term follow-up of a large number of children with pediatric CML enables

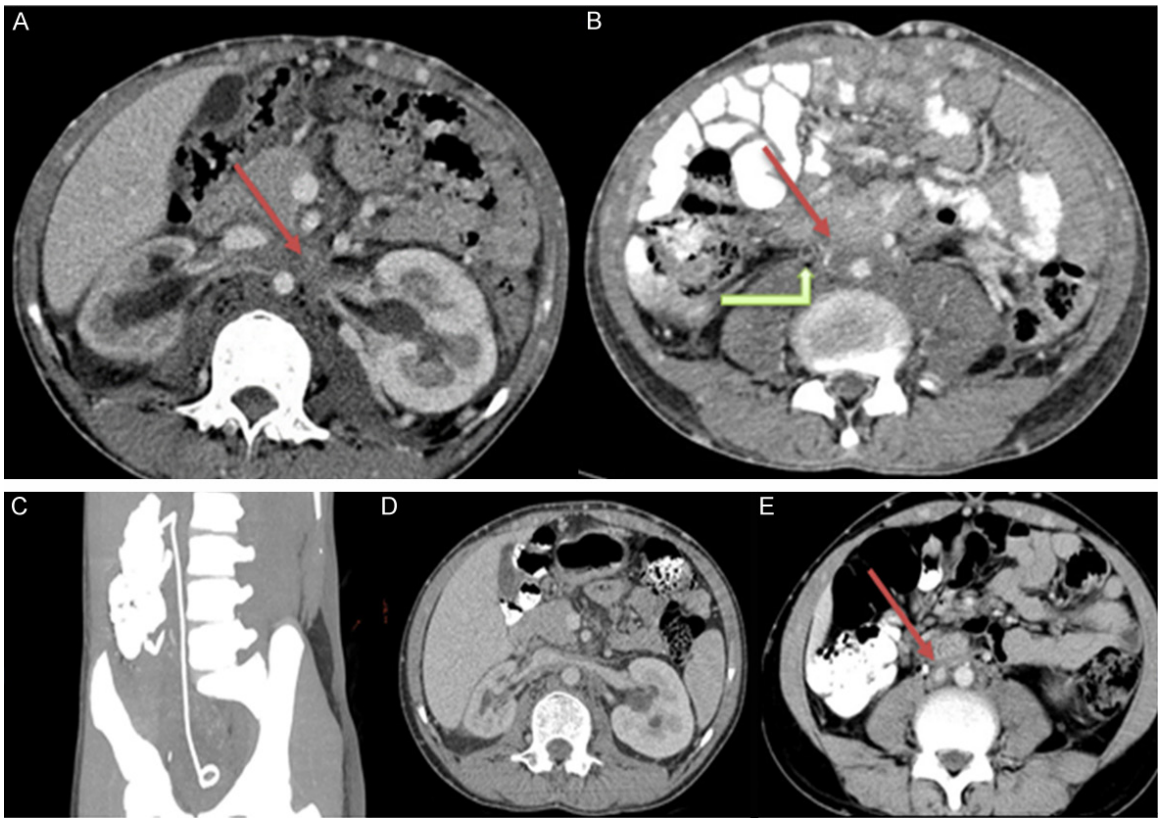

Figure 1. Radiological findings in our patient at diagnosis of RPF (A, B), with the double J stent in-situ (C) and 2 months after stopping imatinib (D, E).

us to encounter rare complications of TKI use as reported in this case report.

RPF is a systemic fibro-inflammatory disorder which most commonly spreads around the abdominal aorta, iliac arteries and into the adjacent retroperitoneum where it causes ureteral obstruction. RPF is rare in pediatric population with only 23 cases reported in literature [6]. They usually manifest with bilateral hydronephrosis, progressive renal failure, hypertension and elevated ESR. Our patient was normotensive and did not have deranged renal function, probably because the left kidney was relatively spared.

Idiopathic RPF constitutes more than 75% of the cases and secondary forms includes cases secondary to malignancies, infections, drugs or radiotherapy [7]. RPF secondary to malignancy has been associated mainly with retroperitoneal metastasis seen in carcinoma of the prostrate, breast, colon or of a primary retroperitoneal tumor such as Hodgkin's and non-Hodgkin lymphomas, inflammatory myoblastic tumor, carcinoids and various types of sarcomas [8]. RPF secondary to CML is not known or reported in literatures. RPF has been associated with drugs like ergot alkaloids, dopamine agonists, beta-blockers, chemotherapeutic agents like carboplatin and methotrexate, biological agents, such as etanercept and infliximab [9].

Among TKIs, a single case of imatinib induced RPF has been reported very recently from China, where a 11 year old girl child had developed intermittent vomiting and engorged abdominal veins after 12 months of initiation of imatinib. Abdominal CT was suggestive of RPF. Unlike our patient, she was continued on imatinib on same dose (400 mg/day) and started on prednisolone (20 mg/day). She gradually improved both clinically and radiologically after four and a half months of prednisolone, which was tapered and continued at a maintenance dose of 5 mg/day. Steroids were not tried in our patient as there was symptomatic improvement following cessation of imatinib, stenting of the ureter as well as lack of evidence for use

of steroids for this indication. The plan is to consider prednisolone if there is any progression in signs and symptoms. The availability of generic forms of dasatinib in India in the last few months has helped us in switching to dasatinib though we are unsure if retroperitoneal fibrosis is a class side-effect as a single case of nilotinib induced RPF has also been reported in a 32 year adult who was on nilotinib maintenance therapy post-myeloablative stem cell transplant [4].

RPF is diagnosed usually by imaging, contrast enhanced CT or MRI. Histological confirmation is difficult, mainly because of the inaccessibility of the mass and difficulty in procurement of sufficient tissue for histopathology. The percentage of biopsy-proven cases varies between 24%-77% in various reports [10].

Though it is not easy to prove if imatinib is the sole cause behind development of RPF in our patient, long term use of imatinib, lack of other predisposing factors, previous reports of TKIs induced RPF and improvement in the symptoms and size of the retroperitoneal mass upon discontinuation of imatinib prompted us to attribute it to the long-term use of imatinib.

Obstructive uropathy is the most common complication in any form of RPF and the initial and foremost treatment is relieving the ureteric obstruction. Initially, conservative approaches like ureteral stents or nephrostomies are done to relieve the obstruction. Surgical or laparoscopic ureterolysis is reserved for those patients in whom conservative techniques have failed. Medical management like glucocorticoids and immunomodulators, though used in certain selected cases as mentioned earlier are not clearly beneficial especially in secondary forms of RPF and were not tried in our patient [11]. In drug-induced RPF, withdrawal of the drug often results in resolution of the disease. The outlook of patients with adequate renal function is good if diagnosed and managed appropriately at an early stage.

Conclusion

Patients on long-term imatinib therapy need to be carefully followed for atypical and rare complications for the sake of early detection and prompt treatment before irreversible damage sets in.

CT of retroperitoneal fibrosis

(**Figure 1A**, **1B**) Axial contrast enhanced CT images show an ill-defined poorly hypoenhancing retroperitoneal soft tissue (red arrow in **Figure 1A**) that is iso-attenuating to muscle. It extends from the level of SMA inferiorly into the pelvis along the iliac vessels. The mass encases the abdominal aorta, its branches, IVC and renal vessels and causes anterior displacement of supra-renal IVC (arrow in **Figure 1A**). Moderate right hydronephrosis and proximal hydroureter is seen due to encasement of mid segment of right ureter (green coloured arrow in **Figure 1B**). There is encasement of the infra-renal IVC with severe luminal narrowing (red coloured arrow in **Figure 1B**).

Figure 1C. Double J stenting on the right side to relieve the ureteric obstruction. Repeat CT abdomen, 2 months later after stopping Imatinib. (**Figure 1D**, **1E**) Axial contrast enhanced CT images show decrease in ill-defined poorly hypoenhancing retroperitoneal soft tissue. The distal IVC (red arrow in image **Figure 1E**) can be visualized in this scan.

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