# Imatinib mesylate-induced kidney injury in the treatment of a gastrointestinal stromal tumor

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## ABSTRACT

Gastrointestinal stromal tumors (GISTs) are a rare type of neoplasm arising within the gastrointestinal tract. Current treatment guidelines employ target-based therapy and adjuvant treatment with imatinib mesylate. We report a case of imatinib-induced renal injury in a 48-year-old male undergoing adjuvant chemotherapy after surgical resection of a rectal GIST. Upon initiation of imatinib therapy, the patient's serum creatinine steadily rose and met criteria for kidney injury after twenty months of therapy. Drug discontinuation led to a normalization of renal function, but upon reinitiating therapy the serum creatinine sharply increased again. The patient's recurrent acute renal injury led to indefinite drug discontinuation. Imatinib toxicities have been well studied; however, there are no reports to date noting its renal effects in the GIST patient population. This case report highlights imatinib as therapy for GISTs, describes an event of imatinib-induced renal injury, and reviews current treatment modalities.

**Key Words:** Imatinib mesylate, Gastrointestinal stromal tumors, Nephrotoxicity

## 1. INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are a rare type of cancer which primarily affect the stomach and small intestine, but can occur anywhere throughout the alimentary tract.[1] Although considered a rare cancer, incidence in the United States is reported to be as high as 4,000 cases annually[2] with a general predominance in males aged 50-79 years.[3] With advances in our understanding of the molecular mechanisms at play in GIST development and progression, our treatment modalities have progressed from surgical resection alone to surgical resection with target-based adjuvant chemotherapy in patients with locally confined disease.

A 1998 study by Moriyama et al. first reported a c-kit gain of function mutation of GISTs.[4] Subsequent studies have shown that 85% of GISTs harbor an activating mutation in KIT, 3%-5% harbor a mutation in PDGFR$\alpha$, and rare cases harbor mutations to SDH and BRAF.[5–7] These findings allowed for the application of previously developed molecular inhibitors of KIT and PDGFR$\alpha$ to be applied to the treatment of GISTs for both adjuvant treatment after primary resection and metastatic disease with a proven survival benefit.[8,9] One such agent is imatinib mesylate, which was first developed for use in chronic myelogenous leukemia (CML). In the past decade, we have seen phase I, II, and III clinical trials showing the efficacy of imatinib in treatment of GISTs.[10–12]

Typically, treatment of GISTs with imatinib can range from 12 weeks to several years.[13,14] For this reason, establishing the systemic toxicities of the drug is important. Safety and

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tolerability has been well established in the CML population, but there are limited reports profiling nephrotoxicity in the GIST population.[14] We report a case of a 48-year-old male treated for a rectal GIST with surgical resection followed by adjuvant imatinib who developed acute renal failure as a result of imatinib toxicity.

## 2. CASE PRESENTATION

The patient is a 48-year-old male with a past medical history of left lower extremity deep vein thrombosis and acute pancreatitis who was referred to our academic center by his primary medical doctor for a rectal mass confirmed on an outpatient CT scan. Subsequent MRI revealed a 3.8 cm mass in the rectum 2.5 mm proximal to the anal sphincter (see Figure 1). FNA biopsy of the submucosal rectal lesion revealed cytology consistent with a rectal GIST.
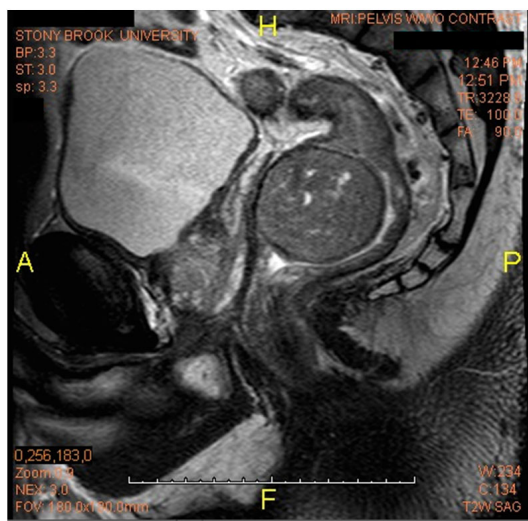


**Figure 1.** Pre-operative MRI Pelvis with Contrast: Subserosal enhancing soft tissue mass within the rectum, measuring 3.8 cm × 3.8 cm

The patient underwent surgical resection with an ultra-low anterior resection and protective loop ileostomy with no perioperative complications. Surgical pathology showed a low-grade rectal GIST with a tumor size of 5.5 cm (see Figure 2). The patient was referred for adjuvant chemotherapy and imatinib mesylate was started at a dose of 400 mg daily. At the start of therapy, the patient had a baseline creatinine (Cr) of 0.76 mg/dl. Initially, the patient tolerated the drug well, with no reported or observed anemia, edema, gastrointestinal upset, fatigue, rash, or hepatic dysfunction. He denied any urinary symptoms and reported no change in appetite or weight loss. His treatment course remained unremarkable – except for a mild serum Cr elevation that did not meet criteria for acute kidney injury (AKI) – until twenty months into treatment when routine lab work showed an acute rise

in his serum Cr to 1.22 mg/dl (see Table 1, Figure 3). The drug was held on this office visit, and at routine follow-up nine weeks later the patient's Cr returned to baseline. Given the patient's tolerance to the drug throughout the treatment course, imatinib was restarted at the previous dose of 400 mg daily after a discussion with the patient. Eight weeks later, laboratory evaluation revealed an AKI with a rise in serum Cr to 1.27 mg/dl. After thorough discussion with the patient and his family, imatinib was discontinued, the patient's Cr normalized, and he has since remained disease free.
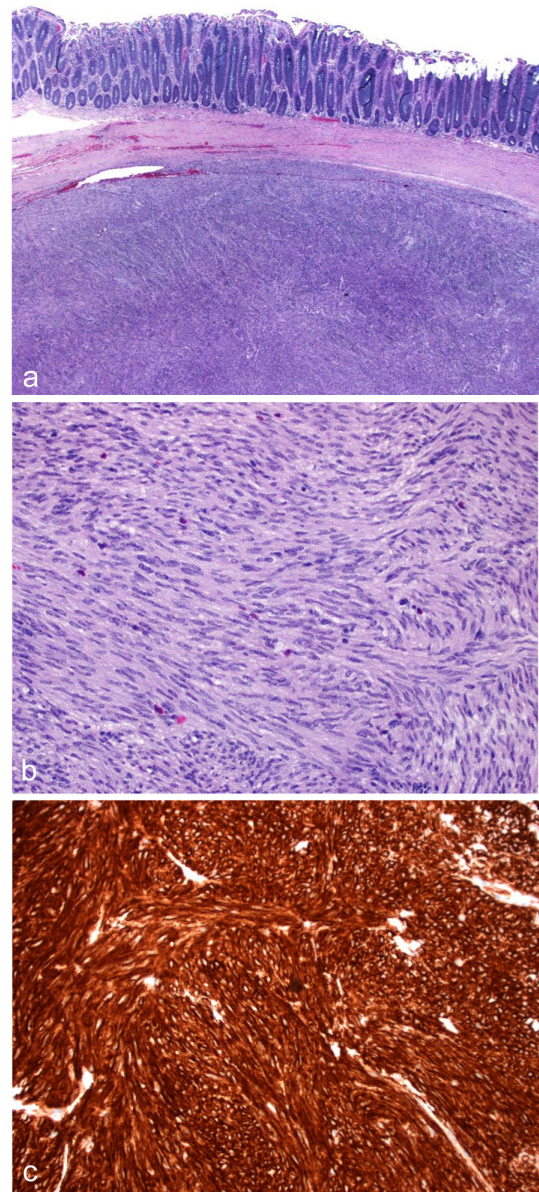


**Figure 2.** Surgical Pathology. a. Rectal GIST with adjacent rectal mucosa (20× magnification); b. The tumor showed characteristic GIST spindle cell morphology with interlacing fascicles and a low histologic grade (mitotic rate of ≤ 5/50 HPF); c. Positive CD117 (c-kit) staining (100× magnification)
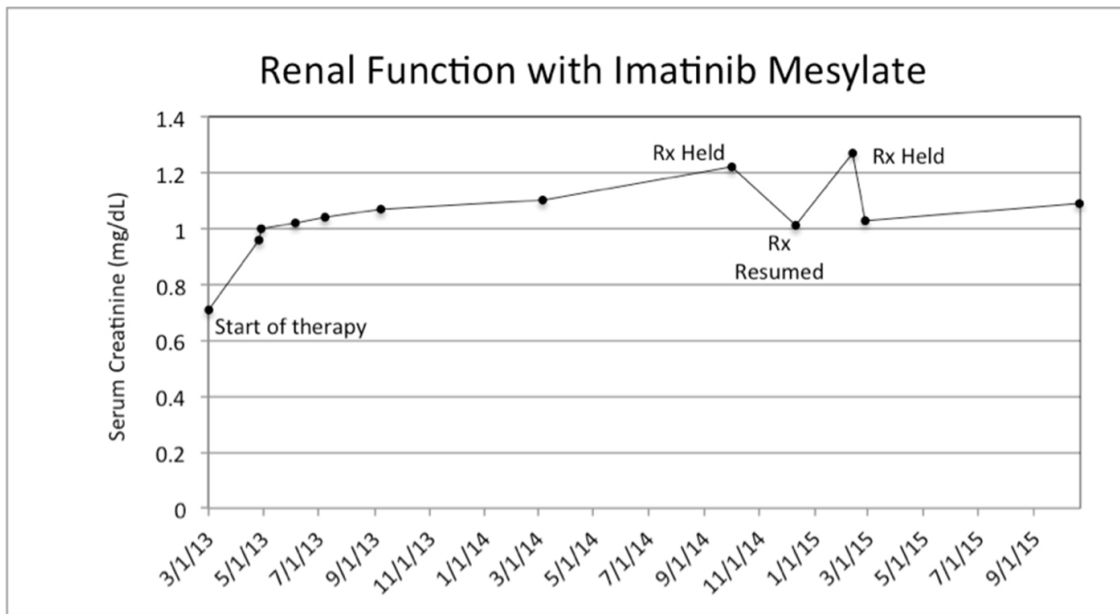
**Figure 3.** Time series plot of the patient's serum creatinine (Cr) levels throughout his treatment course with imatinib mesylate. Initiation of therapy presented with a mild rise in Cr from baseline and criteria met for acute kidney injury at 10/1/2014 and 2/11/2015, respectively. Upon discontinuation of therapy at both instances, the renal injury resolved

**Table 1.** Serum creatinine and BUN levels throughout treatment course with imatinib mesylate

| Serum Creatinine, BUN Throughout Treatment | | |
|---|---|---|
| Date | Creatinine (mg/dl) | BUN (mg/dl) |
| 3/1/2013 | 0.76 | 7 |
| 4/26/2013 | 0.96 | 9 |
| 4/28/2013 | 1.00 | 4 |
| 6/5/2013 | 1.02 | 12 |
| 7/17/2013 | 1.04 | 14 |
| 9/18/2013 | 1.07 | 13 |
| 3/5/2014 | 1.10 | 16 |
| 10/1/2014* | 1.22 | 18 |
| 12/10/2014 | 1.01 | 15 |
| 2/11/2015* | 1.27 | 16 |
| 2/25/2015 | 1.03 | 13 |
| 10/21/2015 | 1.09 | 15 |

*Note.* Dates of medication suspension signified by (*).

## 3. DISCUSSION AND LITERATURE REVIEW

GIST is considered a rare disease, but it is one of the most prevalent sarcoma subtypes and is the most common primary mesenchymal neoplasm of the gastrointestinal tract.[14] As demonstrated in our case, complete surgical resection followed by adjuvant target-based therapy provides optimal outcomes. A review of current guidelines suggests adjuvant imatinib therapy for a minimum of three years in patients with completely resected, primary, higher-risk GISTs.[8,15]

Prior to the advent of imatinib and its application to GIST tumors, surgical resection alone was the mainstay of treatment with reported median survival in the range of 10-23 months.[16,17] The addition of imatinib as adjuvant or neoadjuvant therapy has increased the median survival to 55-60 months.[12,18] Based on this evidence, imatinib mesylate has become the first-line therapy for advanced GISTs as well as for adjuvant treatment. Other targeted agents such as sunitinib and regorafenib are used as second-line agents for metastatic disease, but have not been proven to be of benefit in the adjuvant setting. Current opinion is that imatinib is generally well tolerated and that most side effects are mild to moderate in severity.[19] For this reason, treatment interruption secondary to drug toxicity, as occurred in our case, is a rare occurrence.[11,12,19] The reported rate of treatment discontinuation due to toxicity in the phase II adjuvant study[11] was not reported and < 6% in the phase III study.[13] In neither study was nephrotoxicity observed as an adverse effect of the drug. To the knowledge of the authors of this report, we present the first published case to date of imatinib-induced nephrotoxicity in the GIST patient population.

Demetri et al. have published two comprehensive studies evaluating and highlighting the efficacy and safety of imatinib in metastatic GIST.[11,14] In these studies, the most common adverse events were edema (74%), nausea (52%), diarrhea (45%), and musculoskeletal pain (40%). There have been reports of renal toxicities with target-based therapies in

the past[20] and specifically with imatinib,[21] but all within in the CML population. The molecular mechanism behind the imatinib-induced nephrotoxicity has not been fully elucidated. A 2010 study suggested renal leukemic infiltration from CML disease progression as a mechanism by which the renal dysfunction may occur.[22] A number of studies have suggested that inhibition in PDGF-R signaling on the glomerulus, arteries, tubules, and interstitium in renal cells by imatinib prevents renal tubular cell regeneration.[23, 24] Further studies have provided data suggesting that PDGF-R inhibition can lead to renal fibrosis.[25] These processes have been proven in animal models, but have yet to be fully agreed upon as the sole contributor to the nephrotoxicity of imatinib mesylate. More relevant to this case report, a recent retrospective investigation of renal function in CML patients on imatinib therapy suggests a blunting of tubular creatinine secretion by imatinib mesylate itself.[26] The investigators also demonstrate a restoration of tubular secretion of creatinine on cessation of the drug therapy with an appropriate decrease in serum creatinine. Interestingly, this effect was reversible in our patient as well.

The patient presented in this case report had no prior renal dysfunction, no history of chronic kidney disease, no episodes of diarrhea leading to volume depletion, and no contrast or nephrotoxic agents administered around the time of the identified AKI. Theoretically, the commonly observed imatinib toxicity of peripheral edema could be so dramatic that fluid-third-spacing could lead to intravascular volume depletion and renal hypoperfusion. However, the patient did not exhibit any signs of fluid retention at any point during treatment. Moreover, the patient's only medication was imatinib mesylate and there were no other confounding factors as to the cause of the renal injury. Given the lack of in vivo data characterizing renal injury due to imatinib, the rate by which the renal injury is expected to occur is unclear. In the presented case, the serum creatinine sharply rose at drug initiation, but did not meet criteria for AKI. Thereafter, the serum creatinine steadily rose over a course of six months and the drug was held after the increase in serum creatinine was $\geq 1.5$ times the baseline. Interestingly, drug re-initiation led to a sharp rise in the serum creatinine, which ultimately led to indefinite drug cessation. It remains unclear why the rate of renal injury occurred in distinct fashions between drug initiation and re-initiation.

With regards to drug discontinuation in rectal GISTs, the 2010 National Comprehensive Cancer Network (NCCN) Task Force stratified the risk for progressive disease for patients with GISTs based on tumor site, size, and mitotic index from data which included 111 rectal GIST cases.[27] This patient's rectal GIST measured 5.5 cm in size with a mitotic rate of $\leq 5$ per 50 high-power fields, which carries a moderate (24%) risk of disease progression.[27, 28] The decision to discontinue therapy in this patient was vital because, although the rise in the serum Cr was gradual, the criteria for acute renal injury was met and drug continuation carried the risk of developing fulminant renal failure. Full renal failure and uremia has been reported in CML patients on imatinib.[29] Clinicians have recently reported that transitioning from imatinib mesylate to second-generation tyrosine-kinase inhibitors after incidence of renal injury controls disease progression as well as allows recovery of renal impairment; however, all these cases were in the CML population.[30] Current practice guidelines for imatinib therapy in the treatment of CML recommend monitoring creatinine and making dose adjustments to avoid long-term toxicity. Our case highlights the employment of the same principle in the management of GIST and presents renal toxicity as a cause of concern in imatinib safety and tolerance.

## 4. CONCLUSION

We present a case of GIST treated with surgical resection followed by adjuvant imatinib mesylate. The patient's course was complicated by two episodes of acute kidney injury clearly attributable to imatinib toxicity and ultimately led to the cessation of the drug. We believe this is the first report of acute kidney injury causing discontinuation of adjuvant therapy with imatinib in a patient with a moderate-risk GIST.

## CONFLICTS OF INTEREST DISCLOSURE

## ACKNOWLEDGEMENTS

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