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CASE REPORT

Pleural effusion in a patient with metastatic gastrointestinal stromal tumor treated with imatinib: case report

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ABSTRACT Gastrointestinal stromal tumors are rare malignancies characterized by c-kit and PDGFR-α mutations targeted by imatinib. Pleural effusion is a very rare side effect of imatinib treatment. A 65-year-old female with metastatic gastrointestinal stromal tumor developed electrolyte imbalance, severe peripheral edema and progressively worsening dyspnea 2 months after starting imatinib. Having excluded cardiovascular and pulmonary disorders, imatinib was discontinued and prednisone 25 mg orally daily was begun. The patient's condition improved substantially over the next 48 h with a progressive decrease in dyspnea and a reduction in pleural effusion and peripheral edema. All side effects had resolved within 1 month. In view of the partial response obtained, the patient re-started imatinib after a 1-week interruption. Prednisone was maintained and there was no further toxicity.

KEYWORDS
• gastrointestinal stromal tumor • imatinib • metastatic gastrointestinal stromal tumor • pleural effusion • toxicity

Gastrointestinal stromal tumors (GISTs) are relatively rare malignancies representing less than 1% of all cancers of the GI tract [1]. In Europe the incidence is estimated at 15 cases per million population [2]. The majority of these tumors arise from the interstitial cells of Cajal and express the receptor tyrosine kinase KIT (CD117) protein [3]. Four percent of GISTs are KIT-negative, but 10–15% express PDGFR-α mutations [4,5].

Imatinib mesylate is an oral small-molecule competitive inhibitor of multiple tyrosine kinases (TKIs), including KIT and PDGFR-α [6–8]. Preclinical studies performed on GIST cell lines have confirmed antineoplastic activity, as have clinical trials. Subsequently, imatinib has become the first-line treatment for locally advanced/metastatic GIST and as adjuvant or neoadjuvant therapy [9–14]. Regardless of the stage of disease, imatinib is normally used for prolonged periods of time and can thus be regarded as a treatment for chronic disease. The toxicities associated with treatment should be managed proactively to optimize patient outcome and permit long-term treatment with imatinib. A large number of patients taking part in several clinical trials with imatinib have discontinued treatment due to toxicity; for example, in the SSGXVIII study, slightly more than 25% of patients randomized to the 3-year arm interrupted therapy. The incidence of grade 3/4 events was around 30 and 13.6% of patients in the 3-year arm discontinued imatinib due to adverse events [15]. Thus, the timely management of side effects, prudent dose modifications and continued patient support during treatment with imatinib are essential to optimize long-term outcomes. In another study, an unselected group of patients with chronic myeloid leukemia (CML) undergoing treatment with imatinib showed compliance rates less than 90 in 26% of cases. Fourteen percent had adherence rates less than 80% [16].

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Common toxicities associated with imatinib include diarrhea, fatigue, skin rash and edema, and there is evidence that the severest toxicities occur during the first 3–6 months of treatment, in part attributable to alterations in pharmacokinetics of the drug over time. Such alterations may also account for the differences in toxicity observed between men and women and for the increased toxicity registered in older patients [17,18]. Another uncommon and much debated side effect is imatinib-related cardiotoxicity. Although this adverse effect can occur at any age, its incidence increases with age and seems to be facilitated by the presence of co-morbidities such as pre-existing cardiovascular disease, renal failure, diabetes mellitus, hypertension, coronary artery disease, arrhythmia and cardiomyopathy [19,20]. However, the important EORTC-ISG-AGITG study failed to confirm a definite correlation between imatinib and cardiac toxicity [21].

Other TKIs such as dasatinib can induce specific off-target toxicities, for example, pleural effusion, which may be mediated by PDGRF-β. Diuretics, a short course of steroids and thoracentesis, are normally used to resolve this problem.

Although edema and fluid retention are common side effects of imatinib, pleural and pericardial effusions are infrequently reported [22]. Periorbital edema is, however, very common. In a randomized Phase II trial in patients with imatinib-resistant CML comparing dasatinib and high-dose imatinib, the incidence of edema and fluid retention was higher in the imatinib arm than in the dasatinib arm (42 vs 15% and 45 vs 30%, respectively). No pleural or pericardial effusions were reported in the imatinib arm [23].

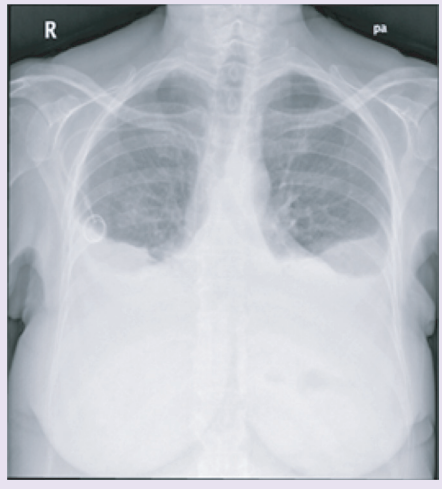

Figure 1. Chest x-ray: bilateral pleural effusion with associated dystelectasis.

The few reports of imatinib-related pleural effusion in the literature are frequently associated with pericardial effusion and often involve patients treated with higher doses of imatinib. In one report of three CML patients who developed concomitant pericardial and pleural effusion during treatment with high-dose imatinib, discontinuation of the TKI resolved the problem. Imatinib-related pleural effusion occurs more frequently in other malignancies. In a Phase I dose-escalation study evaluating imatinib in epithelial ovarian cancer, pleural effusion occurred in six out of 22 patients (grade 3 in four patients) [24,25]. Three out of four sampled pleural effusions contained malignant cells. Cessation of imatinib resolved the problem.

We describe the case of a patient with metastatic GIST who developed bilateral pleural effusion, edema and electrolyte imbalance that rapidly resolved after imatinib suspension and treatment with prednisone. The patient was maintained on prednisone and imatinib was re-started, without further episodes of toxicity.

Presentation of the case

In August 2013, a 65-year-old woman underwent a CT scan that revealed a large mesenteric mass in the central abdomen (maximum diameter 13 cm) associated with multiple liver and abdominal lymph node lesions. An initial diagnosis of an undifferentiated high-grade sarcomatous tumor (NOS) was made. The patient started doxorubicin and after 10 days was admitted to hospital for febrile neutropenia, which resolved after antibiotic and immunostimulatory therapy. Treatment with doxorubicin was continued on an in-patient basis. In accordance with internal institutional guidelines, we reviewed the pathology report and a final diagnosis of gastrointestinal GIST was made (c-kit and DOG1 positive; CD138, cytokeratin, actin and desmin negative; high risk according to Miettinen classification and deletion mutation in *KIT* exon 11 involving codons V559-G565).

In September, the patient started imatinib at a dose of 400 mg daily and after 2 months she developed severe dyspnea, loss of appetite (food intake did not change) and fatigue. Physical examination showed bibasilar dullness to percussion, decreased tactile fremitus and absent breath sounds in the bases, bilateral peripheral edema of the inguinal fold and a weight gain of 2.5 kg.

Daily urine output was around 1200 ml. A short course of diuretics was prescribed by the patient's general practitioner at the onset of the peripheral edema, without, however, an improvement in her condition. A cardiac etiology was excluded by ECG and echo-Doppler. Laboratory data were as follows: hemoglobin 8.9 g/dl, sodium 139 mmol/l, serum protein 58 g/l, serum creatinine 0.87 mg/dl, calcium 7.7 mg/dl, despite calcium 1000 IU orally (p.o.) daily; all other values were unremarkable.

A chest x-ray **(Figure 1)** revealed severe bilateral pleural effusion (reference point: posterior bilateral 8th rib) with associated dystelectasis. Right thoracentesis was performed (approximately 600 ml). The pleural fluid was a clear yellow color (711 total nucleated cells/l [21% neutrophils and 69% lymphocytes], 21.7 g/l total protein, 101 IU/l LDH and 120 mg/dl glucose), suggestive of transudative pleural effusion. Cytological analysis did not reveal neoplastic cells.

A total body CT scan performed to re-evaluate the tumor showed a partial radiological response **(Figure 2)**. After reviewing the laboratory and clinical findings, it was concluded that the pleural effusion was related to imatinib. The drug was immediately discontinued and, after a brief review of the literature on TKI-associated pleural effusion, treatment was started with prednisone 25 mg p.o. daily [26–28]. The patient's general condition improved significantly over the next 2 days. A chest x-ray repeated after a week showed a substantial reduction in the pleural effusion at the level of the 9th-10th ribs **(Figure 3)**, with complete resolution of peripheral edema. Serum calcium was normalized and hemoglobin was 9.7 g/dl. The patient re-started imatinib 200 mg daily and continued full-dose prednisone for another week. One month later, a chest x-ray confirmed the complete resolution of the bilateral pleural effusion **(Figure 4)**. Laboratory data showed normal serum calcium and hemoglobin levels.

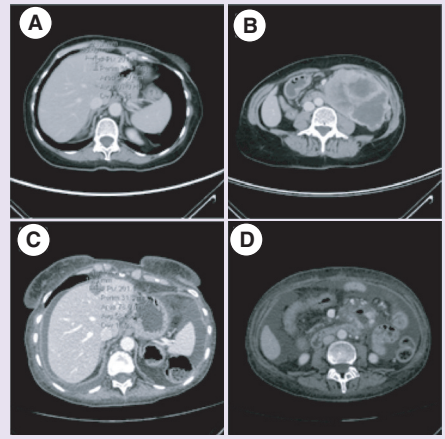

Figure 2. Disease evaluation 1 month after starting imatinib. (A & B) Basal CT scan performed in June 2013. **(C & D)** CT scan performed 1 month after starting imatinib showing a reduction in the size and average density of the primitive gastrointestinal stromal tumor associated with a decrease in the number, size and average density of the liver metastases.

Discussion

Pleural effusion is an extremely rare nonhematological side effect of treatment with imatinib. In a report of three patients published in the literature, pleural effusion probably occurred as a result of high-dose imatinib in the treatment of CML [24]. The successful use of corticosteroids to treat pleural effusion associated with other TKIs, for example, dasatinib or nilotinib, has previously been described, indicating a potentially similar origin. Our patient received a similar dose (25 mg prednisone p.o. daily) and showed a substantial improvement in symptoms within 48 h [26–28]. The similarity in treatment approach and outcome suggests a common pathogenesis for pleural effusion associated with dasatinib, nilotinib and imatinib. A possible role of specific cytokines, for example, PDGFR- β and VEGF in causing endothelial permeability, has been hypothesized. These receptors influence vascular smooth muscle cell and mesangial cell development, and also recruit pericytes to capillaries

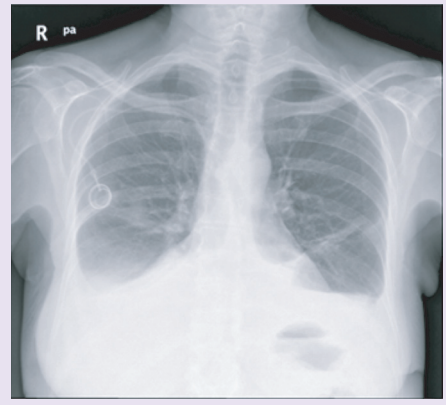

Figure 3. Chest x-ray (after 1 week): reduction in bilateral pleural effusion.

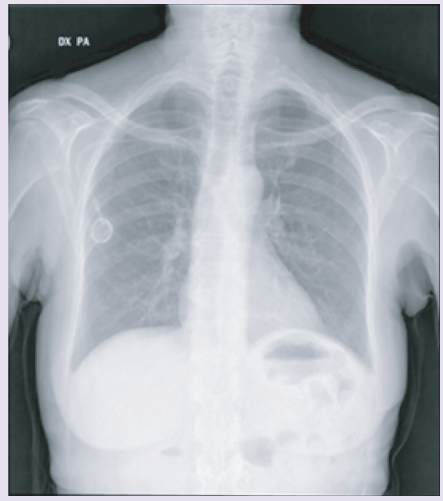

Figure 4. Chest x-ray (after 1 month): complete resolution of bilateral pleural effusion.

[29]. PDGFR-β is involved in the regulation of angiogenesis and interstitial fluid pressure and it has been shown that its blockade by an antagonist results in increased fluid accumulation in patients with solid tumors [30]. The presence of peripheral lymphocytosis often associated with pleural effusion from treatment with dasatinib is suggestive of an immunological mechanism of action. This hypothesis is supported by the high lymphocyte frequency found in the pleural fluid of dasatinib-treated patients [31] and by the response to steroids [27,28]. Interestingly, similar findings were observed for our patient who showed 69% lymphocytes in the pleural fluid and responded well to steroids.

Conclusion

In conclusion, imatinib is effective in treating GISTs, but can inhibit tyrosine kinase in both normal and neoplastic cells. Although relatively rare, clinicians should be aware of its potential toxic effect on the pleural space, which can severely impact quality of life and compromise a therapeutic strategy that has changed the natural history of GISTs.

Future perspective

Pleural effusion is an important side effect that may require treatment discontinuation. Further studies are needed to identify whether its pathogenetic mechanism is the same as that of imatinib-induced peripheral edema or cardiotoxicity as this would lead to better management of toxicity and to improved patient compliance to treatment. Understanding its mechanism of action and the potential role of cytokines or angiogenic regulatory factors could also open up new therapeutic scenarios.

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No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

EXECUTIVE SUMMARY

- Gastrointestinal stromal tumors are relatively rare tumors with an annual incidence of 15 cases per million population.
- Imatinib is the 'gold standard' treatment for patients with gastrointestinal stromal tumor in neoadjuvant, adjuvant and metastatic settings.
- Pleural effusion is a very rare side effect of treatment with imatinib.
- The use of corticosteroids to treat imatinib-related pleural effusion is highly effective and enables imatinib treatment to be continued.
- Although the involvement of cytokines, PDGFR-β and VEGF in the development of pleural effusion has been hypothesized, their exact role is still unclear.

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