

Tuberculous and Non-Tuberculous Granulomatous Lymphadenitis in Patients Receiving Imatinib Mesylate (Glivec) for Metastatic Gastrointestinal Stromal Tumor

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Key Words

Gastrointestinal stromal tumor · Imatinib mesylate · Glivec · Tuberculosis · Granuloma · PET-CT

Abstract

Background: Imatinib mesylate (IM) is the standard treatment for *BCR-ABL*-positive chronic myelogenous leukemia (CML) and is the first-line adjuvant and palliative treatment for metastatic and inoperable gastrointestinal stromal tumor (GIST). IM is not known to be associated with an increased risk for development of granulomatous diseases. **Methods:** We describe our experience with 2 patients (42 and 62 years of age) who developed granulomatous disease during IM treatment for metastatic GIST. **Results:** Mean duration of IM treatment was 12 (range 8–16) months. Enlarged lymph nodes with increased metabolism on FDG-PET-CT examination were detected and resected. Affected sites were supraclavicular (1) and subcarinal/mediastinal (1) lymph nodes. Histological examination revealed caseating and non-caseating granulomas suggestive of tuberculosis and sarcoidosis, respectively. *Mycobacterium tuberculosis* was detected by PCR in lymph nodes of 1 patient who was then successfully treated by anti-tuberculous agents. The other patient had negative sputum test for acid-fast bacilli and PCR-DNA-analysis was negative for *M. tuberculosis* and other mycobacteria. He received no anti-tuberculous therapy and had no evidence of progressive lymphadenopathy or new lung lesions during follow-up. **Conclusion:** Our observations underline the necessity to obtain biopsy material from enlarged or metabolically active lymph nodes developing during IM treatment for timely diagnosis and appropriate treatment

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of these rare complications. Follow-up without treatment is safe for patients without detectable microorganisms by sputum examination and PCR.

Introduction

Gastrointestinal stromal tumors (GISTs) are currently considered a distinct clinicopathologic and molecular disease entity, representing the most common mesenchymal tumors of the GI tract [1]. The discovery of activating mutations in the receptor tyrosine kinases KIT and platelet-derived growth factor receptor- α (PDGFRA) resulted in a dramatic improvement of their diagnosis and treatment [2]. Approximately 30–50% of GISTs behave malignant; half of them have already metastasized at the time of diagnosis [3]. While surgery still represents the gold standard treatment for patients presenting with localized resectable disease, the tyrosine kinase inhibitor (TKI) imatinib mesylate (IM) (Glivec; Novartis, Basel, Switzerland) has emerged as the treatment of choice for patients with inoperable or metastatic disease. While a majority of patients with metastatic disease achieve durable tumor response on IM treatment, some initially responsive patients experience progression due to secondary drug resistance [4]. Application of different sensitive imaging modalities represents the gold standard for early detection of progressive disease during or following IM treatment [5].

Mycobacterial infection is not associated with IM treatment, since only 9 patients have been reported who developed tuberculosis during or after IM treatment for chronic myelogenous leukemia (CML, $n = 8$) and GIST ($n = 1$) [6–10]. In this report, we present our experience with 2 patients who developed lymphadenopathy under IM treatment for metastatic GIST. As this unusual finding might be misinterpreted as progressive GIST, our cases underscore the importance of obtaining a histopathological diagnosis for management of metabolically active or enlarged lymph nodes in GIST patients.

Case Histories

Case 1

A 42-year-old woman was diagnosed with a KIT-positive high-risk GIST of the jejunum (18 cm diameter, 50 mitoses/50 high-power field) with synchronous peritoneal metastasis. She underwent segmental resection of the jejunum and duodenum, infragastric omentectomy, pelvic peritonectomy and excision of the bladder peritoneum resulting in complete removal of gross disease which was then confirmed by 18F-FDG-PET. She was put on postoperative IM 400 mg/day. Progressive recurrent peritoneal disease was diagnosed and resected 8 months later, followed by dose escalation of IM to 800 mg/day. At 16 months from initial diagnosis, 1 suspicious PET-positive supraclavicular lymph node was removed surgically and showed caseating granulomatous inflammation consistent with tuberculosis. PCR examination confirmed infection with *Mycobacterium tuberculosis* (fig. 1, fig. 2). Bronchoscopy with bronchoalveolar lavage (BAL) was performed, but PCR and culture were negative for *M. tuberculosis*. She was started on antituberculous triple therapy with isoniazid, rifabutin and pyrazinamide for 2 months, followed by isoniazid and rifabutin for an additional 4 months. Throughout, IM levels were monitored to ensure sufficient IM exposure during the antituberculous treatment. IM 800 mg was continued for a further 8 months and then had to be stopped because of intra-abdominal progression. During the next 15 months, the patient was switched to sunitinib, sorafenib and nilotinib because of progressive disease.

There was no evidence of reactivation of tuberculosis until her death 29 months after initial diagnosis.

Case 2

A 62-year-old man underwent enucleation of a submucosal tumor of the stomach. Histological evaluation revealed an intermediate-risk GIST. He developed an abdominal recurrence 7 years later. After neoadjuvant IM treatment (400 mg/day) for 8 months, resection of the stomach antrum, gallbladder and atypical resection of the liver (segment III) was performed. One month later, a subcarinal lymph node with increased FDG uptake on PET-CT was detected and suggested metastatic disease. Mediastinoscopy was performed and lymph node biopsy showed granulomatous disease with focal necrosis suggestive of sarcoidosis or tuberculosis (fig. 1, fig. 2). During IM treatment, new lung lesions appeared leading to surgical removal of the lesions. Histological examination showed near totally regressing lung metastasis from GIST, but no evidence of granulomatous disease. He has since remained in continuous complete remission on IM for more than 38 months. The lymph nodes showed decreasing FDG uptake on follow-up FDG-PET-CT. Periodic CT scans did not show any new lymphadenopathy.

Discussion

IM is a competitive TKI that selectively and specifically inhibits ABL, PDGFRA and KIT. The powerful anti-tumoral effect of IM made this drug a prototype of targeted therapy for solid tumors. The drug is usually well tolerated. Infectious and inflammatory complications have not been frequently reported except for rare cases of interstitial lung disease [11], and reactivation of hepatitis B virus [12] and herpes zoster [13]. However, the actual relationship of some of these diseases to IM therapy has not been proven and some might represent a mere coincidence or a complication of the underlying hematological disorder (CML).

To date, a total of 9 patients have been reported to have developed tuberculosis under or after IM treatment; most of them had CML (n = 8) [7–10] and only 1 patient had GIST [6]. The clinicopathological features of these patients are summarized in table 1. Thus with our cases, there are 10 patients who developed tuberculosis under IM for CML (n = 8) and GIST (n = 2) or idiopathic granulomatous disease (n = 1). The duration of IM treatment prior to diagnosis of granulomatous disease ranged from 3 to 72 months (mean 16.5). Most patients received a standard dose of 400 mg/day so that an association with dose escalation seems unlikely.

Ghadyalpatil et al. [9] analyzed data of 1,100 CML patients treated with IM and followed up for possible reactivation of tuberculosis for a period of 6–156 months (mean 49). None of the 21 patients with a confirmed history of tuberculosis showed evidence of reactivation. However, 3 other patients (0.27%) with no past history of tuberculosis developed active tuberculosis under IM therapy at a mean of 17 months from the start of IM. None of the 3 patients had neutropenia or lymphopenia at the time of tuberculosis diagnosis. They responded well to antituberculous therapy given for 6 months and IM was continued at a dose of 600 mg to compensate for potential enzyme induction by rifampicin.

Although these rare cases suggest that a very small subset of patients receiving IM treatment may be more susceptible to tuberculous infections, the mechanisms responsible for development of tuberculosis under IM still remain poorly understood. The review by Ghadyalpatil et al. [9] showed that previous history of tuberculosis does not represent a risk for reactivation under IM treatment as none of the patients with a positive history for

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tuberculosis developed reactivation. On the contrary, Daniels et al. [8] reported similar findings in 3 patients with probable previous contact with tuberculosis and considered a reactivation as the most likely event in their cases. Since most cases of lymph node tuberculosis are caused by reactivation [14] and our patient did not report any contact with infected persons, reactivation remains the most likely explanation in our patient despite having no history of tuberculosis.

All patients including ours had normal leukocyte and lymphocyte counts at the time of diagnosis of granulomatous disease. It has been proposed that imatinib affects T-cell receptor signal transduction, thereby affecting the cellular immunity and the host susceptibility to reactivation of tuberculosis [8]. Furthermore, there are a few reports on reactivation of viral diseases (hepatitis B, varicella zoster) under IM treatment, suggesting that IM might impair the cellular immune system leading to infection reactivation [12, 13]. However, other researchers reported an intact control of primary viral infections in spite of the impaired cytotoxic T-cell response induced by IM [15]. Further testing in our patients after diagnosis of granulomatous disease did not show any differences in T-cell subpopulations (including regulatory T cells) and functionality of natural killer cells, compared to normal controls (data not shown). So it seems possible that IM might not affect control of primary infections but rather control of chronic infections, as proposed by Mumprecht et al. [15].

Interestingly, a recent study showed that *M. tuberculosis* and *M. marinum* use ABL and related tyrosine kinases for entry and intracellular survival in macrophages, and that IM, when administered prophylactically or therapeutically in mice, reduced both the number of granulomatous lesions and bacterial load in infected organs [16]. In that study, IM also acted synergistically with current first-line drugs rifampicin or rifabutin [16]. The authors of that paper concluded that host tyrosine kinases may be implicated in entry and intracellular survival of mycobacteria and discussed that imatinib may have therapeutic efficacy against *M. tuberculosis*. These observations are consistent with the analysis by Ghadyalpatil et al. [9] which showed no evidence of reactivation of tuberculosis under IM. Thus, it remains unclear why a small subset of patients, including ours, receiving IM treatment develops tuberculous lymphadenitis.

One of our patients developed idiopathic granulomatous lymphadenitis under IM for metastatic GIST without detectable infectious agents. The cause of the granulomatous disease in this case is unclear. The clinicopathological features of this patient were consistent with sarcoidosis.

From a clinical view point, there are several aspects to consider for the management of GIST patients. Since PET-CT can detect GIST lesions because of the high FDG uptake, it is often used for monitoring of the therapeutic effect of IM and other TKI [17, 18]. However, PET-CT cannot differentiate between malignant disease, tuberculosis and other infectious diseases or sarcoidosis [19]. As true lymph node metastasis is exceedingly rare in elderly patients with GIST [20], particularly extra-abdominal lymph node metastasis [21], detection of enlarged or metabolically active lymph nodes during IM treatment should not spontaneously be regarded as evidence of progressive or malignant disease, but should prompt further workup for tuberculous lymphadenitis and other idiopathic granulomatous diseases even in patients with extensive disease or unusual localization of metastasis. Surgical biopsy of affected lymph nodes and extensive microbiological investigation to prove or exclude tuberculous lymphadenitis are mandatory for diagnosis, as most patients have no concurrent pulmonary lesions and positive sputum cultures are also uncommon [22].

Patients with tuberculous lymphadenitis should be treated with antimycobacterial therapy, with particular attention to possible drug interactions with IM or other TKI. Given the indolent nature of the granulomatous lymphadenitis in 1 of our patients who did not

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receive antituberculous therapy, observation without therapy appears reasonable for such cases without detectable microorganisms.

Taken together, the presented cases clearly show the relevance of obtaining a histopathological diagnosis despite modern imaging methods in the management of GIST patients, since the incorrect assumption of progressive disease could cause the termination of an efficient treatment with negative effects for the patient.

Disclosure Statement

A. Agaimy and N. Meidenbauer have received honoraria from Fa. Novartis, Nürnberg. Other coauthors declare no conflict of interest.

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Table 1. Clinicopathologic features of granulomatous and tuberculous disease diagnosed under IM treatment (n = 11)

No.	Author	Cases	Age sex	Underlying disease	Period of IM to diagnosis of granulomas	Type/site of granulomatous disease	Diagnosis method for TBC	Treatment outcome
1	Takashima et al. [6]	1	64 M	GIST jejunum	after 3 months 400 mg twice/day	TBC, multiple lung lesions	sputum: AFB stain + PCR + culture +	antituberculous therapy without IM, died soon of cachexia and GIST
2	Senn et al. [7]	1	37 M	BCR-ABL-positive CML	400 mg/day for 1 month then reduced, at 4 months again 400 mg	TBC, peritoneal soft tissues	surgical biopsy: AFB stain – PCR + culture +	6 months antituberculous without IM, then hematopoietic stem cell transplantation. No further complication
3	Daniels et al. [8]	1	38 M	BCR-ABL-positive CML	800 mg/day, 4 years	TBC, apical right upper lobe	sputum: AFB stain + PCR + culture +	successful ATT for 6 months without IM, then IM continued
4	Daniels et al. [8]	1	26 M	BCR-ABL-positive CML	400 mg for 2 years	TBC, paravertebral mass left of Th8	surgical biopsy: AFB stain – PCR – culture +	16 Gy of radiotherapy for 2 months for misdiagnosis as chloroma successful ATT for 6 months
5	Daniels et al. [8]	1	19 M	BCR-ABL-positive CML	400 mg for 1 year	TBC, apical left lower lobe	sputum: AFB stain – culture – (poor sample quality)	successful empirical ATT for 6 months with continued IM
6–8	Ghadyalpatil et al. [9]	3	n.s.	CML	mean 17 months	n.s.	sputum examination in 2 and other examinations in 1	good response to 6-month ATT, concurrently continued IM at 600 mg
9	Salunke et al. [10]	1	43 F	CML	400 mg for 6 years	meningeal tuberculoma	biopsy showed granuloma with acid-fast bacilli	initial response to ATT followed by secondary infarcts 1 month later
10	current	1	42 F	GIST ileum	400–600 mg for 16 months	mediastinal and supraclavicular	PCR-DNA from lymph node	good response to ATT, IM continued at 800 mg
11	current	1	62 M	GIST stomach	400 mg for 8 months	mediastinal and subcarinal	lymph node biopsy negative for AFB and PCR	alive with disease on 800 mg IM, no progressive granulomatous disease

AFB = Acid-fast bacilli; TBC = tuberculosis; ATT = antituberculous treatment.

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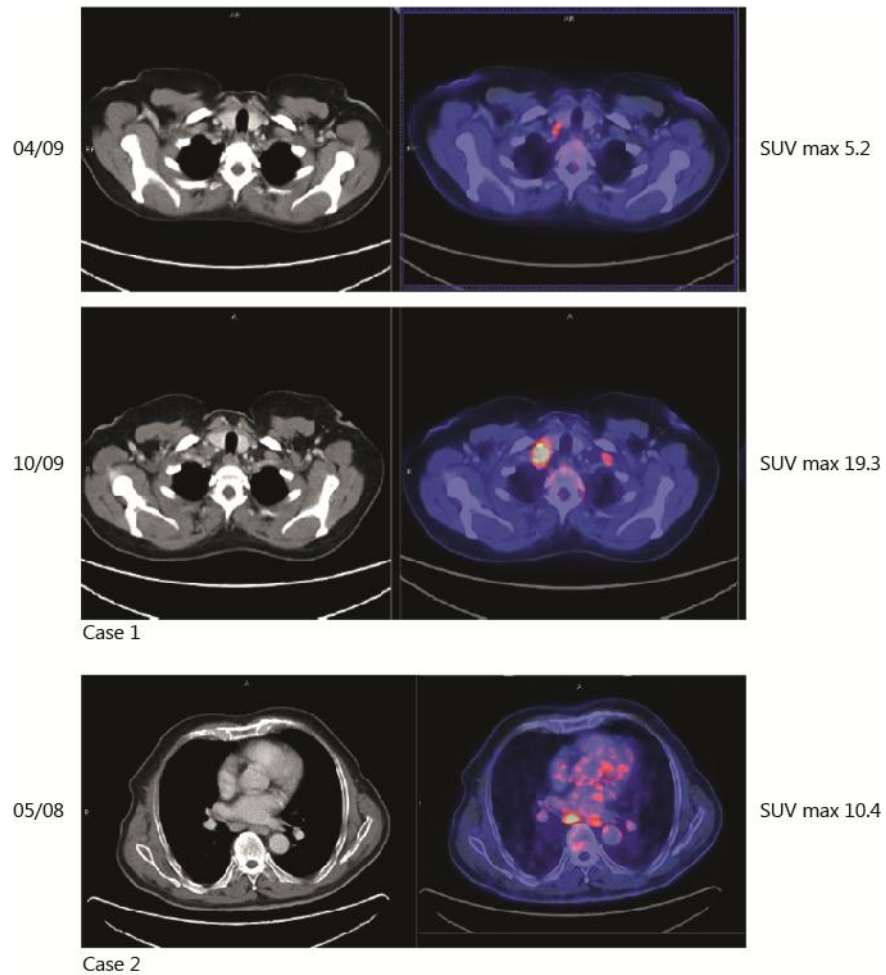


Fig. 1. above (Case 1) Progressive suspicious supraclavicular lymph node with increased FDG uptake was seen on PET-CT. Histology revealed caseating granulomatous lymphadenitis positive for tuberculosis on PCR examination. **below** (Case 2) A PET-positive subcarinal lymph node was surgically removed and showed non-caseating sarcoid-like granulomatous inflammation without detectable mycobacteria.

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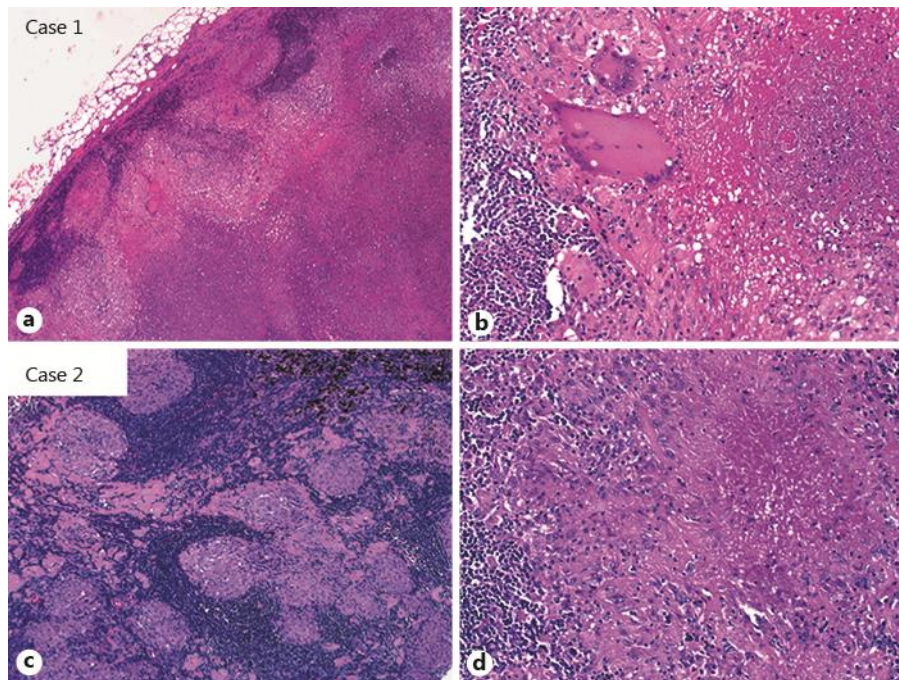


Fig. 2. Histological findings in surgically removed lymph nodes in case 1 (**a, b**) and case 2 (**c, d**). **a** Epithelioid cell granulomas with extensive confluent caseating necrosis bordered by Langhans giant cells. **b** Higher magnification of **a** showed typical caseation and giant cells. **c** Overview of this mediastinal lymph node showed multiple compact epithelioid cell granulomas with intervening anthracotic pigmentation (upper field). **d** Higher magnification showed granuloma with hyaline fibrinoid-type central necrosis but typical caseation was absent.