

DOI: <https://dx.doi.org/10.18203/2319-2003.ijbcp20263796>

Case Report

Disseminated tuberculosis with central nervous system involvement in a patient with chronic myeloid leukaemia receiving dasatinib: cytochrome P450 3A4-mediated drug interaction and multifactorial cytopenia

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Received: 22 July 2026

Revised: 21 September 2026

Accepted: 23 September 2026

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ABSTRACT

Concurrent chronic myeloid leukaemia (CML) and tuberculosis presents substantial management challenges when tyrosine kinase inhibitor therapy must be combined with rifampicin-based anti-tubercular treatment. Rifampicin, a potent inducer of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein, reduces the maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) of dasatinib by 81% and 82%, respectively, potentially compromising molecular disease control. We report a 27-year-old man with BCR::ABL1-positive CML in chronic phase, previously in complete cytogenetic and major molecular response on dasatinib 100 mg daily, who presented with generalised tonic-clonic seizures. Magnetic resonance imaging of the brain showed multiple ring-enhancing lesions with leptomeningeal enhancement and vasculitic infarcts. A clinical diagnosis of disseminated tuberculosis with central nervous system involvement was made and treated empirically; the documented findings met, at most, the “possible” category of the Marais consensus case definition for tuberculous meningitis. Rifampicin-containing anti-tubercular therapy was started and dasatinib was escalated to 140 mg daily. Approximately three and a half months later he was readmitted with severe thrombocytopenia (nadir $10.0 \times 10^3/\mu\text{l}$), a rising leukocyte count ($53.3 \times 10^3/\mu\text{l}$) and life-threatening hypercalcaemia (corrected serum calcium 17.0 mg/dl). Dasatinib was withheld and intensive supportive care was given, after which he was discharged for outpatient follow-up; outcome data beyond discharge were not available. This case illustrates the pharmacokinetic conflict between dasatinib and rifampicin and its clinical consequences when dose escalation within the approved range proves insufficient. Rifabutin substitution, rifampicin-free anti-tubercular regimens, asciminib and therapeutic drug monitoring (TDM) of dasatinib are discussed as management strategies, although none has been validated in this clinical scenario.

Keywords: Chronic myeloid leukaemia, Dasatinib, Tuberculous meningitis, Cytochrome P450 CYP3A4, Drug-drug interaction, Hypercalcaemia, Case report

INTRODUCTION

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm defined by the t(9;22) (q34;q11.2) translocation and the resulting BCR::ABL1 fusion oncogene.

BCR::ABL1 tyrosine kinase inhibitors (TKIs) have brought the life expectancy of most patients in chronic phase close to that of the general population.^{1,2} Dasatinib, a second-generation TKI, is eliminated mainly by CYP3A4-mediated oxidation with a secondary contribution from P-

glycoprotein (ABCB1) efflux, and is therefore susceptible to interaction with CYP3A4 modulators.^{3,4}

Tuberculosis remains a leading infectious cause of death worldwide, with an estimated 10.8 million incident cases and 1.25 million deaths in 2023; India accounts for about one quarter of the global burden.⁵ When the two diseases coincide, rifampicin-the cornerstone of anti-tubercular therapy and one of the most potent known inducers of CYP3A4 and P-glycoprotein-reduces dasatinib exposure by more than 80%.³ BCR::ABL1 inhibition also affects host defence against intracellular pathogens: Abelson tyrosine kinase regulates phagosomal acidification in human macrophages,⁶ and dasatinib, by inhibiting the SRC family kinase LCK, impairs the function of *Mycobacterium tuberculosis*-specific T lymphocytes.⁷ Dasatinib carries the highest reported burden of opportunistic infection among the BCR::ABL1 TKIs,⁸ and tuberculosis arising during TKI therapy has been reported repeatedly,⁹⁻¹¹ yet no evidence-based guidance exists for managing the two diseases concurrently.

The objectives of this report are threefold: to describe the clinical course of tuberculosis with central nervous system (CNS) involvement arising in a patient with well-controlled CML on dasatinib; to analyse the CYP3A4-mediated pharmacokinetic conflict between dasatinib and rifampicin and limits of dose escalation as counter-measure; and to appraise available management options-rifabutin substitution, rifampicin-free regimens, TKI switching and TDM-so as to propose practical monitoring framework for this under-recognized clinical situation.

CASE REPORT

A 27-year-old man, a permanent resident of Pithoragarh district, Uttarakhand, India-a tuberculosis-endemic Himalayan region bordering Nepal and the Tibetan Plateau-presented to the emergency department on 22 August 2025 with a three-day history of multiple generalised tonic-clonic seizures associated with frothing at the mouth, tongue biting and post-ictal confusion. Between episodes he was conscious but disoriented, with reduced verbal responsiveness. There was no preceding fever, headache, vomiting, head trauma or prior seizure.

Medical history

BCR::ABL1-positive CML had been diagnosed approximately four years earlier (2021). His Sokal score at presentation was 1.20 (borderline intermediate/high risk) and his European Treatment and Outcome Study (ELTS) score was 2.03 (intermediate risk). BCR::ABL1 transcript type and baseline and follow-up BCR::ABL1 international scale (IS) values were not available in records reviewed. He had been maintained on dasatinib 100 mg once daily, with documented complete cytogenetic response (CCyR) and major molecular response (MMR) at his most recent assessment before presentation. BCG vaccination status was not documented, baseline interferon-gamma release

assay had not been performed, and he had no history of diabetes mellitus (HbA1c not measured).

Initial clinical evaluation

On arrival he was conscious but confused, with a Glasgow Coma Scale score of E3V2M4 (9/15). Temperature was 38.2 °C, heart rate 112 beats/min, blood pressure 130/80 mmHg, respiratory rate 20 breaths/min and peripheral oxygen saturation 96% on room air. General examination was unremarkable except for neck rigidity with positive Kernig's and Brudzinski's signs; there were no palpable lymph nodes, hepatosplenomegaly or stigmata of chronic liver disease. Despite intravenous levetiracetam and phenytoin, seizures persisted and a midazolam infusion was required for control.

Initial investigations

Haemoglobin was 8.05 g/dl, total leukocyte count $9.51 \times 10^3/\mu\text{l}$ (75% neutrophils, 14% lymphocytes, 8% monocytes) and platelet count $43.3 \times 10^3/\mu\text{l}$. Renal function was normal (blood urea 30 mg/dl, serum creatinine 0.64 mg/dl); aspartate aminotransferase was mildly elevated at 50.9 U/l with a normal alanine aminotransferase of 32.7 U/l. Serum sodium was 132 mmol/l (mild hyponatraemia), potassium 3.85 mmol/l, total calcium 9.1 mg/dl and uric acid 4.3 mg/dl. Serology for HIV, hepatitis B surface antigen and hepatitis C antibody was non-reactive.

Cerebrospinal fluid (CSF) analysis showed raised protein with lymphocytic pleocytosis, normal glucose with a normal CSF:plasma glucose ratio, and an adenosine deaminase (ADA) level within normal limits; the exact cell count and protein concentration were not recorded in the available records. The cartridge-based nucleic acid amplification test (CBNAAT/Xpert MTB/RIF) was negative for *M. tuberculosis*, and CSF Gram stain, bacterial culture and fungal studies were also negative. Serum Toxoplasma IgG was positive; against a national seroprevalence of approximately 24% in India, this was interpreted as likely past exposure, although active infection could not be excluded.¹²

Neuroimaging

Contrast-enhanced magnetic resonance imaging (MRI) of the brain demonstrated multiple conglomerate ring-enhancing lesions across both cerebral hemispheres and the cerebellum, with perilesional vasogenic oedema, leptomeningeal enhancement along the fronto-parietal regions and foci of vasculitic infarction (Figure 1). The pattern was considered most consistent with tuberculous granulomas with meningeal involvement. The principal differential diagnoses for multiple ring-enhancing intracranial lesions in an immunocompromised host are neurocysticercosis, cerebral toxoplasmosis, primary CNS lymphoma, pyogenic abscess and metastatic disease.¹³ Neurocysticercosis typically shows cystic lesions with a visible scolex and lacks meningeal enhancement or

vasculitic infarcts; cerebral toxoplasmosis usually involves the basal ganglia and cortico-medullary junction in severely immunocompromised patients, particularly those with HIV/AIDS; and primary CNS lymphoma typically appears as deep parenchymal lesions with restricted diffusion, without combination of leptomeningeal enhancement and vasculitic infarction seen here.¹³

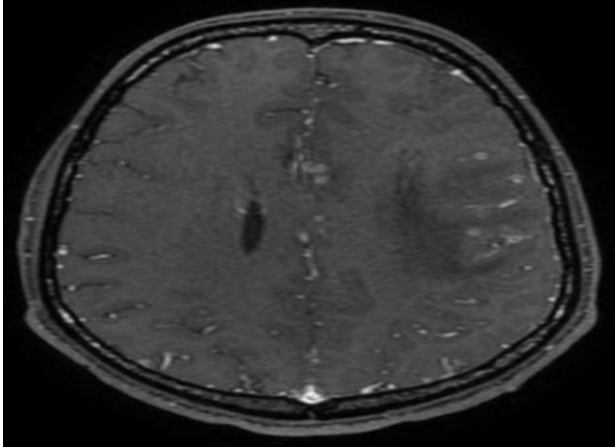


Figure 1: Contrast-enhanced magnetic resonance imaging of the brain showing multiple conglomerate ring-enhancing lesions with perilesional vasogenic oedema, leptomeningeal enhancement and foci of vasculitic infarction, a pattern most consistent with tuberculous granulomas with meningeal involvement.

Diagnosis and initial management

Given the high pre-test probability of CNS tuberculosis in an immunocompromised patient from a highly endemic region, a clinical diagnosis of disseminated tuberculosis with CNS involvement was made and treatment was started empirically. Anti-tubercular therapy comprised isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), pyrazinamide (25 mg/kg/day) and ethambutol (15 mg/kg/day), together with adjunctive dexamethasone as recommended for tuberculous meningitis.¹⁴ Anti-oedema measures including mannitol and hypertonic saline were given. Because of the broad differential diagnosis and the patient's immunocompromised state, empirical anti-toxoplasma therapy was also started, after which the seizures came under control and the sensorium improved. Evidence of tuberculosis outside the CNS was not documented. When the Marais consensus case definition¹⁵ is applied retrospectively to the documented findings, the case falls at most in the “possible” category of tuberculous meningitis (Figure 6).

Pharmacokinetic dilemma and dose escalation

The introduction of rifampicin created an immediate pharmacological problem. Recognising the expected loss of dasatinib exposure, the treating team escalated dasatinib from 100 mg to 140 mg once daily-the highest dose

permitted by the label for chronic-phase CML³-in an attempt to compensate partially. Whether rifabutin substitution was considered at this stage is not documented in the records reviewed. The patient was discharged in a clinically stable condition on this dual regimen, with planned close monitoring of haematological parameters, BCR::ABL1 transcript levels and drug toxicity.

Readmission and clinical deterioration

He was readmitted on 5 December 2025, approximately three and a half months after the initial presentation, with persistent vomiting, generalised weakness and reduced oral intake. Investigations showed worsening anaemia (haemoglobin 6.4 g/dl), severe thrombocytopenia (platelets $10.0 \times 10^3/\mu\text{l}$) and a rising leukocyte count ($37.0 \times 10^3/\mu\text{l}$ on 9 December 2025, increasing to $53.3 \times 10^3/\mu\text{l}$ by 11 December 2025, with 52% neutrophils, 18% lymphocytes and 29% monocytes). Metabolic derangements included life-threatening hypercalcaemia (corrected serum calcium 17.0 mg/dl on 9 December 2025), hypokalaemia (2.5 mmol/l), hyperuricaemia (uric acid 10.0 mg/dl) and acute kidney injury (serum creatinine 1.56 mg/dl, blood urea 55 mg/dl).

Dasatinib was temporarily withheld and aggressive supportive management was given, including intravenous hydration, antiemetics, potassium replacement and bisphosphonate therapy for hypercalcaemia. Because of the patient's critical condition and the need for urgent supportive care, repeat bone marrow examination and comprehensive molecular reassessment were not performed during this admission; the relative contributions of CML progression, dasatinib toxicity, anti-tubercular therapy and tuberculosis itself to the cytopenias could therefore not be established. Serum parathyroid hormone (PTH), PTH-related peptide (PTHrP) and vitamin D metabolites were not measured during the acute illness because treatment of severe symptomatic hypercalcaemia was prioritised, so the mechanism of hypercalcaemia could not be confirmed biochemically.

The hypercalcaemia responded to treatment, with corrected calcium falling from 17.0 to 10.5 mg/dL by 11 December 2025. Following stabilisation the patient was discharged with advice for close follow-up under the haematology and infectious diseases teams. Detailed long-term follow-up data, including subsequent molecular response and treatment modifications, were not available for review.

Investigations

Serial haematological and biochemical parameters are presented in Table 1 and Figures 2 and 3. The data capture two critical time points: the initial presentation with CNS tuberculosis (22 August 2025) and the metabolic and haematological crisis at readmission (December 2025). The fall in haemoglobin (8.05 to 6.1 g/dl), the fall in platelets (43.3 to a nadir of $10.0 \times 10^3/\mu\text{l}$) and the late

leukocytosis with monocytosis reflect the multifactorial aetiology of the cytopenia, while the biochemical profile

shows a hypercalcaemic spike accompanied by hyperuricaemia and acute kidney injury.

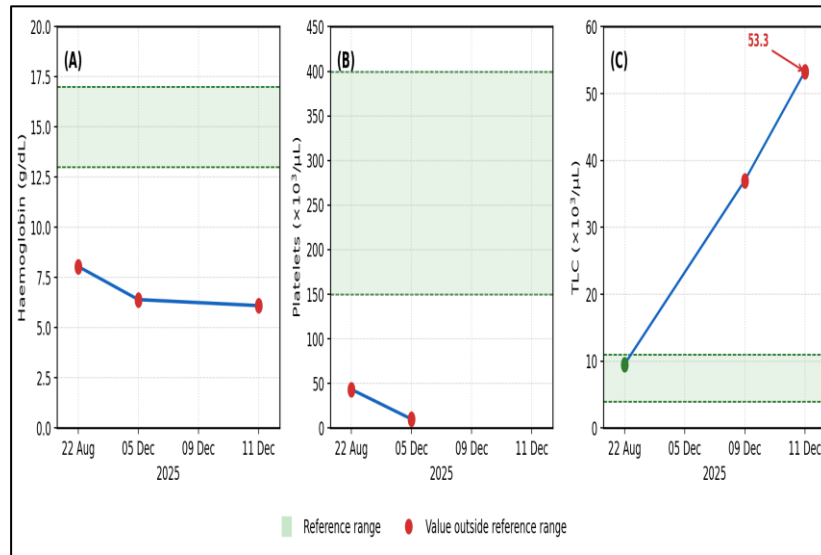


Figure 2 (A-C): Serial haematological parameters during clinical course.

(A) Progressive anaemia, with haemoglobin falling from 8.05 to 6.1 g/dl. (B) Severe thrombocytopenia, with a nadir platelet count of $10.0 \times 10^3/\mu\text{l}$. (C) Leukocytosis at readmission, with the total leukocyte count rising to $53.3 \times 10^3/\mu\text{l}$. Shaded bands represent reference ranges; red markers indicate values outside the reference range. Values not measured on a given date are not plotted.

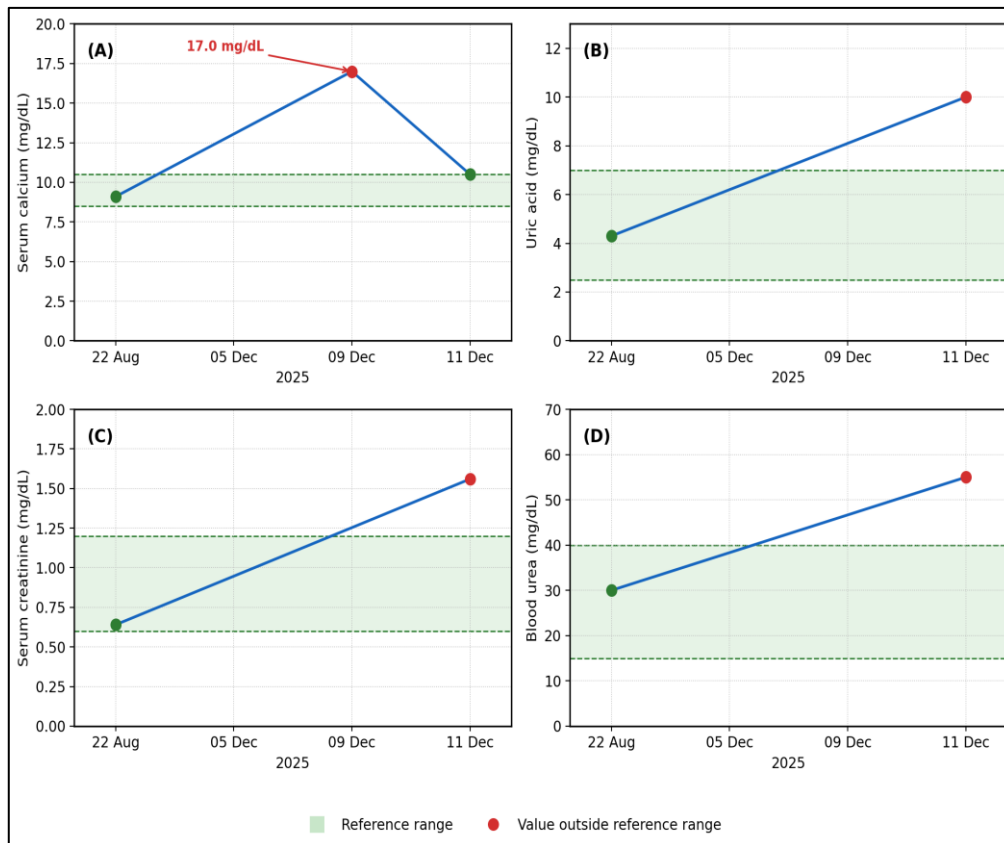


Figure 3 (A-D): Serial metabolic and biochemical parameters showing the crisis at readmission.

(A) Hypercalcaemic spike to 17.0 mg/dl with subsequent improvement to 10.5 mg/dl. (B) Rising uric acid, reaching 10.0 mg/dl. (C, D) Worsening renal function (creatinine 1.56 mg/dl, blood urea 55 mg/dl). Shaded bands represent reference ranges; red markers indicate values outside the reference range. Values not measured on a given date are not plotted.

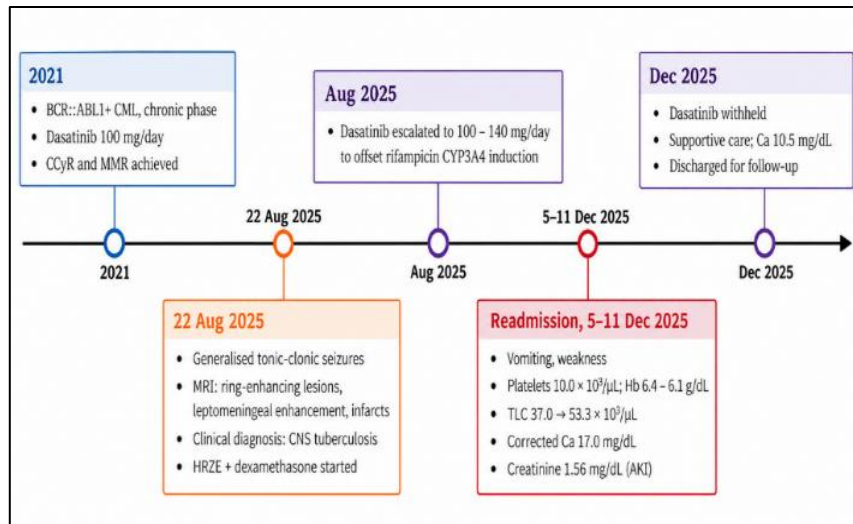


Figure 4: Clinical timeline, from the diagnosis of CML in 2021 through stable disease on dasatinib, presentation with seizures and CNS tuberculosis in August 2025, dasatinib dose escalation to offset the CYP3A4 interaction, and readmission in December 2025 with metabolic crisis and cytopenia leading to dasatinib being withheld.

*Colours denote CML-related events (blue), tuberculosis-related events (orange), the metabolic crisis (red) and treatment decisions (purple). AKI=acute kidney injury; CCyR=complete cytogenetic response; HRZE=isoniazid, rifampicin, pyrazinamide and ethambutol; MMR=major molecular response; TLC=total leukocyte count.

Table 1: Serial haematological and biochemical parameters during the clinical course.

Parameters	Reference range	22 Aug 2025	5 Dec 2025	9 Dec 2025	11 Dec 2025
Haematological parameters					
Haemoglobin (g/dl)	13-17	8.05	6.4	-	6.1
Total leukocyte count ($\times 10^3/\mu\text{L}$)	4-11	9.51	-	37.0	53.3
Neutrophils (%)	40-70	75	-	-	52
Lymphocytes (%)	20-40	14	-	-	18
Monocytes (%)	2-10	8	-	-	29
Platelet count ($\times 10^3/\mu\text{L}$)	150-400	43.3	10.0	-	-
Biochemical parameters					
Corrected serum calcium (mg/dl)	8.5-10.5	9.1	-	17.0	10.5
Uric acid (mg/dl)	2.5-7.0	4.3	-	-	10.0
Serum creatinine (mg/dl)	0.6-1.2	0.64	-	-	1.56
Blood urea (mg/dl)	15-40	30	-	-	55
Sodium (mmol/l)	135-145	132	-	-	-
Potassium (mmol/l)	3.5-5.0	3.85	-	2.5	-
Aspartate aminotransferase (U/l)	10-40	50.9	-	-	-
Alanine aminotransferase (U/l)	10-40	32.7	-	-	-

DISCUSSION

This case illustrates several interconnected problems that arise when tuberculosis complicates CML managed with dasatinib: the CYP3A4-mediated pharmacokinetic conflict, altered host defence, the diagnostic difficulty of CNS tuberculosis in an immunocompromised host, multifactorial cytopenia and severe hypercalcaemia. Each is discussed below.

The rifampicin-dasatinib CYP3A4 interaction

The pharmacokinetic interaction between rifampicin and dasatinib is the central therapeutic problem in this case.

Dasatinib is a Biopharmaceutics Classification System class II compound (low aqueous solubility, high permeability) that undergoes primarily CYP3A4-mediated oxidative metabolism with a secondary contribution from P-glycoprotein efflux, and its exposure increases proportionally with dose.^{3,4}

At 100 mg once daily the steady-state C_{max} is approximately 82.2 ng/mL (coefficient of variation 69%).³ Exposure-response analyses have associated a C_{max} of approximately 50 ng/mL with achieving major molecular response, and trough concentrations above the approximately 2.5 ng/mL with an increased risk of the pleural effusion.⁴

Rifampicin induces CYP3A4 and P-glycoprotein through activation of the pregnane X receptor (PXR, NR1I2), which transcriptionally upregulates CYP3A4 and ABCB1 among other enzymes and transporters.¹⁶ In a dedicated drug-drug interaction study in healthy volunteers, rifampicin 600 mg once daily for eight days reduced the mean C_{max} and AUC of a single 100 mg dose of dasatinib by 81% and 82%, respectively, which would be expected to bring dasatinib C_{max} well below the 50 ng/mL efficacy

threshold (Figure 5).³ Rifampicin meets the regulatory definition of a strong inducer, that is, one that decreases the AUC of a sensitive substrate by 80% or more.¹⁷ The dasatinib label recommends avoiding strong CYP3A4 inducers and states that a dose increase may be necessary if co-administration cannot be avoided, and physiologically based pharmacokinetic modelling indicates that restoring exposure in this setting would require substantially higher doses than used clinically.^{3,18}

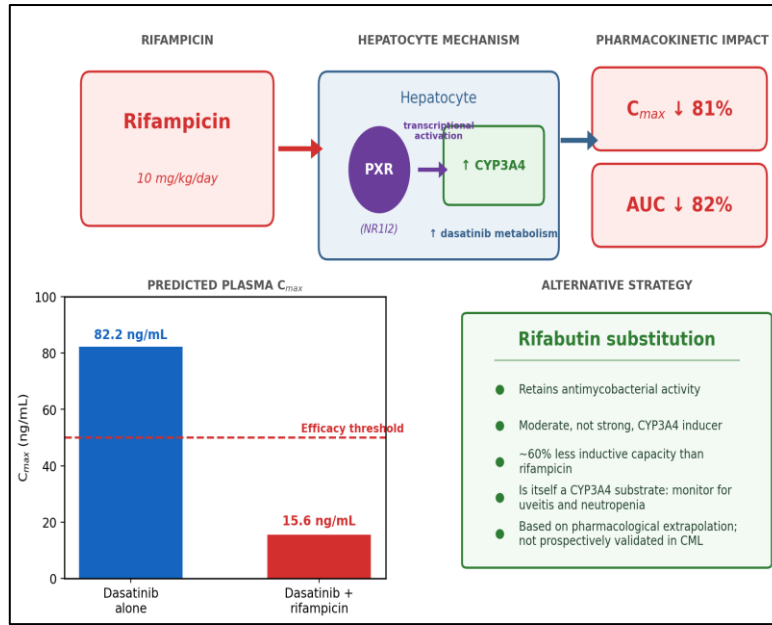


Figure 5: CYP3A4-mediated interaction between rifampicin and dasatinib.

*Rifampicin activates the pregnane X receptor (PXR, NR1I2), upregulating hepatic CYP3A4 expression; the resulting increase in enzyme activity accelerates dasatinib metabolism and reduces its C_{max} and AUC by 81% and 82%, respectively. The bar chart compares the reported steady-state dasatinib C_{max} at 100 mg once daily (82.2 ng/mL) with the value predicted in the presence of rifampicin (approximately 15.6 ng/mL), against the 50 ng/mL efficacy threshold. Rifabutin, a moderate CYP3A4 inducer, is shown as a potential alternative.

In the present case dasatinib was escalated from 100 mg to 140 mg daily. Because enzyme induction reduces exposure multiplicatively, a 40% dose increase applied to an exposure reduced to about 18% of baseline would restore AUC only to approximately 25% of that achieved with 100 mg alone ($0.18 \times 1.4 \approx 0.25$); full compensation would require roughly a five-fold dose increase. Moreover, the inductive effect of rifampicin develops over one to two weeks of continuous dosing, so the reduction during sustained anti-tubercular therapy may be at least as great as that seen in the eight-day healthy-volunteer study.¹⁶ Escalation beyond 140 mg daily would exceed the labelled maximum and increase the risk of toxicity, particularly pleural effusion.^{3,4}

Tuberculosis susceptibility during dasatinib therapy

The occurrence of tuberculosis in a patient with well-controlled CML raises questions about the immunological consequences of TKI therapy. Abelson tyrosine kinase regulates phagosomal acidification in human macrophages

through transcriptional control of the vacuolar-type H^+ -ATPase, and its pharmacological inhibition alters the macrophage handling of intracellular *M. tuberculosis*.⁶ Dasatinib additionally inhibits the SRC family kinase LCK, which is essential for T-cell receptor signalling. In human cells, dasatinib impaired the proliferation, cytokine release (interferon- γ , tumour necrosis factor- α , granulocyte-macrophage colony-stimulating factor), granulysin expression and degranulation of *M. tuberculosis*-specific T lymphocytes; notably, despite this profound loss of T-cell function, intracellular mycobacterial growth in macrophages was still suppressed through dasatinib-triggered lysosomal acidification.⁷ The net effect in vivo therefore reflects a balance between impaired adaptive surveillance and partially preserved innate antimicrobial activity.

Clinically, the ESCMID Study Group for Infections in Compromised Hosts identified dasatinib as having the strongest off-target immunosuppressive activity among the BCR::ABL1 TKIs, with documented associations with

cytomegalovirus reactivation and *Pneumocystis jirovecii* pneumonia.⁸ Tuberculosis complicating TKI therapy has been reported with imatinib and with dasatinib, and the coexistence of CML and tuberculosis has been described as a recurring clinical problem.⁹⁻¹¹ The present case suggests that the effects on adaptive immunity may predominate in vivo, particularly when compounded by the physiological stress of severe infection.

Diagnostic challenges of central nervous system tuberculosis

The diagnosis of CNS tuberculosis in this patient was difficult. Despite meningeal signs and MRI findings suggestive of a tuberculous aetiology, the CSF was microbiologically negative. This does not exclude the diagnosis: in a systematic review and meta-analysis, the pooled sensitivity of Xpert MTB/RIF on CSF was 85% against definite tuberculous meningitis and 81% against probable disease, so a substantial minority of true cases test negative.¹⁹ Similarly, CSF ADA lacks the sensitivity to exclude tuberculous meningitis, and its diagnostic performance varies considerably with the cut-off applied.²⁰ The Marais consensus case definition (Figure 6) integrates

clinical features, CSF findings, cerebral imaging and evidence of tuberculosis elsewhere; with imaging available, a total score of 12 or more is required for “probable” and 6-11 for “possible” tuberculous meningitis, in each case after reasonable exclusion of alternative diagnoses.¹⁵ Applied retrospectively to the documented findings, the patient scores 1 clinical point (altered consciousness; the three-day symptom duration falls short of the more-than-five-day criterion), 1-4 CSF points (lymphocytic predominance is documented, whereas appearance, cell count and protein concentration were not recorded, and the glucose ratio was normal), 3-5 imaging points (tuberculomas and infarcts, with a further 2 points only if the meningeal enhancement involved the basal meninges) and no points for extra-CNS tuberculosis. The resulting score of 5-10 places the case, at most, in the “possible” category. Because empirical anti-toxoplasma therapy was given concurrently, the clinical improvement cannot be attributed to anti-tubercular therapy alone. The diagnosis in this case therefore rests on clinical judgement—the neuroimaging pattern, the endemic setting and the immunocompromised state—rather than on consensus criteria for probable disease, and this should be borne in mind when interpreting the case.

Marais consensus case definition for tuberculous meningitis	
Marais S et al. Lancet Infect Dis 2010;10:803-812	
CLINICAL CRITERIA (maximum 6)	
Symptom duration > 5 days	+4
Systemic symptoms suggestive of tuberculosis	+2
History of recent close contact with a tuberculosis case	+2
Focal neurological deficit (excluding cranial nerve palsy)	+1
Cranial nerve palsy	+1
Altered consciousness	+1
CEREBROSPINAL FLUID CRITERIA (maximum 4)	
Clear appearance	+1
White cell count 10-500 cells/ μ L	+1
Lymphocytic predominance (> 50%)	+1
Protein concentration > 1 g/L	+1
CSF to plasma glucose ratio < 50%, or glucose < 2.2 mmol/L	+1
CEREBRAL IMAGING CRITERIA (maximum 6)	
Hydrocephalus	+1
Basal meningeal enhancement	+2
Tuberculoma	+2
Infarct	+1
Pre-contrast basal hyperdensity	+2
EVIDENCE OF TUBERCULOSIS ELSEWHERE (maximum 4)	
Chest radiograph suggestive of active tuberculosis	+2
Chest radiograph showing miliary tuberculosis	+4
CT / MRI / ultrasound evidence of extra-CNS tuberculosis	+2
Acid-fast bacilli or M. tuberculosis cultured from another site	+4
DIAGNOSTIC CATEGORIES	
■ Definite	Acid-fast bacilli seen in CSF, M. tuberculosis cultured from CSF, or a positive CSF nucleic acid amplification test
■ Probable	Total score $\geq$ 12 when cerebral imaging is available ($\geq$ 10 without imaging), with at least 2 points from CSF or imaging criteria, and exclusion of alternative diagnoses
■ Possible	Total score 6-11 with imaging (6-9 without imaging), and exclusion of alternative diagnoses
Applied retrospectively to the documented findings, the present case scores 5-10 (clinical 1; CSF 1-4, as cell count, protein and appearance were not recorded; imaging 3-5, depending on basal meningeal involvement; extra-CNS evidence 0), i.e. at most POSSIBLE tuberculous meningitis — below the score of 12 required for 'probable' with imaging.	

Figure 6: Marais consensus case definition for tuberculous meningitis, with criteria grouped by clinical features, cerebrospinal fluid findings, cerebral imaging and evidence of tuberculosis elsewhere, together with diagnostic categories.¹⁵

*Applied retrospectively to the documented findings, present case scores 5-10, corresponding at most to possible tuberculous meningitis.

Multifactorial cytopenia

The progressive cytopenia cannot be attributed to a single cause; at least four overlapping mechanisms merit consideration. First, marrow infiltration by the malignant clone can itself cause cytopenias, particularly with progression to accelerated phase, and the rising leukocyte count at readmission ($53.3 \times 10^3/\mu\text{L}$ with 29% monocytes) raises this possibility. Second, dasatinib causes clinically significant myelosuppression, with grade 3-4 neutropenia and thrombocytopenia each occurring in approximately one fifth to one third of patients with chronic-phase CML.³ Third, anti-tubercular drugs contribute through several mechanisms, including rifampicin-associated immune thrombocytopenia and isoniazid-associated sideroblastic anaemia arising from interference with pyridoxine metabolism.²¹ Fourth, tuberculosis itself causes cytopenias through marrow infiltration by granulomas, haemophagocytosis and the systemic inflammatory response; pancytopenia and thrombocytopenia are more frequent in disseminated than in pulmonary disease, and the haemogram typically improves with effective anti-tubercular therapy.^{21,22} Identifying the dominant contributor at readmission was not possible without bone marrow examination, repeat cytogenetics and BCR::ABL1 transcript monitoring at that time point, none of which were available.

Hypercalcaemia: granulomatous versus paraneoplastic aetiology

The severe hypercalcaemia at readmission has two plausible mechanisms. Granulomatous disease, including tuberculosis, is a recognised cause of PTH-independent hypercalcaemia: activated macrophages within granulomas express 1 α -hydroxylase (CYP27B1), converting 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which increases intestinal calcium absorption and bone resorption independently of PTH. The biochemical hallmarks are suppressed PTH with elevated 1,25-dihydroxyvitamin D.²³ The alternative is hypercalcaemia of malignancy, mediated by PTHrP secretion or osteolytic bone involvement, which in CML is uncommon and generally associated with advanced-phase disease.²³

Because this patient was last documented to be in chronic phase, granulomatous calcitriol-mediated hypercalcaemia is the more plausible explanation, and the rapid improvement after supportive care is compatible with this mechanism. However, disease progression could not be excluded at readmission, and PTH, PTHrP and vitamin D metabolites were not measured, which precludes definitive mechanistic attribution.

Potential management strategies

No evidence-based guidelines exist for the concurrent management of CML and active tuberculosis, and each of

the partially validated strategies available carries significant limitations.

Rifabutin substitution is the most widely discussed approach. Rifabutin retains antimycobacterial activity against *M. tuberculosis* while exerting substantially less CYP3A4 induction than rifampicin.^{16,24} However, rifabutin is itself a CYP3A4 substrate, and co-administration with a drug possessing weak CYP3A4 inhibitory properties such as dasatinib could increase rifabutin exposure, requiring monitoring for uveitis and neutropenia.^{3,24} This approach rests on pharmacological extrapolation rather than prospective clinical data in CML.

Rifampicin-free anti-tubercular regimens are a second option. The World Health Organization recommends the six-month all-oral BPaLM regimen (bedaquiline, pretomanid, linezolid and moxifloxacin) for eligible patients with drug-resistant tuberculosis, alongside other shortened regimens.²⁵ Although developed for drug-resistant disease, their rifampicin-free composition makes them pharmacologically attractive for patients receiving CYP3A4-substrate TKIs. Their use for drug-susceptible tuberculosis remains investigational, and bedaquiline and linezolid carry their own toxicities, notably QT prolongation and myelosuppression, the latter particularly unwelcome in a patient who is already cytopenic.

Switching to imatinib, nilotinib or bosutinib does not resolve the conflict, because each depends on CYP3A4 for its elimination. Asciminib, which the 2025 European LeukemiaNet recommendations include among first-line options, is more promising: in healthy subjects, rifampicin reduced asciminib AUC by only approximately 13-15%, a change not considered clinically meaningful given its wide therapeutic window.^{2,26} These data derive from single-dose studies in healthy volunteers, however, and no clinical experience of asciminib with rifampicin-based anti-tubercular therapy in patients with active tuberculosis has been reported; access and cost may also be limiting in endemic settings.

TDM of dasatinib, where available, could provide a rational basis for dose adjustment during co-administration with rifampicin or rifabutin, using the proposed targets of a C_{max} of approximately 50 ng/mL for molecular response and a trough concentration below approximately 2.5 ng/mL to limit the risk of pleural effusion.⁴ TDM-guided dosing with BCR::ABL1 IS monitoring at four-to-six-weekly intervals would be a rational approach, although dasatinib TDM is not routinely available in most settings, least of all in the resource-limited, tuberculosis-endemic regions where this scenario is most likely to arise.

In summary, the management of concurrent CML and tuberculosis should ideally incorporate: substitution of rifabutin for rifampicin where available; consideration of rifampicin-free regimens or a switch to asciminib in consultation with infectious diseases specialists and haematologists; BCR::ABL1 IS monitoring at four-to-six-

weekly intervals during concurrent therapy; TDM of dasatinib where feasible; weekly haematological monitoring during the intensive phase of anti-tubercular therapy; and a multidisciplinary approach involving clinical pharmacologists, haematologists and infectious diseases physicians.

Limitations

This report has several limitations inherent to a retrospective single-case description. Tuberculosis was diagnosed clinically without microbiological confirmation, the documented findings meet at most the “possible” category of the Marais case definition, evidence of extra-CNS tuberculosis was not documented, and concurrent anti-toxoplasma therapy confounds the interpretation of the treatment response. Dasatinib plasma concentrations were not measured, so the loss of exposure is inferred from published pharmacokinetic data rather than demonstrated in this patient. BCR::ABL1 transcript levels, cytogenetics and bone marrow examinations were not obtained at readmission, so disease progression could not be confirmed or excluded. PTH, PTHrP and vitamin D metabolites were not measured, leaving the mechanism of hypercalcaemia unconfirmed, and follow-up data beyond discharge were not available.

CONCLUSION

This case illustrates the pharmacokinetic conflict between dasatinib and rifampicin and the clinical consequences that may follow when dose escalation within the approved range cannot compensate for an approximately 82% reduction in drug exposure. The absence of standardised guidance for concurrent CML and tuberculosis represents a real gap in clinical practice, particularly in tuberculosis-endemic regions. Priorities for future work include prospective pharmacokinetic studies of rifabutin-dasatinib co-administration with TDM, clinical evaluation of asciminib and of rifampicin-free regimens in patients with CML and drug-susceptible tuberculosis, incorporation of latent tuberculosis screening into routine pre-TKI assessment in endemic regions, and international consensus guidance integrating pharmacokinetic modelling, drug monitoring data and clinical outcomes.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Bhairumali M, Sankar A, Ronanki K, Singh HS, Bairwa M. Disseminated tuberculosis with central nervous system involvement in a patient with chronic myeloid leukaemia receiving dasatinib: cytochrome P450 3A4-mediated drug interaction and multifactorial cytopenia. *Int J Basic Clin Pharmacol* 2026;15:1402-11.