CASE REPORT

Invasive aspergillosis complicating treatment with tyrosine kinase inhibitors

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SUMMARY

We describe three cases of pulmonary aspergillosis (PA) in three patients without traditional risk factors for invasive aspergillosis infection, such as prolonged neutropenia or high dose systemic corticosteroid therapy. All three patients developed PA while taking tyrosine kinase inhibitors (TKI) and sustained greater clinical improvement once TKI were withdrawn. Our case series supports the theory TKI treatment can increase susceptibility to PA without causing neutropenia. Recognition that TKI treatment may predispose to invasive aspergillosis will allow for rapid recognition of affected patients and more effective management of future cases.

BACKGROUND

The mitogen-activated protein kinase (MAPK) signalling pathway is involved in the pathophysiology of numerous cancers, including melanoma, leukaemia, pancreatic, colon, lung, biliary tract, salivary gland and thyroid carcinoma.^{1 2} As a consequence, tyrosine kinase inhibitors that lead to MAPK pathway inhibition are increasingly used in the treatment of malignant disease. Treatment with tyrosine kinase inhibitors (TKI) causes a degree of immunosuppression and has been associated with the development of various infections including gastroenteritis, upper respiratory tract infection, acute bronchitis, pneumonia, bursitis, cellulitis and pyelonephritis.^{3–5} A randomised double-blind placebo-controlled study of a highly selective p38 MAPK inhibitor demonstrated increased risk of infection compared with placebo (11% vs 5%), particularly serious infections (4.8% vs 0%).³

An important infection of severely immunocompromised patients is acute pulmonary aspergillosis (PA), which is most commonly associated with prolonged neutropenia or treatment with high dose systemic corticosteroids.^{6 7} More indolent forms of PA are associated with chronic lung disease and milder immunodeficiencies. Here we describe three cases of PA developing in patients receiving TKI treatment, an association that has only recently been reported with ibrutinib.^{8–14}

CASE PRESENTATION**Patient 1**

A 63-year-old woman was commenced on ibrutinib 420 mg once daily for chronic B cell lymphocytic leukaemia (CLL). Previous chemotherapy treatment

included two cycles of fludarabine, cyclophosphamide and rituximab (FCR) over 40 months prior, and two cycles of reduced intensity FCR 27 months prior, to starting ibrutinib. She had also received 4 months of ofatumumab (monoclonal antibody to CD20) as part of a trial, which was stopped 4 months before commencing ibrutinib due to a rising white cell count. She required one tapering course of systemic steroids for autoimmune haemolytic anaemia 8 months prior to commencing ibrutinib.

Figure 1 (A) Bilateral nodular consolidation on CT chest. (B) Liver nodule on CT imaging of the upper abdomen. (C) Space-occupying lesions demonstrated on MRI brain.

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Figure 2 (A) Bilateral macronodules with surrounding halos on CT chest. (B) Resolution of macronodules with residual focal scarring on repeat CT chest.

On day +10 of ibrutinib treatment the patient presented with fever and cough productive of yellow sputum and was treated with 7 days of co-amoxiclav and clarithromycin. She re-presented to hospital on day +15 of ibrutinib treatment with persistent fevers and rigors, and new mild left lower limb pyramidal weakness. There were multiple new densities throughout both lungs on her chest x-ray. Neutrophil count was 1.39. CT scanning revealed multiple bilateral pulmonary (figure 1A), liver (figure 1B) and thyroid nodules and space occupying lesions of the brain (figure 1C). CT guided biopsy of a right lower lobe lung nodule demonstrated fungal hyphae on histopathology and was culture positive for *Aspergillus fumigatus*. Additional liver and skin biopsies demonstrated the presence of *Aspergillus fumigatus* on histopathological analysis, with growth also on fungal culture. Thyroid nodule fine needle aspiration showed necrosis and ghosts of fungal hyphae only. Brain biopsy was not performed. Despite treatment with triple antifungal therapy (ambisome, voriconazole and amphotericin B) and ibrutinib, the patient developed a new pustular lesion to the left arm. Skin punch biopsy demonstrated necrosis, fungal spores and hyphae suggestive of *Aspergillus* on histopathology, and fungal culture demonstrated *Aspergillus fumigatus*. There was also radiological progression on CT chest. Once ibrutinib therapy was stopped no new lesions developed either clinically or radiologically. The patient was discharged home with posaconazole and flucytosine but continued to clinically deteriorate due to aggressive CLL and died on day +267.

Figure 3 (A) Left upper lobe cavitating lesion on CT chest. (B) Filling in of left upper lobe cavity on repeat CT chest.

Patient 2

A 58-year-old woman with chronic myeloid leukaemia was treated with a succession of TKI over 8 years, initially with imatinib, followed by nilotinib, dasatinib and finally changing to bosutinib 500 mg once daily due to intolerance of the previous TKI. She had not received any other chemotherapy agent or systemic corticosteroids and had no history of neutropenia. She presented on day +61 of bosutinib therapy with breathlessness and was treated with a course of amoxicillin with no clinical improvement. The patient re-presented to our hospital on day +89 with fever, cough and dyspnoea. Construction work was being conducted within her home during this time. Chest x-ray demonstrated bilateral patchy areas of consolidation. Neutrophil count was 7.37. CT scan demonstrated multiple bilateral pulmonary macronodules with surrounding halos characteristic of PA (figure 2A). Blood and sputum cultures were negative. Serum galactomannan was not performed. The patient was too hypoxic to have a bronchoscopy. She was commenced empirically on ambisome, imipenem and amikacin, and the bosutinib was stopped. She made steady clinical and radiological improvement, and the antibiotics were stopped after 2 weeks. After 12 days the ambisome was switched to oral voriconazole for 2 months. She made a full clinical recovery, and repeat CT scanning showed resolution of the macronodules with residual focal scarring (figure 2B). Although patient 2 lacked microbiological evidence of *Aspergillus* infection, the CT changes and steady clinical and radiological improvement with antifungal treatment were highly suggestive of PA rather than other infective diagnoses.

Patient 3

A 72-year-old man underwent gastrectomy for a gastrointestinal stromal tumour of the stomach and was subsequently commenced on imatinib 200 mg once daily, increasing to 300 mg, then 400 mg once daily after 6 months. After 12 months of imatinib treatment, routine interval CT imaging revealed a new small cavitating left apical lung lesion at the site of a previously stable solid nodule (figure 3A). Although the patient remained asymptomatic, subsequent imaging over the next 12 months showed slowly progressive changes with the development of a new cavitating left upper lobe lesion and patchy nodular infiltrates. The patient was never neutropenic. Bronchoscopy was performed and bronchoalveolar lavage fluid from the left upper lobe contained fungal hyphae when examined by microscopy, and was culture positive for *Aspergillus fumigatus* and *Aspergillus flavus*. Bacterial and mycobacterial cultures were negative. He was treated initially with voriconazole 200 mg twice daily, which was stopped due to rash. Although voriconazole may increase plasma levels of TKIs, the dose of imatinib did not have to be adjusted after the introduction of voriconazole. The measured voriconazole levels were within target therapeutic range. Repeat CT scan demonstrated progressive changes and intravenous caspofungin was commenced for 40 days. After 4 months, CT imaging demonstrated further progression and the patient was commenced on itraconazole, which was stopped within 2–3 weeks due to tremor and an influenza-like reaction. At this point imatinib was stopped and subsequently there was radiological improvement (figure 3B). Bronchoalveolar lavage demonstrated microbiological improvement with a negative *Aspergillus* culture despite the patient not having received further antifungal treatment.

DISCUSSION

Here we describe three cases of PA which did not at the time of developing the infection have the conventional high-risk factors for this infection (eg neutropenia, high dose systemic corticosteroids),^{6,7} but were taking TKI. Patient 1 had biopsy-proven disseminated PA. Patient 2's CT changes and steady clinical and radiological improvement with antifungal treatment was highly suggestive of PA rather than other infective diagnoses. Patient 3 had radiological and microbiological evidence of slowly progressive PA. Withdrawal of TKI treatment was associated with no further progression of disseminated aspergillosis for patient 1, despite prior progression on antifungals. Withdrawal of TKI treatment and concurrent antifungal treatment was associated with clinical and radiological improvement in patient 2. Patient 3 demonstrated radiological and microbiological improvement on withdrawal of TKI, despite suboptimal antifungal therapy due to drug intolerance. These cases suggest that despite not causing neutropenia, treatment with TKI does increase susceptibility to *Aspergillus* infection. Our case series also suggests withdrawal of TKI promotes clinical recovery and should be considered in patients with significant evidence of active *Aspergillus* infection. Azole sensitivity testing is not routinely performed at our hospital but would have been important if any of our cases had exhibited poor clinical response to single agent azole therapy.

If invasive pulmonary aspergillosis is suspected clinically, early diagnostic tests should include blood and sputum cultures, serum galactomannan and early CT chest. Bronchoscopy with bronchoalveolar lavage, or diagnostic tissue sampling with transbronchial or transthoracic biopsies, are useful to obtain microbiological diagnosis, but may not be suitable for all patients.

A recent retrospective study shows increased incidence of invasive fungal infection in CLL patients taking ibrutinib.⁸ Invasive aspergillosis accounted for 27/33 cases with 11/27 demonstrating cerebral involvement. Another retrospective study has shown 37.2% of patients receiving ibrutinib for lymphoid cancer developed invasive fungal infection.⁹ Multiple case reports also support an association of invasive aspergillosis with ibrutinib therapy,^{10–14} with several case reports suggesting an association with cryptococcal infection.^{14–20} Mucormycosis and *Pneumocystis jirovecii* with ibrutinib therapy have also been described.^{21–23}

There is considerably less data to support an association between either imatinib or bosutinib treatment with invasive fungal or *Aspergillus* infection. There is one report of early-onset mucormycosis in a patient with acute lymphoblastic leukaemia receiving imatinib alongside other immunosuppressive treatment,²⁴ and one case of *Candida krusei* and *Candida glabrata* pneumonia in a patient receiving imatinib only for chronic myeloid leukaemia.²⁵

Recently, Herbst *et al* described a macrophage cell signalling pathway (Toll-like receptor 9 (TLR)-Bruton's Tyrosine Kinase (BTK) calcineurin-Nuclear factor of activated T-cells pathway (NFAT)) that requires activation of Bruton's Tyrosine Kinase. This macrophage signalling pathway is critically important for rapid recruitment of neutrophils. A deficient early chemokine response leads to impaired neutrophil recruitment and reduced immunity against *Aspergillus* infection in zebrafish.²⁶ BTK's importance in the innate immune system's response to fungal infection has been demonstrated in murine models and has been implicated in immune responses to *Candida* infection.²⁷ Ibrutinib, imatinib and bosutinib inhibit BTK, and these findings provide a potential mechanism by which TKI could predispose to PA in patients with a normal circulating neutrophil count.

Recognition that TKI may predispose to invasive aspergillosis, and potentially other fungal infections, such as cryptococcosis and mucor,^{14–21} will allow rapid recognition of affected patients and more effective management of future cases.

Learning points

- ▶ Long-term steroids and prolonged neutropenia are considered typical risk factors for developing invasive aspergillosis infection.
- ▶ Treatment with tyrosine kinase inhibitors (TKI) may be a risk factor for invasive aspergillosis.
- ▶ A high index of suspicion in patients with fever, cough and imaging consistent with invasive aspergillosis in patients taking TKI treatment is recommended, with early commencement of antifungal therapy.
- ▶ Stopping TKI treatment while treating for invasive aspergillosis may promote recovery.
- ▶ A potential mechanism for TKI predisposing to invasive aspergillosis with a normal circulating neutrophil is through inhibition of a macrophage cell signalling pathway that is critically important for rapid recruitment of neutrophils against *Aspergillus*.

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