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Case report

Opportunistic coinfection with *Pneumocystis jirovecii* and *Coccidioides immitis* associated with idelalisib treatment in a patient with chronic lymphocytic leukaemia

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SUMMARY

We describe a case of opportunistic coinfections with *Coccidioides immitis* and *Pneumocystis jirovecii* following treatment with idelalisib, a phosphoinositide 3-kinase inhibitor, for chronic lymphocytic leukaemia. This is the first case of pulmonary coccidioidomycosis reported in association with idelalisib. We review challenges related to diagnosis of opportunistic infections in this context. This report illustrates (1) the uncommon occurrence of two opportunistic infections concurrently or in rapid succession, (2) the importance of maintaining a broad differential diagnosis in the setting of an atypical imaging finding, slow clinical response or when immunomodulatory drugs are used, and (3) the challenges associated with non-invasive serological testing in individuals with haematological malignancy on immunomodulatory therapy.

BACKGROUND

Pneumocystis jirovecii pneumonia (PJP) is one of the most common and severe infections in immunocompromised patients.[1] PJP commonly presents with dyspnoea, fever and cough. Imaging findings are variable, but imaging with either chest radiograph or CT scan typically demonstrates bilateral ground glass opacities without or with cysts and rarely, discrete thin-walled cavitary lesions.[2] It is well documented that idelalisib, a phosphoinositide 3-kinase inhibitor, increases the risk of developing PJP, and it is recommended that patients on this agent take PJP prophylaxis for up to 6 months following treatment discontinuation.[3 4]

Coccidioidomycosis is a disease caused by the dimorphic fungus *Coccidioides*, which is endemic to the southwestern USA, including central California. Among immunocompetent hosts, *Coccidioides* infections are often subclinical but can manifest as self-limited acute or subacute community acquired pneumonia.[5] Immunocompromised hosts most often demonstrate pulmonary involvement, although extrapulmonary involvement can also occur. A case series of 55 patients with haematological malignancy complicated by *Coccidioides* infection has been described, of which pulmonary involvement was present in 95% of cases. Although most patients had received cytotoxic chemotherapy, none were on a modern immunomodulatory regimen.[6]

We present the case of an elderly man with advanced chronic lymphocytic leukaemia (CLL) and interstitial lung disease (ILD) who developed PJP and ruptured cavitary coccidioidomycosis following treatment with idelalisib. This, to our knowledge, is the first report of pulmonary *Coccidioides* infection in association with idelalisib. This case illustrates a possible relationship between idelalisib and *Coccidioides* infection.

CASE PRESENTATION

An elderly Caucasian man with advanced CLL (Rai stage IV, Binet stage C) on idelalisib and mild ILD of unknown aetiology was admitted to our hospital in the fall of 2017 with 1 month of fever, non-productive cough and progressive shortness of breath. One week prior to admission, a chest radiograph showed a new left basilar consolidation concerning for community acquired pneumonia. His symptoms did not improve after a 7-day course of levofloxacin 750 mg daily. A lifetime non-smoker, he denied recent sick contacts, but he reported extensive recent travel in China, Southeast Asia and central California.

On arrival to our hospital, the patient had a temperature of 36.4°C, respiratory rate of 24 breaths/min, pulse of 103 beats/min and an oxygen saturation of 91% on ambient air. He appeared uncomfortable, and his respiratory examination was significant for diffuse crackles.

INVESTIGATIONS

His white cell count was 13×10^9/L. CT of the chest without contrast showed a mass-like consolidation in the left lower lobe as well as numerous irregular pulmonary nodules throughout all lobes with surrounding halos of ground glass opacification. Progressive mediastinal and bilateral hilar lymphadenopathy compatible with CLL was also noted (figure 1A,B).

Direct fluorescent antibody testing on bronchoalveolar lavage fluid (BAL) was positive for *Pneumocystis jirovecii*. BAL bacterial, fungal and acid-fast bacteria cultures demonstrated no growth, and

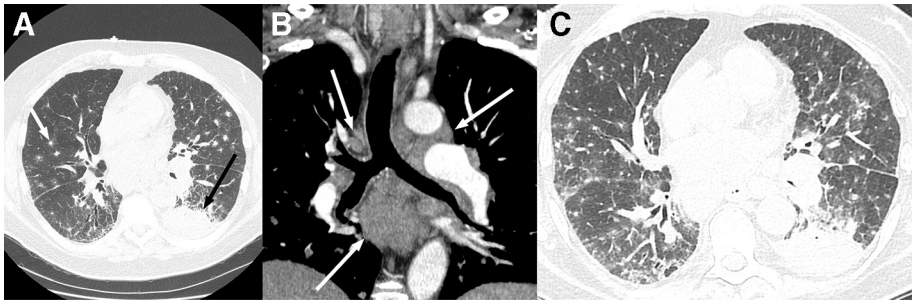

Figure 1 A–C. Baseline axial CT on lung windows (A) demonstrates a dominant region of consolidation in the left lower lobe (black arrow) and multiple bilateral small nodules with halos of ground glass opacity (white arrow). Coronal contrast enhanced CT on mediastinal windows (B) shows symmetric bilateral hilar and mediastinal (white arrows) lymphadenopathy compatible with CLL. A follow-up CT 1 month later, (C) shows multiple new small scattered bilateral pulmonary nodules. In this case, the dominant left lower lobe consolidation likely corresponds to coccidioidomycosis infection, whereas the small scattered bilateral nodules likely correspond to *Pneumocystis jirovecii* infection. CLL, chronic lymphocytic leukaemia.

extensive serum antibody testing was negative for other pathogens, including *Histoplasma*, *Cryptococcus* and *Coccidioides* spp. Serum beta-D-glucan testing was also negative.

TREATMENT

The patient was started on intravenous vancomycin 750 mg two times a day, piperacillin-tazobactam 4.5 g every 6 hours and azithromycin 500 mg daily prior to bronchoscopy. The patient completed a 21-day course of therapy with trimethoprim-sulfamethoxazole (TMP-SMX) 3.5 double strength (DS) tabs every 8 hours (15 mg/kg/day) for PJP. Idelalisib was discontinued, and the patient was started on PJP prophylaxis with TMP-SMX 1 DS tab daily.[3]

OUTCOME AND FOLLOW-UP

Three months later, the patient reported moderate improvement in his symptoms but had continued dyspnoea on exertion and an ongoing supplemental oxygen requirement. A follow-up chest CT demonstrated persistent left lower lobe consolidation with necrotic features and new small scattered bilateral pulmonary nodules (figure 1C). Given concern for a possible superimposed anaerobic infection, treatment with amoxicillin/clavulanate 875/125 mg two times a day was initiated. However, after 90 days of treatment, he reported no further improvement in his symptoms. A repeat chest CT showed new cavitation within the left lower lobe consolidation and a new left-sided pleural effusion. Given evidence of radiographic progression, a thoracentesis was performed, and pleural fluid cytology showed findings consistent with CLL. Fine-needle aspiration of the left lower lobe mass showed numerous, variably sized, ovoid to circular spherules and endospores, and tissue fungal culture eventually grew *Coccidioides immitis*. No malignant cells were observed. Repeat serum immunodiffusion for *Coccidioides* spp was negative, serum complement fixation was uninterpretable due to anticomplement activity and enzyme immunoassay antigen for *Coccidioides* was not detected. *Coccidioides* serum antigen was not detected from BAL fluid from the right and left lung, but adenosine deaminase activity was elevated at 29.7. Treatment with fluconazole 800 mg daily was initiated, and he was discharged home. Further anti-CLL therapy was deferred until his acute infectious issues were under control.

Two weeks into fluconazole therapy, the patient was readmitted with progressive respiratory decline and hypoxaemia. On examination, he appeared fatigued and tachypneic with decreased breath sounds on the left side and crackles at the right base; imaging showed progressive pleural effusions, left greater than right. Despite initial symptom relief after placement of a left-sided chest tube, his course was complicated by cavity rupture into the left pleural space and by the development of a bronchopleural fistula. Due to his comorbidities and rapid decline in functional status, surgery was not pursued. Over the next 2 weeks, he received liposomal amphotericin B 500 mg daily (5 mg/kg) for severe *Coccidioides* infection. However, his oxygen requirement continued to escalate, prompting additional treatment for 7 days with intravenous vancomycin 1 g two times a day and piperacillin-tazobactam 4.5 g every 6 hours for possible superimposed bacterial pneumonia. After a discussion with his family and providers, the patient elected to return home and transition to comfort-focused care. He was discharged home with hospice services, where he died peacefully 2 days later.

DISCUSSION

This case illustrates (1) the uncommon occurrence of two opportunistic infections concurrently or in rapid succession, (2) the importance of maintaining a broad differential diagnosis in the setting of an atypical imaging finding, slow clinical response or when immunomodulatory drugs are used and (3) the challenges associated with non-invasive serological testing in individuals with haematological malignancy on immunomodulatory therapy.

This is the first case report of two fungal opportunistic infections diagnosed in series following idelalisib use. While imaging on initial presentation was compatible with PJP, we cannot exclude the presence of concurrent *Coccidioides* infection. Even if the two infections occurred in rapid succession, the diagnosis of *Coccidioides* was likely delayed due to (1) the presence of a preceding diagnosis of an alternative opportunistic pathogen and (2) the perception that the patient would be unlikely to have a second opportunistic infection, especially since immunomodulatory therapy had been suspended. This diagnosis was made only following an invasive procedure for another indication and demonstrates that it is important to consider multiple opportunistic infections in patients when aspects of the history and/or imaging are unusual.

Ultimately, coccidioidomycosis was diagnosed by culture and pathology, not by serology, illustrating the limited reliability of serological markers in immunocompromised patients. Unfavourable test characteristics have also been reported with serological testing for other endemic fungal infections in this patient population; for example, *Histoplasma* antibody testing is less sensitive in immunocompromised hosts, so it is recommended to test for the more sensitive *Histoplasma* antigen in that population.[7] In prior case reports of disseminated *Coccidioides*

infection in immunocompromised patients, serological testing was negative. In these cases, the diagnosis was also confirmed on pathology.[8 9] This case further supports the observation that serum antibody testing for *Coccidioides* may be unreliable in immunosuppressed patients, so providers must maintain a high index of suspicion for endemic fungi and adjust diagnostic plans accordingly.

In conclusion, this case emphasises that clinicians caring for patients on immunobiological agents should be vigilant about potential opportunistic infections and coinfections. As the use of immunobiological agents becomes more widespread, atypical presentations with coexisting or unusual opportunistic infections may become more common. We, therefore, encourage providers to maintain a high index of suspicion for endemic fungi in the immunocompromised population with relevant risk factors, even when serological testing is negative.

Learning points

- Although extremely rare, two opportunistic infections occurring concurrently or in rapid succession should be considered in patients who are immunocompromised.
- It is important to maintain a broad differential diagnosis in patients who are immunocompromised, who have atypical imaging findings or who have a slow clinical response.
- Serological testing in individuals with haematological malignancy on immunomodulatory therapy can be unreliable and a broad differential diagnosis must be maintained while evaluating and treating these patients.

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