



Case report

Invasive pulmonary aspergillosis and pulmonary tuberculosis in a patient treated with infliximab for Crohn's disease



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ABSTRACT

We report a case of concurrent development of active pulmonary tuberculosis and invasive pulmonary aspergillosis (IPA) in a patient who received therapy with infliximab for Crohn's disease. He has been treated with antitubercular therapy and liposomal amphotericin B for 8 weeks. His clinical course was complicated by paroxysmal atrial fibrillation requiring maintenance therapy with amiodarone, respiratory failure due both to pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamases (ESBL)-producing *Klebsiella pneumoniae* and pleural effusion requiring chest drainage. At discharge, a maintenance regimen based on the administration of isavuconazole 200 mg daily, moxifloxacin 400 mg daily and isoniazid 300 mg daily was chosen to avoid multiple drug-drug interaction between rifamycins, antifungal triazole agents and antiarrhythmic drugs. At 3 months of follow-up his clinical conditions were dramatically improved, high resolution chest tomography (HRCT) showed reduction of parenchymal lesions and no changes both in sinus rhythm and QTc interval were noticed. Besides the complexity and the peculiarity of the clinical scenario, this case underlines the risk of invasive fungal infections linked to the administration of TNF- α antagonists in gastroenterological setting and the importance of accurate evaluation of drug-drug interactions when choosing the antimicrobial therapies.

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Introduction

Tuberculosis is a known infective complication that may occur after the administration of TNF- α antagonists. Accumulating evidence suggests that biologic drugs for autoimmune diseases also play a role in the development of other opportunistic infections such as aspergillosis [1–7]. The concurrent development of both active tuberculosis and acute invasive aspergillosis in a single patient who underwent infliximab therapy has been only described once [3] and it raises questions about the pharmacological interactions between antitubercular, antifungal drugs and other therapies for concomitant diseases.

Case report

A 48-year-old Northern African man affected by Crohn's disease, protein-energy malnutrition and lymphopenia presented with fever, cough and respiratory failure in March 2018. He had received therapy with infliximab in December 2017. He received the last dose one month before the development of symptoms. His baseline Mantoux tested negative. At admission, a high resolution computed tomography (HRCT) showed bilateral pleural effusion, large parenchymal consolidation on the upper-right lobe, bilateral nodular consolidations, multiple mediastinic lymphadenopathies. We performed bronchoalveolar lavage (BAL) that showed positivity for *M. tuberculosis* PCR (XPert MTB/RIF[®]). QuantiFERON[®]-TB Gold Plus test resulted indeterminate. We then started antitubercular therapy with rifampicin 600 mg, isoniazid 300 mg, ethambutol 1200 mg and pyrazinamide 1500 mg plus pyridoxine 300 mg 3 times per week. He was also on treatment with dexamethasone 8 mg twice daily and on total parenteral nutrition due to the poor clinical condition.

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At admission he had WBC 2,300/uL, lymphocytes 440/uL, CD4+250/uL, hemoglobin 9.9 g/dL, C-reactive protein (CRP) 2.68 mg/dL (upper normal value 0.5). He reported penicillin allergy. The ECG on admission showed sinus rhythm with a QTc interval of 390 ms. Three days later, he developed atrial fibrillation that was successfully cardioverted with amiodarone. He remained afebrile for the following 7 days and the steroid dosage was slowly tapered to 4 mg of dexamethasone per day. Over the next two days he developed fever with chills and progressive worsening of dyspnea. All the blood cultures resulted negative.

Five days later, he developed respiratory failure, and another HRCT showed worsening of the pleural effusion and of the parenchymal lesions, with the appearance of new areas of consolidation. CRP was 12.7 mg/dL. Empiric therapy with linezolid and meropenem was added. In addition, we performed a second bronchoscopy and a thoracentesis. The Gene Xpert MTB/RIF® test resulted negative both on BAL fluid (BALF) and on pleural fluid. BALF culture resulted positive for extended-spectrum beta-lactamase producer (ESBL) *Klebsiella pneumonia* and methicillin-resistant *Staphylococcus aureus* (MRSA). Moreover, galactomannan determination on BALF resulted strongly positive and, therefore, liposomal amphotericin B (L-AmB) therapy was started at 3 mg/kg/day.

Despite a slight improvement during the first days of antimicrobial therapy, ten days after the BAL he developed again respiratory failure (PaO₂/FiO₂ ratio: 129). We performed another HRCT that showed worsening of the bilateral pleural effusion that required left chest drainage tube placement. Oxygen therapy and dexamethasone (8 mg I.V. BID) were reintroduced. After that, he became afebrile and CRP levels declined (from 13.9 mg/dL to 1.4 mg/dL during the next ten days). Antibiotics were interrupted after 21 days. In the meantime, steroidal therapy was progressively tapered. He stopped ethambutol and pyrazinamide after 8 weeks of treatment and he continued with TB maintenance therapy; chest drainage tube was removed after 27 days. During L-AmB therapy hypokalemia occurred, with daily need for potassium supplementation.

After 8 weeks of antifungal therapy, L-AmB was interrupted, rifampin was substituted with moxifloxacin 400 mg per day and isavuconazole was started at 200 mg every 8 h for the first 48 h, followed by 200 mg daily, along with daily ECG monitoring. No significant alterations in sinus rhythm and QTc interval were seen during therapy with isavuconazole compared to baseline ECG on admission. After the withdrawal of L-AmB, potassium levels returned normal. He was discharged after 83 days of hospitalization in good clinical conditions on maintenance therapy with isavuconazole 200 mg daily, moxifloxacin 400 mg daily and isoniazid 300 mg daily.

After discharge, no alteration in sinus rhythm and QTc interval was noticed at weekly follow-up. On follow-up chest HRCTs performed one and three months later, pulmonary lesions and pleural effusion were significantly reduced.

He received a total of 24 weeks of antitubercular and antifungal therapy.

Discussion

The use of biologic drugs for treating autoimmune diseases, including TNF- α antagonists, is associated with an increased risk of opportunistic infections [1,6,8].

Risk of invasive aspergillosis in patients treated with TNF- α antagonists is assumed to be low compared with TB and it is higher in patients with neutropenia [1]. However, only 35 cases of aspergillosis following TNF- α antagonist therapies are reported [1–57].

The concurrent development of tuberculosis and invasive aspergillosis has been rarely described, mostly in onco-hematologic settings [3,9]. We report the second case of such co-infection after TNF- α antagonists-based therapy [3]. Moreover, the described

case raises important issues about the management of pharmacologic interactions between the prescribed drugs.

Although voriconazole is a first line drug for the treatment of invasive aspergillosis [10], its use is limited by multiple potential drug-drug interactions, as it is both substrate and inhibitor of CYP3A4, CYP2C9, CYP2B6 and CYP2C19 cytochromes [11]. Thus, we started aspergillosis treatment with L-AmB, since the coadministration of rifampin or rifabutin could have significantly reduced the voriconazole serum concentration by inducing CYP3A4 cytochrome, while the administration of isoniazid might have increased voriconazole concentration by inhibiting CYP2C19 cytochrome [12]. In addition, we pursued this therapeutic choice to avoid the interaction between voriconazole and amiodarone, which might have prolonged QTc interval [13].

Once the patient had to be discharged, we interrupted L-AmB therapy and we prescribed oral isavuconazole as maintenance therapy. Isavuconazole is a recommended alternative primary therapy for IPA which demonstrated non-inferiority to voriconazole, with lower rates of drug-related hepatobiliary, ocular, and skin disorders [10]. It is the only triazole agent that shortens the QTc interval, with no evidence of associated increased cardiac risk [14]. Isavuconazole has fewer drug-drug interactions than other triazoles, but it is metabolized by the CYP3A4/5 pathway. Coadministration with rifamycins is contraindicated because of reduction in isavuconazole plasma concentration [15].

In this case, isavuconazole was chosen as maintenance therapy for IPA because of the favorable interaction profile with amiodarone; interaction with rifampin was prevented by substituting it with moxifloxacin 400 mg once daily. We assumed that the effect of isavuconazole in shortening QTc might have balanced the effect of moxifloxacin in prolonging it.

In conclusion, management of opportunistic infections in patients receiving biological therapies requires a multidisciplinary approach, and the possibility of concomitant infections should always be considered. Moreover, the best therapeutic approach should be evaluated case by case, taking into account the drug-to-drug interactions.

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Ethical approval

None required.

Conflict of interest

None, for all authors.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication.

Authors contributions

Conception and design of study: Buonomo Antonio Riccardo, Viceconte Giulio, Compare Debora, Nardone Gerardo, Servillo Giuseppe, Borgia Guglielmo, Gentile Ivan.

Acquisition of data: Buonomo Antonio Riccardo, Viceconte Giulio, Compare Debora, Zappulo Emanuela

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