CASE REPORT

Acute fibrinous organising pneumonia: a manifestation of trimethoprim-sulfamethoxazole pulmonary toxicity

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SUMMARY

A 50-year-old man was treated with trimethoprim-sulfamethoxazole (TMP-SMX) for acute arthritis of his right big toe. Within a few days, he developed dyspnoea, hypoxaemia and diffuse pulmonary infiltrates. Symptoms improved with discontinuation of the antibiotic but worsened again with its reintroduction. An open lung biopsy was performed. We describe the workup performed and the factors that pointed to a final diagnosis of TMP-SMX-related pulmonary toxicity in the form of acute fibrinous organising pneumonia.

BACKGROUND

This is a case of an unusual manifestation of pulmonary drug toxicity in relation to a very commonly prescribed antibiotic.

CASE PRESENTATION

A 50-year-old man developed acute arthritis of the right big toe and was treated with a methylprednisolone dose pack and trimethoprim-sulfamethoxazole (TMP-SMX) course for 10 days. By the third day of treatment he developed dyspnoea on exertion, which progressed 2 days later to pleuritic chest pain along with epigastric discomfort. In the emergency room, his O₂ saturation was 89% on room air; there was no fever or rash. His blood tests revealed leucocytosis with neutrophilia. A CT of the chest revealed no pulmonary embolism but significant bibasilar infiltrates (figure 1). The patient was diagnosed with pneumonia and released on levofloxacin. Ten days later, he continued to worsen and was admitted to our hospital for further workup. His admission occurred 5 days after completion of a 10-day course of TMP-SMX.

The patient is a farmer and had denied recent travels. He quit smoking 15 years earlier but continued to chew tobacco. His medical history was significant for asthma, which he developed after exposure to a combine full of mice 10 years previously. His usual symptoms of cough and wheezing have been well controlled with a regimen of inhaled oral and nasal steroids. Six weeks prior to development of arthritis he reported redness in the left eye. A diagnosis of left episcleritis was made and he was treated with topical ketorolac with resolution.

INVESTIGATIONS

On admission, the patient's oxygen saturation was 89% on 1 L of oxygen. He was in sinus tachycardia

Figure 1 Bibasilar infiltrates with interstitial changes on initial presentation.

(rate 115 bpm), having mild respiratory distress with 28 breaths/min. He was alert and oriented with preserved mentation, and his physical examination was unremarkable except for prolonged expirations with bibasilar crackles and swelling in the right big toe. Repeat imaging showed worsening bibasilar infiltrates (figure 2). He was found to have persistent leucocytosis with continued neutrophilic predominance. He was evaluated with B-type

Figure 2 Worsening of bibasilar infiltrates.

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natriuretic peptide, creatine kinase (CK) MB and troponins, which all returned within normal limits. HIV test was negative. CK, erythrocyte sedimentation rate and C reactive protein were mildly elevated but P-ANCA (antineutrophil cytoplasmic antibody), C-ANCA and antinuclear antibody were negative. Viral direct fluorescent antibody (DFA), fungal serologies, sputum and blood cultures were negative.

Bronchoscopy with bronchoalveolar lavage was performed, it revealed granulocytosis but no eosinophilia or alveolar haemorrhage. As the patient's clinical status was not improving and his oxygen needs had increased to 5 L, an open lung biopsy was performed on his third hospital day. Pathology revealed features of organising pneumonia. Cultures were negative. A rheumatology consult did not identify a systemic diagnosis but confirmed the diagnosis of acute gouty arthritis.

TREATMENT

High-dose steroids were started and the patient's oxygenation improved. On discharge to a rehabilitation facility, he was started on TMP-SMX three times weekly for pneumocystis pneumonia prophylaxis. The reintroduction of TMP-SMX occurred 14 days after completion of the initial course.

For acute onset dyspnoea, which developed 2 weeks post-discharge, a CT angiogram revealed a pneumomediastinum and persistent bibasilar infiltrates without any pulmonary emboli (figure 3). The patient followed up at our clinic 3 weeks after discharge. Pulmonary function testing (PFT) showed a forced expiratory volume in 1 s (FEV1) of 43% predicted, forced vital capacity (FVC) of 38% predicted with DLCO (diffusing capacity) of 24%. Re-evaluation of the patient's biopsy was suggestive of acute fibrinous organising pneumonia with focally increased eosinophils suggestive of a drug reaction (figure 4). TMP-SMX was stopped and replaced with pentamidine. The patient was kept on a steroid taper. He soon described an improvement 'like a switch was turned on'.

OUTCOME AND FOLLOW-UP

One month after discontinuation of TMP-SMX, a repeat CT showed improvement of his pulmonary infiltrates (figure 5).

Figure 3 Persistence of bibasilar infiltrates with presence of pneumomediastinum.

Figure 4 Reactive bulging pneumocytes, fibrin 'balls' (black arrows), background of inflammatory cellular alveolar wall infiltration and rare eosinophils (red arrows).

Another month later, his room air O₂ saturation was 96% and his 6 min walk distance was 360 m with lowest O₂ saturation recorded at 91% on room air. A repeat PFT showed an FEV1 of 54%, FVC 55% and DLCO 47%.

DISCUSSION

Acute fibrinous and organising pneumonia (AFOP) was described in 2002¹ as an acute lung injury pattern that is distinct from diffuse alveolar damage (DAD), bronchiolitis obliterans with organising pneumonia (BOOP) and eosinophilic pneumonia (EP). On histology, AFOP is characterised by the patchy presence of intra-alveolar fibrin 'balls', organising pneumonia and interstitial lymphocytic infiltrates. Absent on histology are the characteristic hyaline membranes of DAD, the plugs of granulation tissue of BOOP and the intra-alveolar eosinophilic accumulation of EP. Of the 17 cases described by Beasley *et al*, 6 did demonstrate rare eosinophils. AFOP was thought to be associated with collagen vascular disease, occupational exposures and infections. One patient's association was thought to be

Figure 5 Marked improvement of underlying pulmonary infiltrates.

drug-related (amiodarone). Poor prognostic outcomes were associated with need for mechanical ventilation.

Since then, multiple case reports of AFOP were described: idiopathic,² in connection with collagen vascular disease including systemic lupus erythematosus,³ but also in connection with medications such as abacavir⁴ and decitabine.⁵

Drug-induced lung disease can be difficult to diagnose as it can have a host of radiological and pathological manifestations. In addition, it is most often a diagnosis of exclusion. A history of drug exposure, improvement with discontinuation and recurrence on reintroduction are supportive of the diagnosis.⁶ A search of TMP-SMX lung toxicity on the Web⁷ reveals patterns of subacute pneumonitis, pulmonary infiltrate with eosinophilia, non-cardiogenic pulmonary oedema, acute respiratory distress syndrome and drug hypersensitivity. Drug-induced interstitial lung disease caused by administration of TMP-SMX was confirmed in a study of 10 patients.⁸ Unfortunately, it was a radiological study without pathological correlates.

Learning points

- ▶ Drug-induced lung disease diagnosis is supported by a history of drug exposure, improvement with discontinuation of the drug and recurrence on challenge. It should conform to previous clinical, radiological and pathological descriptions and is a diagnosis of exclusion.
- ▶ Acute fibrinous and organising pneumonia (AFOP) is a distinct pattern of acute lung injury with multiple associations including collagen vascular disease, infection, occupational and drug exposures.
- ▶ Trimethoprim-sulfamethoxazole (TMP-SMX) is associated with drug-induced lung disease: consider AFOP as an additional pattern of injury.
- ▶ AFOP associated with TMP-SMX responds to drug discontinuation and steroids.

In our case, the patient's symptoms and radiological manifestations occurred within a few days of starting TMP-SMX. His symptoms worsened further when he finished the steroid taper and was on the antibiotic unopposed. Clinical improvement after open lung biopsy and institution of high-dose steroids was reversed when the antibiotic was reintroduced at a lower dose for prophylaxis. Sustained improvement did not occur until after final discontinuation. Other diagnoses were excluded based on culture results, serologies and pathology.

As described above, TMP-SMX is associated with interstitial lung disease. In addition, AFOP has been reported to occur with drug exposures (amiodarone, abacavir and decitabine). Therefore, we believe our case report provides one pathological manifestation of a widely used antibiotic and we propose to add AFOP as a recognised entity associated with TMP-SMX.

Contributors SZA wrote the initial manuscript and performed the initial literature review. JC provided the pathological pictures and comments. FJ was the attending physician of the patient, and provided the final manuscript including the revision.

Competing interests None.

Patient consent Obtained.

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