CASE REPORT

Pulmonary co-infection with *Nocardia* and *Aspergillus* in a patient with adult-onset Still's disease receiving steroids and tacrolimus

Durga Prasanna Misra, Jyoti Ranjan Parida, Abhra Chandra Chowdhury, Vikas Agarwal

Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Correspondence to
Dr Durga Prasanna Misra, durgapmisra@gmail.com

Accepted 30 October 2014

SUMMARY

Patients on immunosuppression are at risk of unusual infections. We present a man diagnosed to have adult-onset Still's disease who, on high-dose oral steroid and tacrolimus, developed a cavitating pneumonia due to co-infection with *Aspergillus flavus* and *Nocardia*. Timely diagnosis and institution of appropriate therapy resulted in a favourable clinical outcome. Such co-infection in a patient receiving tacrolimus is rare in the published literature. This case serves to emphasise the need to be vigilant for unusual infections in patients who are immunosuppressed, either due to drugs or underlying disease condition.

BACKGROUND

Patients on immunosuppressive medication are at risk of acquiring unusual infections. Nocardiosis usually occurs in the context of corticosteroid or other immunosuppressant use, haematological malignancies, HIV infection or transplant recipients; infection may be limited to lungs or it may undergo systemic dissemination involving brain, skin and soft tissues.[1] Risk factors for *Aspergillus* infection include prolonged corticosteroid usage, T-lymphocyte immunosuppressants, neutropaenia and haematopoietic cell transplant recipients; it can be localised to the lungs or may disseminate to other organs such as the central nervous system.[2] Co-infection with *Nocardia* and *Aspergillus* is, however, extremely rare; we present a case of a man with a diagnosis of adult-onset Still's disease on high-dose steroid and tacrolimus, who developed pulmonary infection with these pathogens as an adverse effect of immunosuppression.

CASE PRESENTATION

A 37-year-old man presented to us in August 2013 with a history of quotidian fever, symmetric inflammatory polyarthritis affecting the large joints of upper and lower limbs, sore throat, weight loss of 20 kg over the past year, associated with neutrophilic leucocytosis and negative antinuclear antibodies, and rheumatoid factor. His serum ferritin was markedly elevated (7000 ng/mL), erythrocyte sedimentation rate measured by Westergren method was 110 mm/h and serum C reactive protein was also high (12.8 mg/dL). A diagnosis of adult-onset Still's disease was made as per the Yamaguchi criteria,[3] after excluding other causes of fever (bone marrow, CT of the thorax and abdomen, and echocardiography were normal; blood and urine cultures showed no growth). The patient had already been treated with prednisolone, methotrexate, sulfasalazine and hydroxychloroquine in combination (table 1) for 9 months without adequate symptom relief. Use of biological agents was not feasible due to financial constraint. P-glycoprotein expression on peripheral blood lymphocytes was increased, accounting possibly for the steroid resistance,[4] hence the patient had been started on prednisolone 1 mg/kg/day (60 mg) and tacrolimus 5 mg/day. In addition to blocking the calcineurin pathway, tacrolimus also decreases P-glycoprotein expression, thereby possibly resulting in improved steroid responsiveness; this was the reason behind the choice of this drug.[5] The patient developed deranged glycaemic status due to the steroids, and so was started on insulin. Serum tacrolimus trough levels were in the therapeutic range. With this, over the next 2 months, his joint pains and fever almost completely subsided and he was able to resume his job as an electrician.

Two months after the first admission, the patient presented to us with a history of loose stools for 16 days, small in amount, 7–8 times a day, initially watery, later admixed with blood and mucus. In addition, he reported a left-sided pleuritic chest pain for the past 6 days. He reported a decrease in urine output for the day prior to admission. He did not have fever or any other systemic symptoms. Examination revealed mild pallor and dehydration; he had no tachycardia (pulse 80/min), hypotension (blood pressure 130/80 mm Hg) or tachypnoea (respiratory rate 18 breaths/min). Respiratory system examination revealed diminished air entry in the left lower chest; otherwise systemic examination was unremarkable.

INVESTIGATIONS

Haemogram was normal except for mild anaemia (haemoglobin 11.9 g%, total leucocyte count 5900/mm^3, platelet count 157 000/mm^3). Serum chemistry was normal (serum creatinine 1.3 mg%, serum albumin 3.5 g%, serum bilirubin 0.3 mg%, aspartate transaminase 5 U/L and alanine transaminase 26 U/L). Chest X-ray showed a well-defined nodular shadow in the left lower lung zone (figure 1A).

DIFFERENTIAL DIAGNOSIS

The patient likely had bacterial dysentery in view of the blood in the stools. Keeping this in context

To cite: Misra DP, Parida JR, Chowdhury AC, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2014-207335

Table 1 Details of medications prior to presenting to us

Medication	November 2012	December 2012	February 2013	May 2013	July 2013
Prednisolone (mg/day)	15	20	10	20	20
Methotrexate (mg/week)	15	15	20	20	15
Hydroxychloroquine (mg/day)	200	200	200	200	200
Sulfasalazine (mg/day)	–	–	1000	2000	2000

with the findings of decreased breath sounds in the left lower lung and the well-defined nodular shadow in the lower lung field, a possibility of Gram-negative bacteraemia originating from the gut and seeding the lung was entertained. However, odd for this was lack of features of systemic inflammatory response on examination (no fever, tachycardia, tachypnoea, hypotension) or investigations (no leucocytosis or thrombocytosis) as well as subacute onset over a period of 16 days. A plausible explanation was that systemic symptoms were masked due to high-dose steroid intake.

However, in view of the above mentioned oddities, as well as the patient's immunosuppressed state, possibility of unusual infections (eg, fungal or tubercular) had to be considered. Hence it was imperative to get a microbiological diagnosis.

TREATMENT

The patient was given broad spectrum antibiotic coverage with piperacillin-tazobactam and teicoplanin. With rehydration, his urine output improved on the first day of admission. His blood sugars were controlled with insulin. A CT of the chest (figure 2) was performed to further characterise the lung nodule—to our surprise, it showed consolidation with cavitation in the left lingual and left upper lobe, along with small nodules in the right lung parenchyma as well. Bronchoalveolar lavage cultures initially grew *Escherichia coli* and *Pseudomonas* sensitive to piperacillin-tazobactam, hence the medication was continued. In view of the multifocal cavitating lung nodules, echocardiography was used to look for endocarditis, but no structural abnormalities or vegetations were detected. Blood cultures were sterile.

By day 10 of admission, fungal cultures grew *Aspergillus flavus* (septate branching hyphae at acute angles), and by day 13, growth of *Nocardia* was also confirmed from the bronchoalveolar lavage fluid. Infection with *Nocardia* and *Aspergillus* was more consistent with the clinical picture. Also, on piperacillin-tazobactam for more than a week, the lung shadows in the left lower zone continued to increase, with the left middle zone shadow in the parahilar region becoming prominent (figure 1B). Hence piperacillin-tazobactam was stopped, and the patient was started on injectable amphotericin B (for aspergillosis) and injectable ceftriaxone with oral cotrimoxazole (for nocardiosis). Amphotericin B was given for 6 weeks, and then changed over

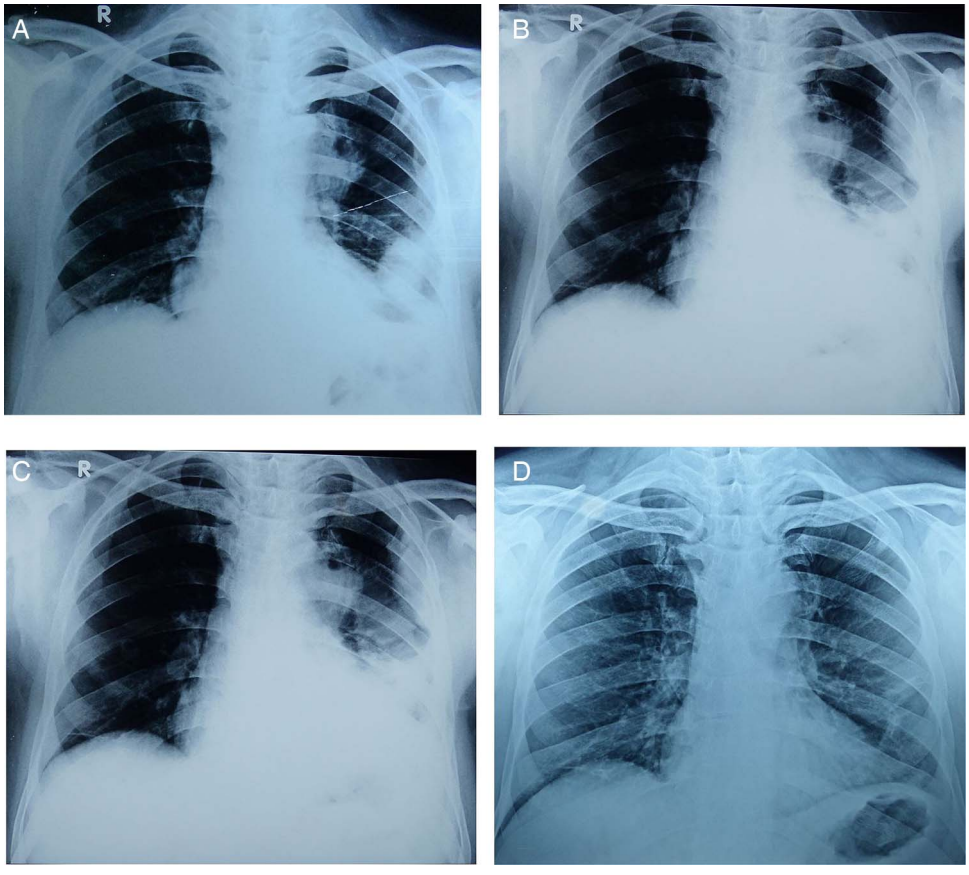

Figure 1 Chest X-ray (A) on the day of admission showing well-defined nodular shadow in the left lower lung zone and (B) on day 10 after admission showing increase in left lower zone shadows, with the left middle zone shadow in the parahilar region becoming prominent. (C) Chest X-ray 4 weeks after starting therapy for *Nocardia* and *Aspergillus*, showing resolving left lower zone shadows, with the left middle zone shadow having disappeared. (D) Chest X-ray 4 months after starting therapy for *Nocardia* and *Aspergillus*, showing almost complete resolution of previous shadows.

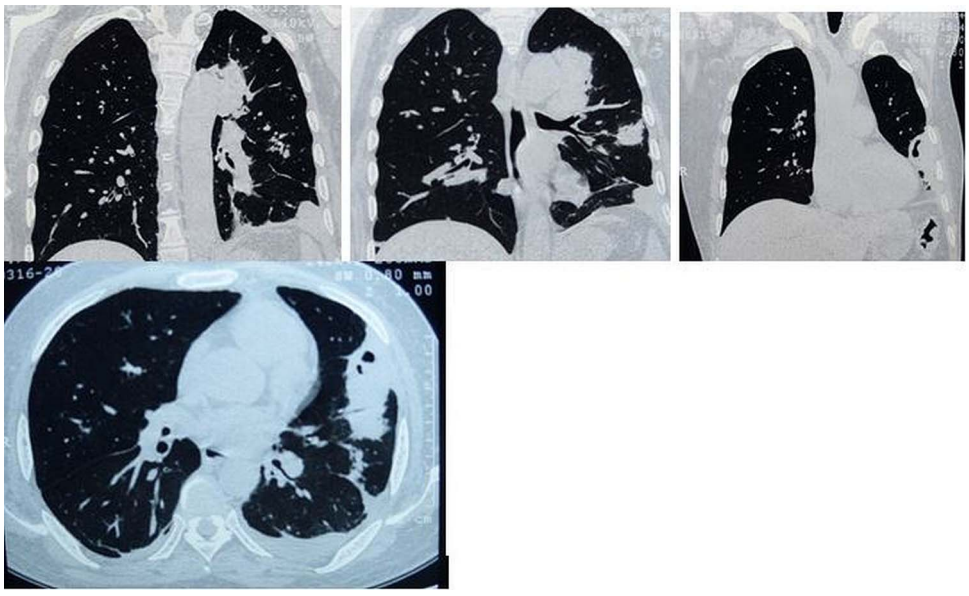

Figure 2 CT of the chest showing consolidation with cavitation in the left lingual and left upper lobe, along with small nodules in the right lung parenchyma.

to oral voriconazole to complete 2 months of antifungal therapy. Injectable ceftriaxone was given for a month. Subsequently, oral cotrimoxazole alone was continued for nocardiosis, with a plan to give total duration of therapy for 1 year.

OUTCOME AND FOLLOW-UP

With the above treatment regimen, the lung shadows showed gradual improvement over the next month (figure 1C), and after 4 months of treatment, had almost completely resolved (figure 1D). The steroid dose was gradually tapered, and at his most recent hospital visit after 9 months of treatment, the patient was completely asymptomatic. The adult-onset Still's disease was also in remission on 5 mg daily prednisolone and the patient had resumed work as usual.

DISCUSSION

Table 2 was derived from a search on PubMed regarding data on co-infection with *Nocardia* and *Aspergillus*. Information available was limited by accessibility to full text of these articles. Eight such cases could be identified[6–13]; most of them were on a background of solid organ transplantation. A common theme identified was risk attributable to steroid therapy. It is to be noted that our patient was receiving high-dose steroid therapy. Timely diagnosis and appropriate combination therapy to target both the microbes, wherever possible, resulted in a favourable outcome. Tacrolimus therapy had not been previously reported to predispose to this unusual co-infection; also none of these reports were on a background of autoinflammatory disease such as adult-onset Still's disease.

The present case serves to highlight the need to have an open mind when encountered with infection in the setting of immunosuppression. A clue to unusual infection in this patient was lack of significant systemic inflammatory response (no fever, leucocytosis or thrombocytosis) in spite of multiple pulmonary cavitary lesions; the high dose of steroids could also have masked any constitutional symptoms. Early diagnosis and appropriate therapy resulted in a favourable outcome. This case serves to emphasise that unusual infections such as these need prolonged therapy (1 year in the case of nocardiosis) to prevent recurrence.

Table 2 Co-infection with *Nocardia* and *Aspergillus*—a review of the literature

Reference	Year of publication	Country	Underlying disease	Immunosuppressant	Outcome
6	1984	USA	Chronic granulomatous disease	None	Not available
7	1990	USA	Renal transplant	Azathioprine 50 mg/day, prednisolone 15 mg/day	Fatal (diagnosis made postmortem)
8	1993	USA	Cardiac transplantation	Not available	Successfully treated
9	2000	Spain	Not available	Glucocorticoid	Not available
10	2005	The Netherlands	Near-drowning	None	Full recovery with liposomal amphotericin B, amikacin, meropenem and cotrimoxazole
11	2008	USA	Chronic graft-versus-host disease following haematopoietic stem cell transplant	Not available	Not available
12	2008	Saudi Arabia	Angioimmunoblastic T-cell lymphoma	Prednisolone, mycophenolate mofetil, alemtuzumab	Successfully treated with liposomal amphotericin B, amikacin and cotrimoxazole
13	2010	USA	Lung transplant	Not available	Not available

Learning points

- Unusual infections are more likely in a setting of immunosuppression.
- A high index of suspicion for such infections should be maintained in a patient with obvious infection but lacking a robust systemic inflammatory response.
- Steroid therapy is an important risk factor for infections.
- Prolonged therapy may be needed for such infections.

Contributors All authors were involved in conception and design, acquisition of the data, and analysis and interpretation of the data. DPM and ACC drafted the article; JRP and VA revised it critically for important intellectual content. All authors gave final approval of the version published.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Anagnostou T, Arvanitis M, Kourkoumpetis TK, *et al*. Nocardiosis of the central nervous system: experience from a general hospital and review of 84 cases from the literature. *Medicine* 2014;93:19–32.
2 Karthaus M, Buchheidt D. Invasive aspergillosis: new insights into disease, diagnostic and treatment. *Curr Pharm Des* 2013;19:3569–94.
3 Yamaguchi M, Ohta A, Tsunematsu T, *et al*. Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992;19:424–30.
4 van Kalken CK, Broxterman HJ, Pinedo HM, *et al*. Cortisol is transported by the multidrug resistance gene product P-glycoprotein. *Br J Cancer* 1993;67:284–9.
5 Picchianti-Diamanti A, Rosado MM, Scarsella M, *et al*. P-glycoprotein and drug resistance in systemic autoimmune diseases. *Int J Mol Sci* 2014;15:4965–76.
6 Casale TB, Macher AM, Fauci AS. Concomitant pulmonary aspergillosis and nocardiosis in a patient with chronic granulomatous disease of childhood. *South Med J* 1984;77:274–5.
7 Carter JM, Green WR, Callender CO, *et al*. Pulmonary cavitation with Nocardia and Aspergillus in a renal transplant patient. *J Natl Med Assoc* 1990;82:527–8, 30–1.
8 Monteforte JS, Wood CA. Pneumonia caused by Nocardia nova and Aspergillus fumigatus after cardiac transplantation. *Eur J Clin Microbiol Infect dis* 1993;12:112–14.
9 Fernandez Pelaez JM, Sanchez Martin E, Polo Romero FJ, *et al*. [Lung infection caused by Aspergillus fumigatus and Nocardia asteroides as complication of glucocorticoid treatment]. *Med Clin (Barc)* 2000;114:358.
10 van Dam AP, Pruijm MT, Harinck BI, *et al*. Pneumonia involving Aspergillus and Rhizopus spp. after a near-drowning incident with subsequent Nocardia cyriacigeorgici and N. farcinica coinfection as a late complication. *Eur J Clin Microbiol Infect Dis* 2005;24:61–4.
11 Hamadani M, Benson DM Jr, Blum W, *et al*. Pulmonary Nocardia and Aspergillus co-infection in a patient with chronic graft-versus-host disease. *Transpl Infect Dis* 2008;10:24–6.
12 Al-Anazi KA, Aljurf MD, Al-Mohareb FI, *et al*. Successful management of invasive pulmonary nocardiosis and aspergillosis in a patient with T-cell lymphoma: a case report. *Clin Med Case Rep* 2008;1:65–71.
13 Cabada MM, Nishi SP, Lea AS, *et al*. Concomitant pulmonary infection with Nocardia transvalensis and Aspergillus ustus in lung transplantation. *J Heart Lung Transplant* 2010;29:900–3.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit http://group.bmj.com/group/rights-licensing/permissions.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:
- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow