Austrian syndrome, ceftriaxone-induced agranulocytosis and COVID-19

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SUMMARY

We present a case of a 75-year-old woman with Austrian syndrome: pneumonia, meningitis and endocarditis all due to *Streptococcus pneumoniae*. Transoesophageal echocardiogram demonstrated a large mitral valve vegetation with severe mitral regurgitation. She was treated with intravenous ceftriaxone and listed for surgical repair of her mitral valve. Preoperatively, she developed an idiosyncratic drug-induced agranulocytosis secondary to ceftriaxone, which resolved on cessation of the medication. However, while awaiting neutrophil recovery, she developed an acute deterioration, becoming critically unwell. This deterioration was multifactorial, with acute decompensated heart failure alongside COVID-19. After multidisciplinary discussion, she was considered too unwell for surgery and palliated.

BACKGROUND

Streptococcus pneumoniae (pneumococcus) is a gram-positive, alpha-haemolytic bacterium. It is a major cause of infection in both adults and children, with manifestations including lobar pneumonia and meningitis. Invasive pneumococcal disease is defined as an infection with isolation of *S. pneumoniae* from a normally sterile site, such as blood or cerebrospinal fluid (CSF). Pneumococcal bacteraemia can occur with the presence or absence of pneumococcal pneumonia, but when bacteraemia is present secondary complications such as meningitis, arthritis and endocarditis can occur.[1]

Austrian syndrome is the triad of pneumococcal pneumonia, meningitis and endocarditis. It was clinically described in 1881 by Osler and later termed Austrian syndrome after Robert Austrian, who described the affinity of *S. pneumoniae* to the aortic valve and the simultaneous presence of meningitis in 1957.[2] Pneumococcus is responsible for less than 3% of native valve endocarditis, but causes rapid valvular destruction.[3] Furthermore, fewer than 1% of patients with pneumococcal endocarditis display the Austrian triad; however, this rare syndrome has a high mortality.[3 4]

Idiosyncratic drug-induced neutropenia is extremely rare with an incidence of 2.4–15.4 cases per million.[5] Antibiotics are known causative agents, including ceftriaxone; however, this is normally a very safe and tolerated therapy.[6] A literature search has revealed only 15 other reported cases of ceftriaxone-induced agranulocytosis.[6 7]

CASE PRESENTATION

A 75-year-old woman presented to the hospital with a 10-day history of malaise and new agitation and confusion. She had seen her general practitioner 2 days before admission and was prescribed nitrofurantoin for a suspected urinary tract infection. She was an independent and active woman with a background of chronic obstructive pulmonary disease, hypothyroidism and hypertension.

On initial examination, the patient was visibly agitated with a Glasgow Coma Score (GCS) of 11 (eyes 4, verbal 2, movement 5). On general inspection, she was clammy, and no rash was observed. On pulmonary auscultation, wheeze and crackles were heard in the upper zone of the right lung. Her initial observations were as follows: heart rate of 112 beats per minute, blood pressure of 121/58 mm Hg, respiratory rate of 28 breaths per minute, oxygen saturation of 94% on room air and temperature of 38.1°C. Her lactate on arterial blood gas was 2.1 mmol/L.

A septic screen was completed which included bloods, blood cultures, a chest radiograph, a urine sample and legionella/pneumococcal urinary antigens. The chest radiograph demonstrated a right upper lobar pneumonia (figure 1). Bloods supported an infection (white cell count (WCC), 35.8×10^9 cells/L; neutrophils, 33.8×10^9 cells/L; and C reactive protein (CRP), 458 mg/L) and showed an acute kidney injury (AKI) (creatinine, 256μmol/L; baseline creatinine, 90 μmol/L). She was therefore diagnosed with a community-acquired pneumonia, AKI and a presumed delirium. She was admitted under the medical team and commenced on vancomycin and clarithromycin as per local hospital guidelines for penicillin allergic patients and given intravenous fluids, but she did not require oxygen therapy. Her urine microscopy demonstrated no abnormality (25 WCC/μL, 31 red blood cells/μL and no significant organism growth).

Unfortunately, despite treatment of her sepsis, her altered level of consciousness did not improve (GCS of 11). The day following admission, a CT of the brain was requested and she was referred to the intensive care unit for assistance with safe transfer to the CT scanner.

INVESTIGATIONS

On review by the critical care team, she was noted to have neck stiffness, persistent fevers and an altered level of consciousness. A diagnosis of meningoencephalitis was considered, and she was admitted to the high-dependency unit for monitoring of her GCS. CT of the brain demonstrated no pathology to explain her altered mental state and no evidence of raised intracranial pressure. A lumbar puncture was subsequently performed, and she was started on empirical ceftriaxone and acyclovir in addition

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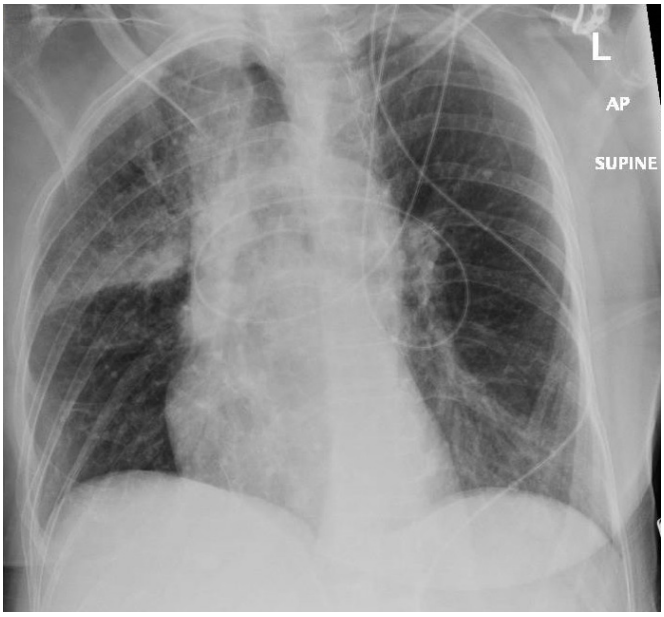

Figure 1 Chest radiograph on admission demonstrating a right upper lobar pneumonia.

to her current antibiotic regime. The CSF results were as follows: WCC of 156×10^6/L (predominantly polymorphs), protein of 4.08 g/L and glucose of <0.5 mmol/L (serum blood glucose of 11.3 mmol/L), and PCR was positive for *S. pneumoniae*. In addition, blood cultures were also now positive for *S. pneumoniae,* and the urinary pneumococcal antigen was positive.

The patient had invasive pneumococcal disease with pneumococcal bacteraemia, pneumococcal meningitis and evidence of a lobar pneumonia. It was now apparent that the agitation was secondary to meningitis. Following microbiology consultation, acyclovir and vancomycin were ceased, and an echocardiogram was suggested to exclude infective endocarditis (IE), given the possibility of Austrian syndrome. Transthoracic echocardiogram (TTE) described a posterior mitral valve leaflet prolapse with a large vegetation, a severe eccentric mitral regurgitation and a left ventricular ejection fraction of 65%. On examination, a pansystolic murmur could be heard, but there were no other features of IE.

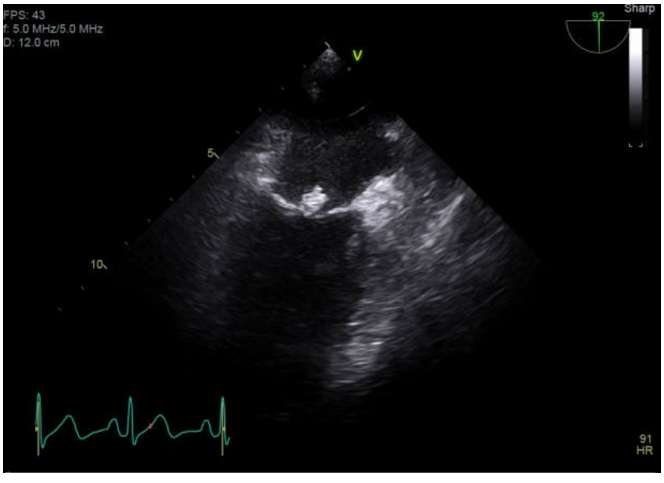

Figure 2 Transoesophageal echocardiogram revealing a large posterior mitral valve leaflet vegetation.

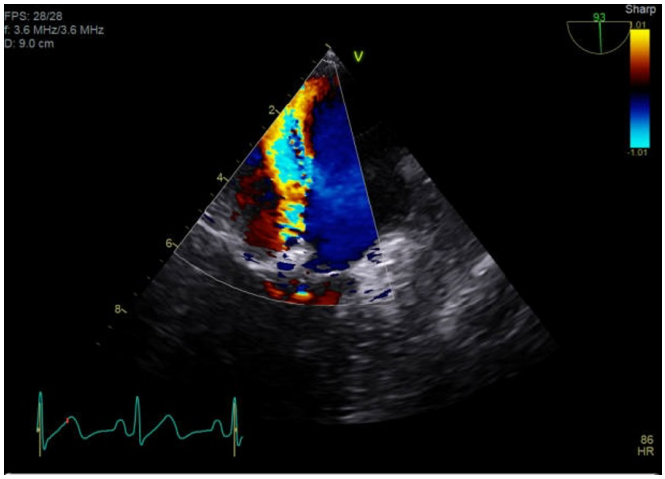

Figure 3 Transoesophageal echocardiogram showing severe mitral regurgitation.

DIAGNOSIS

A diagnosis of Austrian syndrome was made on day 4 of the patient's admission, after a collective analysis indicated the triad of pneumococcal pneumonia, meningitis and endocarditis.

TREATMENT

With the diagnosis of Austrian sydrome, the patient was to complete a 4-week course of intravenous ceftriaxone. In addition, the patient received a 4-day course of dexamethasone for meningitis. Clinically she did not require respiratory, cardiovascular or renal support, but she remained very agitated with a persistent GCS of 11. She was reviewed by cardiology for endocarditis who advised she would require a transoesophageal echocardiogram (TOE) and cardiothoracic surgery to repair the mitral valve. However, in her current condition with active infection, altered cognition and renal impairment, a TOE and surgery would be inappropriate, although this should be reconsidered if she were to improve.

Over the following weeks, she gradually began to improve. Her cognition returned to normal and she was completely coherent. Her renal function recovered to near baseline.

Unfortunately, on day 21 she developed an increasing oxygen requirement and dyspnoea. A chest radiograph demonstrated evidence of pulmonary oedema. The patient had now developed heart failure secondary to mitral valve regurgitation. She was managed with continuous positive airway pressure and diuresed with intravenous furosemide. A further review by cardiology advised the commencement of milrinone and intravenous nitrate to systemially vasodilate the patient, reduce afterload and offload the left ventricle. With this management, she improved and the intravenous nitrate and milrinone were weaned off. She was subsequently started on hydralazine and isosorbide mononitrate. A TOE confirmed a posterior mitral valve leaflet mass approximately 15×8 mm in size, with severe central mitral valve regurgitation into a minimally dilated left atrium (figures 2 and 3). She was referred to the cardiothoracic team at the regional cardiothoracic centre for mitral valve repair.

On day 30, the patient was transferred to the cardiothoracic centre for a preoperative coronary angiogram and subsequent mitral valve repair. However, on day 32 she developed neutropenic sepsis (neutrophils, 0.36×10^9 cells/L). The patient was subsequently moved to an isolation room on the cardiothoracic ward, and the surgical valve repair was postponed.

The patient's neutrophil count had gradually declined since her admission count of 33.8×10^9 cells/L and continued to fall to a nadir of 0.02×10^9 cells/L. She was also anaemic (haemoglobin, 71 g/L; mean cell volume, 97.5 fL), but this had been stable since her critical care admission with no clinical evidence of bleeding and a normal oesophago-gastro-duodenoscopy . Her platelet count was normal throughout. She was reviewed by haematology for investigation of neutropenia and anaemia.

A haemolysis screen was completed: bilirubin was normal (5 μmol/L), lactate dehydrogenase was elevated (779 U/L), haptoglobin was low (<0.1 g/L), reticulocyte count was normal (97.2×10^9 cells/L) and the direct Coombs test was negative, excluding an autoimmune haemolysis. Blood film showed mild rouleaux and paucity of white cells other than mature lymphocytes but was not leucoerythroblastic, and there were no overt features of haemolysis, including no fragments. A haematological malignancy was considered but thought unlikely given the blood film and lack of pancytopenia. In addition, serum paraproteins were not identified on electrophoresis and Bence Jones protein was not detected. Regardless, she was offered a bone marrow aspirate but declined. The patient's invasive pneumococcal disease was a potential cause of neutropenia, but a viral screen was negative for HIV, hepatitis B and C, parvovirus, cytomegalovirus and Epstein-Barr virus. Haematinics were normal, demonstrating no nutritional deficiencies, excluding this potential explanation.

It was therefore supposed her agranulocytosis was due to an idiosyncratic drug reaction, with hydralazine and ceftriaxone being the most likely culprits. Hydralazine had been stopped before the development of her neutropenia, and with this new information ceftriaxone was now changed to vancomycin. Within 5 days of ceftriaxone cessation, her neutrophil count recovered, suggesting ceftriaxone was the offending agent. With a normal neutrophil count, she was again listed for surgical valve repair.

Unfortunately, on day 39 while awaiting surgery she deteriorated, becoming critically unwell. She had developed a new sudden hypoxia, maintaining oxygen saturations of only 85% while receiving oxygen at 15 L/min via a non-rebreather mask. She was therefore intubated on the ward and transferred to the intensive care unit. A pan CT was performed, which demonstrated bilateral pulmonary ground-glass opacification with septal thickening, bilateral pulmonary effusions and bilateral consolidation in the mid-upper zones (figure 4).

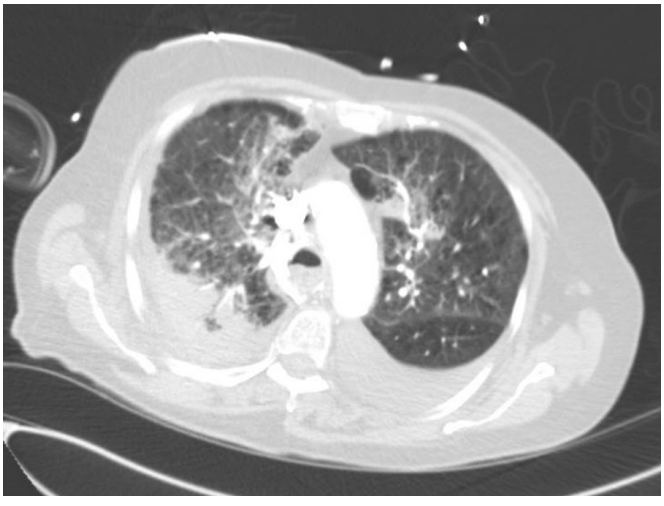

Figure 4 CT of the chest demonstrating bilateral ground-glass opacification and pleural effusions.

To complicate matters, her admission coincided with the outbreak of COVID-19 in the UK, and following the deterioration she tested positive for SARS-CoV-2. Regrettably, we cannot be certain of the cause of this deterioration, although likely multifactorial. Her endocarditis with resultant severe mitral regurgitation and heart failure is the most probable contributor; however, we cannot ignore the significance of COVID-19, especially given the profound hypoxia and ground-glass appearance on CT. Irrespective of the cause, she remained critically unwell, and after a multidisciplinary discussion she was deemed too unstable for emergency valve repair with an extremely poor prognosis and thus palliated.

DISCUSSION

Delirium is defined as a disturbance of attention, awareness and cognition that is acute and fluctuating.[8] It is estimated that 20% of patients aged >65 years are delirious on admission to hospital.[9] There are multiple causes of delirium, the most common being infections, fluid and electrolyte disturbance, and medication. Given the patient's non-specific presentation, the radiological evidence of a community-acquired pneumonia on admission and the incidence of delirium in the elderly, it is understandable how delirium was diagnosed in our patient. However, the case highlights the importance of keeping a broad differential for delirium.

Older patients with bacterial meningitis are more likely to present with delirium rather than the classical triad of fever, neck stiffness and altered level of consciousness.[10] However, bacterial meningitis remains an uncommon disorder. In a retrospective study of 81 older patients admitted to hospital for evaluation of fever and altered mental state, CSF cultures were negative for bacterial growth in 80 of 81 patients.[11] Despite being uncommon, it is a diagnosis that requires consideration, especially given pneumococcal meningitis has a mortality rate of 20%–30% even with appropriate antibiotics.[12 13] Unfortunately, meningitis was initially not recognised in our patient, leading to a delay in diagnosis and treatment.

Austrian syndrome is a difficult condition to diagnose and requires an awareness of its existence. In particular, the diagnosis of endocarditis is often delayed. Typically, patients lack the classical peripheral stigmata of endocarditis, and pathological murmurs are a late occurrence.[14] However, when these signs do eventually appear, the presentation is often fulminant and haemodynamic instability immediately precedes circulatory collapse.[15] In addition, the coexistence of other foci of infection may distract clinicians from searching for other diagnoses. For diagnosis of valvular vegetations, abscesses and perforations, TOE is superior to TTE. Therefore, TOE should be performed in all patients with a clinical suspicion of endocarditis if an initial TTE is negative or non-diagnostic.[16] Fortunately, in this case, the microbiologist had knowledge of the syndrome and thus recommended an echocardiogram to investigate for endocarditis once pneumococcal meningitis and bacteraemia were identified. We were then able to arrange a TTE and subsequent TOE, which both demonstrated a large mitral valve vegetation and severe regurgitation.

Surgical intervention for IE is indicated for acute valvular regurgitation or evidence of heart failure. However, even with surgical intervention, pneumococcal endocarditis has a mortality of 32%.[17] Comparatively, the mortality with conservative management with antibiotics alone is 60%, with only 17% of

cardiac vegetations disappearing with antibiotic therapy.[3] The patient in this case report had both indications for surgical intervention to repair or replace the mitral valve. Unfortunately, while awaiting surgical intervention, she became neutropenic and thus surgery was postponed.

Neutropenia is usually defined as an absolute neutrophil count (ANC) of $<1.5\times10^9$ cells/L. Agranulocytosis refers to the absence of granulocytes and is associated with an ANC of $<0.2\times10^9$ cells/L. The most common causes of an acquired neutropenia are infections, medications, nutritional deficiencies and haematological malignancies.[18] Our patient had a severe unexplained neutropenia (0.02×10^9 cells/L) in the context of sepsis and underwent appropriate investigation. Ultimately, following investigation, it was felt her neutropenia was medication-induced.

Cytotoxic and immunosuppressive agents are the most common causes of medication-associated neutropenia, but the patient was not prescribed such medications. Other medications are associated with severe idiosyncratic drug-induced neutropenia, but this is extremely rare.[19] Causative agents include antibiotics, antiplatelet agents, antithyroid drugs, neuroleptics and antiepileptics, and neutropenia typically occurs within 3 months of starting the new drug. Our patient had started ceftriaxone 31 days before the identification of her neutropenia, which had been prescribed as the single antibiotic to treat her Austrian syndrome.

Ceftriaxone had been chosen as in our hospital it is the first-line therapy to treat invasive pneumococcal disease. The pneumococcus was also sensitive to penicillin, and thus penicillin could have been an alternative narrow-spectrum option. However, the patient had a documented type 4 hypersensitivity reaction to penicillin with mouth ulcers. A trial of penicillin had been contemplated but decided against, as it was thought that the higher dose and prolonged duration required would increase the risk of further adverse reactions, and we had what we thought was a safe and effective alternative. However, given the complication of using ceftriaxone and the pneumococcus being sensitive to penicillin, with retrospect one could consider whether the outcome would have been different had penicillin been trialled.

Learning points

- Elderly patients with meningitis may present with delirium rather than the classical features of fever, neck stiffness and altered level of consciousness.
- Austrian syndrome is rare, but an awareness of its existence may allow quicker diagnosis.
- Endocarditis should be actively sought if pneumonia and meningitis coexist.
- Pneumococcal endocarditis often runs a fulminant course, and therefore prompt surgical intervention is required.
- Ceftriaxone is a rare cause of drug-induced neutropenia.

Since the first reported cases in late 2019, from Wuhan, China, infection with SARS-CoV-2 has become a worldwide pandemic.[19] The UK had its first confirmed case of COVID-19 on 30 January 2020.[20] Our patient was admitted to the hospital 17 days after this date but 27 days before the first confirmed case at her presenting hospital. Although without complete certainty, we feel it is highly unlikely the patient had infection with SARS-CoV-2 on admission, and therefore she likely contracted the virus during her inpatient stay. Unfortunately, it is probable COVID-19 contributed to her deterioration although she already had a poor prognosis. Nevertheless, this highlights the importance of preventing nosocomial transmission.

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REFERENCES

1 Bogaert D, De Groot R, Hermans PWM. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004;4:144–54.
2 Austrian R. Pneumococcal endocarditis, meningitis and rupture of the aortic valves. *JAMA Internal Medicine* 1957;99:539–44.
3 Rakočević R, Shapouran S, Pergament KM. Austrian Syndrome - A Devastating Osler's Triad: Case Report and Literature Review. *Cureus* 2019;11:e4486.
4 Velazquez C, Araji O, Barquero JM, *et al*. Austrian syndrome: a clinical rarity. *Int J Cardiol* 2008;127:e36–8.
5 Andrès E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. *Curr Opin Hematol* 2008;15:15–21.
6 Genchanok Y, Tolu SS, Wang H, *et al*. Agranulocytosis from outpatient antimicrobial treatment with ceftriaxone: a case report. *Perm J* 2019;23:18–190.
7 Uy N, Thiagarajan P, Musher DM. Cephalosporin side chain idiosyncrasies: a case report of ceftriaxone-induced agranulocytosis and review of literature. *Open Forum Infect Dis* 2015;2:ofv007.
8 Slooter AJC, Otte WM, Devlin JW, *et al*. Updated Nomenclature of delirium and acute encephalopathy: statement of ten societies. *Intensive Care Med* 2020;46:1020–2.
9 Cole MG, Primeau FJ. Prognosis of delirium in elderly hospital patients. *CMAJ* 1993;149:41–6.
10 Gaillemin O, McGill F. Have a high index of suspicion for meningitis in adults. *Practitioner* 2016;260:25–30.
11 Warshaw G, Tanzer F. The effectiveness of lumbar puncture in the evaluation of delirium and fever in the hospitalized elderly. *Arch Fam Med* 1993;2:293–7.
12 Durand ML, Calderwood SB, Weber DJ, *et al*. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med* 1993;328:21–8.
13 Aronin SI, Peduzzi P, Quagliarello VJ. Community-Acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998;129:862–9.
14 Collazos J, García-Cuevas M, Martínez E, *et al*. Prosthetic valve endocarditis due to *Streptococcus pneumoniae*. *Arch Intern Med* 1996;156:2141.
15 Poulsen JB, Moser C, Espersen K, *et al*. Austrian syndrome. *BMJ Case Rep* 2011;2011:bcr0920103368.
16 Habib G, Lancellotti P, Antunes MJ, *et al*. 2015 ESC guidelines for the management of infective endocarditis. *Eur Heart J* 2015;36:3075–128.
17 Edlin JC, Metwalli A, Finney SJ, *et al*. Postcardiotomy extracorporeal membrane oxygenation in a patient with Austrian syndrome. *BMJ Case Rep* 2020;13:e233564.
18 Schwartzberg LS. Neutropenia: etiology and pathogenesis. *Clin Cornerstone* 2006;8 Suppl 5:S5–11.
19 Cucinotta D, Vanelli M. Who Declares COVID-19 a pandemic. *Acta Biomed* 2020;91:157–60.
20 Coronavirus (COVID-19) in the UK. Available: https://coronavirus.data.gov.uk/ [Accessed 10 May 2020].