Rare disease

Primary pulmonary botryomycosis presenting with septic shock and acute lung injury

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Summary

Botryomycosis is a rare chronic suppurative bacterial infection involving mostly subcutaneous tissues and less frequently other organs. It can be diagnosed by histological examination and culture of the granules. Botryomycosis is mostly caused by *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* but the exact pathogenesis remains uncertain. Treatment often requires a combination of both surgical debridement and long-term antimicrobial therapy. The patient is a young woman known to have Down's syndrome. She had a dramatic presentation with septic shock and acute lung injury with persistence of pulmonary sepsis postoperatively. The importance of postoperative critical care is illustrated by this case in which a young patient underwent major surgery while septic and haemodynamically unstable. According to our research this is the first case of pulmonary botryomycosis reported in Down's syndrome and the first case which developed septic shock requiring vasoactive drugs and ventilation in the intensive care unit.

BACKGROUND

Botryomycosis is rare and pulmonary involvement is very rare. This is only the second case of pulmonary botryomycosis reported in Saudi Arabia and (it would appear) in the Middle East in general. It is the first such case to present with septic shock and acute lung injury and it is the first case of pulmonary botryomycosis in a Down's syndrome patient. Even within the context of such a rare condition as pulmonary botryomycosis, the clinical/radiological findings were unusual in that previous reported cases of pulmonary botryomycosis have presented as a lung mass masquerading as cancer, whereas our case presented with empyema and clinical sepsis. This case serves to illustrate the important place of aggressive yet controlled intensive care unit (ICU) care, in particular early goal directed therapy (EGDT), non-invasive positive pressure ventilation (NIPPV) and protected ventilatory strategy, in accordance with the accepted evidence base, in order to safely deliver an acutely ill postoperative patient to near-complete recovery. The case is a useful reminder to be constantly vigilant and to consider broad differential diagnoses including rare entities especially when clinical presentation, radiological features and operative findings are somewhat unusual. Botryomycosis (bacterial pseudomycosis) is a rare chronic suppurative (and sometimes) granulomatous bacterial infection that affects the skin/subcutaneous tissues (80%) and sometimes internal viscera (20%). Apart from human disease it has also been described in certain mammals.¹ The disease was originally discovered by Otto Bollinger in 1870² and its name (a misnomer) coined by Sebastiano Rivolta in 1884. The name refers to its grape-like granules (Gr. *botryo* = grapes) and the erroneously implied fungal aetiology (Gr. *mykes* = fungus). In 1913 the first case of human botryomycosis (with involvement of the liver) was described,³ and in 1919 the bacterial nature of the

infection was elucidated.⁴ *Staphylococcus aureus* is the commonest organism causing this infection, although it can also be caused by *Pseudomonas aeruginosa* or several other species of bacteria. Histologically the characteristic lesion is a circumscribed microgranule composed of a dense rim of eosinophilic material that surrounds densely packed microorganisms. This striking histological pattern, the Splendore-Hoeppli phenomenon, is not unique to botryomycosis but is also seen in a few other fungal and bacterial infections including actinomycosis, mycetoma, sporotrichosis and phycomycosis.⁵ There are approximately 130 documented cases of human botryomycosis (from extensive literature search), and its pathogenesis is not completely understood. However, it is usually described in individuals with impaired immunity.

CASE PRESENTATION

A 23-year-old woman with Down's syndrome presented to the Emergency Room with a 1-month history of shortness of breath, productive cough and recurrent fever. She did not have haemoptysis and there was no history of weight loss, anorexia, night sweats, choking or significant dental problem. She was the youngest of seven siblings and was well cared for by her mother. She had been seen in a private clinic and started on clarithromycin for 10 days. Physical examination revealed an ill-looking woman with fever of 39.5°C, tachypnoeic respiratory rate 34/min, heart rate 125/min and 88% oxygen saturation on room air. The Acute Physiology and Chronic Health Evaluation II Score was 16. There was stony dullness over the right chest with absent air entry and coarse crepitations in the right lung base. Chest x-ray and thoracic CT scan showed a right-sided sizeable empyema with underlying total lung collapse and multiple fluid air loculi (figures 1 and 2). Laboratory tests showed leucocytosis with total count

Figure 1 Chest x-ray showing right-sided pleural collection with underlying lung collapse.

Figure 2 CT chest showing right sizeable pleural collection, with mediastinal shift to left and multiple air-fluid loculi in the underlying collapsed lung.

of 17 600 (neutrophil 80%), and haemoglobin 9.4 g/dl. Renal function tests revealed urea 9 mmol/l and creatinine 92 μ mol/l indicating prerenal azotaemia, while liver

function tests revealed low albumin 1.9 g/dl and raised alanine transaminase 52 U/l and aspartate transaminase 80 U/l with elevated γ glutamyl transpeptidase 199 U/l.

Erythrocyte sedimentation rate and C reactive protein were 138 mm and 26 mg/l respectively.

The patient was referred to a thoracic surgeon. Chest tube insertion was carried out but failed to drain any significant fluid, soon after which the patient was taken to theatre for video-assisted thoracoscopy which was converted to open thoractomy for decortication with pleurectomy and debridement as required. During the operation she received seven units of packed red blood cells, four units of fresh frozen plasma in addition to colloid and crystalloids.

Histological examination of the intraoperative specimen revealed dense inflammatory granulation tissue with marked fibrin deposition and focal haemorrhage in pleural tissue with adjacent lung parenchyma showing dense nodular mixed acute and chronic inflammatory cell infiltrates. Several characteristic eosinophilic microgranules were identified within the infiltrate and in some of these bacterial cocci were present at the core surrounded by eosinophilic material. The granules were highlighted by Giemsa and Periodic acid-Schiff stain, and some groups of cocci were Gram-positive (figure 3A–D). A diagnosis of pulmonary botryomycosis (bacterial pseudomycosis) was rendered.

Postoperatively, she was transferred intubated and ventilated to the ICU where she developed frank septic shock 1 h after admission with blood pressure of 70/42. She was treated according to ICU protocol with EGDT⁶ including vasopressor agents and antibiotics tazocin and levofloxacin for severe community acquired pneumonia. Vancomycin was added on account of prior antibiotic therapy.⁷ We adopted a protective ventilatory strategy

comprising synchronised mandatory ventilation/pressure control at 18/min targeting tidal volume (V_t) of 6 ml/kg, fractional inspired oxygen at 1.0 weaned to 0.6 and positive end expiratory pressure of 10 cm H_2O ; and the patient was weaned off norepinephrine after 24 h. After 7 days of ventilation, she was given an extubation trial after passing all SBT (spontaneous breathing trial) criteria except for rapid shallow breathing index which was 115. Unfortunately she again developed septic shock with blood pressure of 74/42 not responding to fluid resuscitation, and required re-intubation and recommencement of norepinephrine infusion which was escalated up to 30 μ g/min on the following day. After another 3 days of ventilation she was haemodynamically stable not requiring norepinephrine, passed all SBT criteria, and successful extubation trial was carried out requiring intermittent NIPPV. The patient stayed in ICU for 1 week off ventilation on low flow oxygen at a rate of 2 l/min by nasal cannula with occasional need for NIPPV. During this time she was intermittently febrile. Repeat CT chest after 2 weeks in ICU revealed considerable improvement compared to preoperative CT. She was transferred to the ward after a total stay of 20 days in ICU, on vancomycin and meropenem. In the medical ward she remained stable but antibiotics was changed to moxifloxacin after developing a drug eruption. She continued on moxifloxacin and intermittent oxygen for 1 month on the ward after which she was discharged home. At the time of discharge chest x-ray showed almost complete resolution (figure 4).

During her admission in hospital repeated microbial cultures on blood, sputum, urine, central venous line tip and

Figure 3 (A) Replacement of normal lung parenchyma by a dense mixed acute and chronic inflammatory infiltrate and scattered botryomycotic microgranules (arrows) (H&E, $\times 40$); (B) Botryomycotic microgranule (centre) with haemotoxyphilic core of bacterial cocci (long arrow) and eosinophilic rim (Splendore-Hoeppli phenomenon, short arrow) (H&E, $\times 100$); (C) Botryomycotic microgranule with central haemotoxyphilic cocci more clearly evident (H&E, $\times 400$); (D) Faintly Gram-positive cocci within microgranule core (arrow) (Gram, $\times 400$).

pleural fluid were negative. In addition pleural fluid was negative for acid fast bacilli and fungi.

DISCUSSION

Visceral botryomycosis has been mostly reported in patients with underlying immunosuppression, although it is also described in individuals without underlying illness.^{8–10} Our patient had Down's syndrome, which is associated with a variety of immunologic impairments, for example, decreased neutrophil and monocyte function, altered levels of complement components, lowered T cell function including response to specific antigens and abnormal cytokine production, that are thought to be related to the increased susceptibility to infection, autoimmune disease and malignancies.^{11 12} Our patient had leucocytosis at presentation, but her total and differential white cell counts returned to normal during the course of ICU therapy. She never had leucopenia and she was HIV-negative.

It appears that a number of factors alone or in combination might contribute to the pathogenesis of botryomycosis. These include trauma, presence of foreign body,¹³ size of inoculum, organisms of low virulence (eg, reduced virulence from antibiotic exposure), and host factors. The host factors are mostly related to impaired immune function as illustrated by previous case reports in patients with diabetes mellitus, cystic fibrosis, alcoholism, chronic granulomatous disease,¹⁴ steroid treatment, HIV/AIDS,¹⁵ malnutrition and other immune disturbances.

Normally, cellular defence against bacteria involves instant killing by neutrophils and monocytes/macrophages whose bactericidal ability is enhanced by interaction with cytokines released by various cells of the

immune system, especially T lymphocytes, macrophages and endothelial cells. The main cytokines involved in recruiting and activating neutrophils are tumour necrosis factor α (TNF α), interleukin (IL) 8 and IL-17. TNF α can stimulate secretion of IL-1 from macrophages which promotes extracellular pathogen killing by neutrophils. In situations of cytokine dysfunction bactericidal activity of neutrophils and macrophages is impaired leading to defective intracellular killing of immunoglobulin G coated organisms. In the presumed pathogenesis of botryomycosis, in this way pyogenic bacteria subsequently survive to cause a low-grade chronic infection in which the resultant tissue reaction is altered and instead of causing a suppurative infiltrate there are mixtures of acute and chronic inflammatory cells, a tendency to granuloma formation and characteristic microgranules. The Splendore-Hoepli phenomenon giving rise to the eosinophilic or amphophilic rim of the microgranules results from deposition of Ab-Ag-complement complexes, cell debris and fibrin. It is thought to be a localised immunological response to an antigen-antibody precipitate related to the inciting infectious agent, and probably prevents phagocytosis and intracellular killing of the infectious agent leading to chronicity of infection.

The occasional case of botryomycosis has been described in normal patients without underlying illness or immunodeficiency including a case of pulmonary botryomycosis.¹⁰

The dramatic presentation with septic shock may be explained by the fact that she had been sick for a period before presentation as evidenced by a very low albumin level on admission (1.9 g/dl) and anaemia (9 g/dl). Persistence of fever and relapse of septic shock shortly after

Figure 4 Chest x-ray at discharge showing almost complete resolution with only mild focal shadowing in the right mid zone.

postoperative recovery might be explained by a number of factors including:

- ▶ Resistance of the botryomycotic bacteria to antibiotics
- ▶ Poor penetration of tissues (necrotic and viable) by antibiotics
- ▶ Poor penetration of botryomycotic granules by antibiotics resulting in reduced exposure of bacteria (which lie at the core of granules) to antibiotics
- ▶ The timing of the surgery could be an important factor. In the current case, the patient was transferred hastily from emergency department to operating theatre while still septic and haemodynamically unstable. Bhatti et al⁸ describe a patient with pulmonary botryomycosis who was worked up and stabilised adequately before surgery (lung lobectomy) was carried out. The postoperative course was relatively untroubled and recovery to good health was relatively quick. Although exact time of surgery should be tailored to the individual case being considered, the current case and review of available literature together would suggest that delaying surgery until physiological stability is achieved is advisable in these circumstances.
- ▶ The exact type of surgery performed is likely to have had an impact on subsequent patient recovery. The mainstay of management in botryomycosis (be it cutaneous/subcutaneous or visceral) is surgical debridement of affected tissues. In the current case during the intended decortication and pleurectomy, diseased lung parenchyma was also fortuitously removed (which also allowed a definitive histological tissue diagnosis to be made). Furthermore, it is worth bearing in mind that decortication is a major operative procedure requiring full thoracotomy and is poorly tolerated by critically ill patients.¹⁶

This case serves to illustrate the important place of aggressive yet controlled ICU care, in particular EGDT, NIPPV and protected ventilatory strategy, in accordance with the accepted evidence base, in order to safely deliver an acutely ill postoperative patient to near-complete recovery as confirmed by the last chest x-ray before discharge (figure 4).

According to our research this is the first case of pulmonary botryomycosis reported in Down's syndrome and the first case which developed septic shock and required vasoactive drugs and ventilation in ICU. It is the second reported case of pulmonary botryomycosis in the Middle East.

Finally, the case is a useful reminder to be constantly vigilant and to consider broad differential diagnoses including rare entities especially when clinical presentation, radiological features and operative findings are somewhat unusual. Even within the context of such a rare condition as pulmonary botryomycosis, the clinical/radiological findings were unusual in that previous reported cases of pulmonary

botryomycosis have presented as a lung mass masquerading as cancer whereas our case presented with empyema and clinical sepsis.

Learning points

- ▶ Pulmonary botryomycosis is very rare.
- ▶ Accurate diagnosis requires histopathological examination.
- ▶ Surgical debridement and antibiotics is the mainstay of management.
- ▶ Clinoradiological features at presentation often mimic malignancy.
- ▶ Other modes of clinical presentation are much rarer and can include septic shock with acute lung injury.

Competing interests None.

Patient consent Obtained.

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