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BRIEF REPORT

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Life-threatening hemoptysis in adults with community-acquired pneumonia due to Panton-Valentine leukocidin-secreting *Staphylococcus aureus*

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Abstract Three new consecutive cases of life-threatening hemoptysis in adults with community-acquired pneumonia due to Panton-Valentine leukocidin-secreting *Staphylococcus aureus* are presented, focusing on the particular clinical presentation of this new entity. Between December 1999 and March 2001, three adults aged from 23 to 67 years were admitted to our respiratory intensive care unit for massive hemoptysis and septic shock associated with community-acquired *Staphylococcus aureus* pneumonia. Isolates were sent to the Centre National de Référence des Toxémies Staphylococciques in Lyon, France, where they were found to secrete Panton-Valentive leukocidin. The clinical course was similar in the three patients, with massive hemoptysis and septic shock necessitating mechanical ventilation. Two patients died rapidly; necropsy showed pulmonary vascular necrosis in one of them. The third patient recovered after appropriate antibiotic therapy. Leukocidin/neutrophil interactions in the pulmonary vasculature may cause severe hemoptysis in patients with community-acquired *Staphylococcus aureus* pneumonia secreting Panton-Valentine leukocidin. Adult patients with massive hemoptysis and suspected community-acquired pneumonia should receive antibiotic regimens covering *Staphylococcus aureus*.

Keywords *Staphylococcus aureus* · Pneumonia · Hemoptysis · Adult respiratory distress syndrome (ARDS)

Introduction

Staphylococcus aureus (*Sa*) accounts for 1-9% of cases of community-acquired pneumonia (CAP) [1] and up to 20% in intensive care units [2]. It typically involves patients over 60 years of age with predisposing factors. The clinical course is generally subacute, but the mortality rate is high despite appropriate antibiotic therapy. Hemoptysis is uncommon in adults [3, 4] and reports of massive hemoptysis have been described especially in children [5, 6, 7]. We describe three new consecutive cases of life-threatening hemoptysis in adults with *Sa*-CAP, discuss the role of Panton-Valentine leukocidin (PVL) and focus on the particular clinical presentation of this new entity recently referred to as "*Staphylococcus aureus* necrotising pneumonia" [6].

Case reports

Patient 1

On 30 December 1999, a 67-year-old smoker and alcoholic was referred to our hospital with massive hemoptysis for bronchial artery opacification and embolization (BAO). He had undergone surgery for throat cancer in 1994 and was on enalapril for hypertension. Two days prior to admission he had been prescribed amoxicillin and steroids for chills, dry cough and fever. On admission his temperature was 38°C, heart rate 110 beats/min and respiratory rate 22 breaths/min under high-tension oxygen mask. His blood pressure was 140/70 mmHg. Physical examination was normal except for diffuse pulmonary crackles. Chest X-ray examination showed alveolar opacities of the left lung; alveolar opacities were diffuse over the entire lungs on pulmonary computed tomography (CT), but CT was non-contributory regarding the cause of massive hemoptysis. Blood gas values on 9 l oxygen/min were as follows: pH 7.28, PCO_2 40 mmHg (5.3 kPa) and PO_2 80 mmHg (10.6 kPa). The circulating white-cell count was 4000×10^9/l, hematocrit 39% and platelet count $207{,}000\times10^9$/l. The prothrombin time was 78% and creatinine 117 μmol/l. Electrocardiogram was normal and mitral stenosis was ruled out by cardiac echography. Fiberoptic bronchoscopy (FB) showed active bleeding, predominantly from the left main stem bronchus, with bilateral flooding. Tracheal aspiration (TA), telescopic protected brushing (TPB) and blood culture (BC) were performed for microbiological analysis. Direct examination of Gram-stained smears of TA and TPB was negative.

The patient's condition deteriorated after FB, necessitating mechanical ventilation; PaO_2/FIO_2 was 65 mmHg. Gentamicin and metronidazole were added because of suspected anaerobes. BAO showed a left bronchial artery with inferior lobe bronchus opacification reflecting arterial erosion. The bleeding persisted despite bronchial artery embolization and septic shock necessitated adrenaline administration. He died of multi-organ failure 24 h after admission, with continued hemoptysis. Necropsy was not carried out. Cultures of blood and bronchial brushing specimens yielded methicillin-resistant *Sa*. The presence of the gene encoding PVL production was detected by the Centre National de Référence des Toxémies à Staphylocoques [7]. Indirect immunofluoresence and cultures for adenovirus, influenza, para-influenza and respiratory syncytial virus were negative. Culture for aspergilli and acid-fast bacilli (AFB) was negative. Tests for anti-glomerular basement membrane antibody (AGBMA), antineutrophil cytoplasmic antibody (ANCA) and antinuclear antibody (ANA) were negative.

Patient 2

On 3 February 2000, a 38-year-old smoker was referred to our hospital for massive hemoptysis and acute respiratory failure. He had been prescribed amoxicillin the previous day for a flu-like syndrome. On the day of admission he had developed acute respiratory failure with massive hemoptysis and septic shock. He was intubated at home for mechanical ventilation and transferred to our intensive care unit. On admission his temperature was 35.2°C, heart rate 105 beats/min and blood pressure 39/23 mmHg. Physical examination showed diffuse crackles on pulmonary auscultation and the patient was anuric. There were no skin lesions. Chest X-ray examination showed extensive bilateral alveolar infiltrates. Blood gas values on mechanical ventilation with 100% oxygen were as follows: pH 6.99, PCO_2 100 mmHg (13.3 kPa) and PO_2 54 mmHg (7.2 kPa); PO_2/FIO_2 was 54 mmHg. The circulating white-cell count was 800×10^9/ml, hematocrit 45% and platelet count 71,000 $x10^9$/ml. The prothrombin time was 38%, partial thromboplastin time 69/30 and creatinine 339 μmol/l. Electrocardiogram was normal and mitral stenosis was ruled out by cardiac echography. FB showed bilateral diffuse active bleeding. TA performed for direct examination of Gram-stained smears was negative.

On the basis of the previous case (1) of *Sa* pneumonia revealed by massive hemoptysis, antibiotic therapy was started with cefotaxime, ofloxacin, vancomycin and rifampicin, but the patient died 2 h later of multi-organ failure, before BAO could be performed. Blood cultures remained sterile but culture of the tracheal aspirate yielded a methicillin-sensitive *Sa* secreting PVL. Tests for viruses, fungi and autoantibodies (see case report 1) were negative. Autopsy revealed necrotic lesions of the bronchial wall, epithelial damage with necrotic lesions and numerous cocci. There was no parietal infiltration by neutrophils nor bronchial suppuration. In some regions the pulmonary capillaries were occluded by neutrophils, while in others entire portions of the alveolar septa were necrotic, accounting for the intra-alveolar hemorrhage.

Patient 3

On 12 March 2001, a 25-year-old man was referred to our chest department with hemoptysis. He had a 2-day history of cough and mucopurulent sputum. On the day of admission he had presented to the emergency room with dyspnea, where he was given oxygen supplementation and antibiotic therapy with amoxicillin. He was admitted to our intensive care unit when hemoptysis occurred. On admission his temperature was 39°C (with chills and sweating), heart rate 113 beats/min, blood pressure 84/46 mmHg and respiratory rate 40 breaths/min. Physical examination showed crackles over the right lung and finger-pulp infection. Chest X-ray examination showed bilateral but left-predominant alveolar opacities; pulmonary CT was non-contributory regarding the etiology of hemoptysis. Blood gas values on 15 l oxygen/min were pH 7.47, PCO_2 35 mmHg (4.6 kPa) and PO_2 85 mmHg (11.3 kPa). The circulating white-cell count was 700×10^9/l, hematocrit 40% and platelet count $105{,}000\times10^9$/l. The prothrombin time was 83%, partial thromboplastin time 40/30 and creatinine 106 μmol/l. Electrocardiogram was normal and mitral stenosis and left heart endocarditis were ruled out by cardiac echography. Worsening dyspnea necessitated mechanical ventilation and increasing hemoptysis necessitated continuous aspiration; PO_2/FIO_2 was 96 mmHg. TA and TPB performed for direct examination of Gram-stained smears showed Gram-positive cocci.

Based on our previous experience, antibiotic therapy was extensive with oxacillin, gentamicin and vancomycin. Hemodynamic failure necessitated adrenaline administration during the first three hospital days. Culture of blood, TA, TPB samples and infected finger pulp yielded a methicillin-sensitive *Sa* secreting PVL. Antimicrobial chemotherapy was reduced to oxacillin and gentamicin. Hemoptysis ceased within 48 h. After a short weaning period, the patient self-extubated on day 11. He was discharged 23 days after admission. The above-mentioned tests for viruses fungi and autoantibodies (case 1) were negative. Three months after discharge there were no clinical or radiological sequelae.

The three patients described here presented life-threatening hemoptysis related to *Sa* necrotising pneumonia. There was no epidemiological link between the three patients. However, patient 1 was infected with the super-adapted PVL secreting methicillin-resistant *Sa* strain that was recently described in the French community [8]. The other two *Sa* isolates were not clonal as determined by pulse field gel electrophoresis (data not shown).

Discussion

Community-acquired *Sa* pneumonia in adults is rare, but the prognosis is grim, with an overall mortality rate of

30% [1, 3], increasing to 84% in patients with underlying disease [4]. The clinical manifestations are similar to those of other forms of bacterial pneumonia and hemoptysis is rarely described [1, 3, 4, 9].

Although our patients suffered from adult respiratory distress syndrome (ARDS) as defined by clinical, radiological and PO_2/FIO_2 criteria and the absence of left ventricular dysfunction, there were no histological lesions i.e. hyaline membranes, diffuse alveolar damage and fibroblastic deposition, suggesting that radiological lesions were not predominantly due to ARDS, but to intense bleeding and alveolar flooding. We found no cause for hemoptysis other than *Sa*-CAP in our patients. The only inhaled noxious product was tobacco smoke in two patients (cases 1 and 2). Heart disease (congestive heart failure and mitral stenosis) was ruled out by cardiac echography. Only patient 2 had evidence of renal failure, thrombocytopenia and clotting disorders, but these were related to septic shock; indeed, necropsy revealed no specific lesions other than those resulting from bacterial pneumonia. Tuberculosis and aspergillosis were also ruled out. Goodpasture's syndrome, microscopic polyangiitis and systemic lupus erythematosus were unlikely causes of the hemoptysis, as tests for AGBM, ANCA and ANA autoantibodies were negative. Finally, fiberoptic bronchoscopy showed no endobronchial lesions, and CT (cases 1 and 3) and lung necropsy (case 2) showed no underlying parenchymal, bronchial or vascular disease.

We thus hypothesize that the life-threatening hemoptysis in our patients was most likely related to the Panton-Valentine leukocidin produced by the *Sa* isolates, as in two recent pediatric reports [5, 6]. Our patients had diffuse alveolar hemorrhage (DAH), but erosion of larger vessels was also probable. Indeed, endoscopy showed bilateral active bleeding in each case. Furthermore, in case 1 bronchial arteriography revealed left lower endobronchial opacification reflecting arterial erosion, but bleeding persisted despite BAO. Finally, necrotic lesions of the tracheal mucosa and alveolar septa were observed at necropsy in case 2. These pathological findings are similar to those described by Lina et al. [10] and Gillet et al. [6] and referred to as "*Staphylococcus aureus* necrotising pneumonia" [6].

Although the precedence of an influenza-like syndrome was observed in two of our adult patients (cases 1 and 2), direct search for pneumotropic virus in pulmonary secretions always remained negative. PVL belongs to a family of synergohymenotropins secreted by fewer than 2% of *Sa* strains [10, 11]. It is found in 75% of patients with furunculosis [12]. Its pathogenicity is related to its toxicity for white cells, especially neutrophils, to which it binds via a G-protein-coupled specific membrane receptor [13]. This interaction leads to PVL-concentration-dependent neutrophil adhesion to endothelial cells, followed by capillary dilation, leukocyte diapedesis and vascular necrosis due to release of oxygen metabolites, IL-8, LTB4 and enzymes, as demonstrated in animal models [14, 15]. We hypothesized that a similar phenomenon occurs in the pulmonary vascular beds of our patients leading to intense bleeding and alveolar flooding, an unusual mechanism of dyspnea among patients with CAP. In addition, the pathogenicity of PVL might explain the leucopenia also observed in two of our patients (2 and 3) [6].

Staphylococcus aureus producing the Panton-Valentine leukocidin represents a rare cause of pulmonary infection in adults but is remarkable for its severity and mode of revelation. The combination of life-threatening hemoptysis and sepsis in a patient with suspected CAP must alert clinicians to instigate an antibiotic regimen covering *Sa* as soon as possible [16]. If, despite active antibiotic chemotherapy, hemorrhaging persists, desmopressin might be useful to stop alveolar bleeding, as recently suggested in patients with *Leptospira interrogans*-CAP [17].

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