**Dyspnoea, haemoptysis and fever progressing to acute respiratory failure. A didactic story with a happy ending.**

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**Introduction**

The rapid progression of dyspnoea, haemoptysis and fever to acute respiratory failure within a short period of time in an otherwise healthy child presents a challenge to the differential diagnosis. Correct diagnosis and targeted treatment are keys to patient survival. Essential investigations include basic laboratory tests, blood gases and a chest scan. Correct interpretation of the initial data determines the future direction of a more detailed investigation and treatment strategy.

**Case report**

12-year-old otherwise healthy girl presented to paediatric emergency with rapidly progressive dyspnoea, haemoptysis and fever. Flu-like symptoms during the last 5 days were reported by the girl's parents. The attending physician examined the girl and ordered CRP (C-reactive protein), blood gases, chest X-ray and gene expert (rapid PCR tests for Respiratory Syncitial Virus, Sars-Co-V2 and influenza). Dysphonia, fatigue, tachypnea and bilateral crackles dominated the physical findings. The capillary CRP was over 160 mg/L and the chest scan (figure 1 and podcast 1) was markedly pathological. The PCR test was positive for Influenza A. The girl's condition deteriorated rapidly and her SAT02 dropped below 80 %, so a paediatric pulmonologist and an intensive care physician were called. The girl was admitted to the intensive care unit. She received oxygen and rehydration therapy, blood was taken for laboratory tests and a chest CT (computed tomography) was ordered.



Figure 1 the initial PA (postero-anterior) chest radiograph

CHALLENGE POINT

What different directions in the differential diagnosis would be linked by dyspnoea, rapid progression, haemoptysis, cough, fever, chest scan findings and a history of influenza A?

LEARNING REFLECTION

What's most likely to be going on?

Which laboratory tests will help us differentiate these conditions?

*Podcast 1 – pneumologist, ICU specialist (mp4- 1)*

*The initial PA chest radiograph showed evidence of bilateral ill-defined multifocal opacities in the middle and lower lung fields.*

*These symptoms may be present in fulminant pneumonia, for which dyspnoea, haemoptysis, rapid progression, bilateral crackles and fever would be suggestive. There would be a massive increase in inflammatory markers.*

*Another possibility is acute vasculitic syndromes such as Good Pasture syndrome or granulomatosis with polyangitis. In these syndromes there is dyspnoea, haemoptysis and bilateral pulmonary infiltrates on chest scan. It can also be triggered by influenza. A typical diagnostic marker is the presence of antibodies (c-ANCA, anti-GBM).*

*Pulmonary tuberculosis (TB) must also be excluded. TB can cause haemoptysis, cough and fever. The progression of the disease can be rapid in some cases, but a gradual progression over several weeks is more likely. A chest scan may show nodules or masses in the lungs. There is usually a history of close contact with TB and a positive IGRA (interferon gamma release assay) test.*

*Our girl could also have a pulmonary embolism (PE): Rapid progression of the disease, dyspnoea and chest pain are hallmarks of PE, and haemoptysis and fever may also be present. However, neither the medical history nor the radiological findings are consistent with PE.*

**Case progression**

Laboratory results were available within one hour of admission (Fig. 2). The blood count showed significant leukopenia. CRP and PCT (procalcitonin) were elevated above normal. Autoantibodies were negative. The IGRA test was negative. The most likely diagnosis was pneumonia. The clinical presentation and leukopenia in contrast with high levels of CRP and PCT strongly suggest necrotising pneumonia caused by Panton-Valentine leucocidin (PVL)-producing Staphylococcus aureus (Fig. 3).

*Figure 2 Laboratory results within one hour of admission*

|  |  |
| --- | --- |
| WBC | 1,5 109/l |
| RBC | 2,44 1012/l |
| Hb | 74 g/l |
| PLT | 101 109/l |
| CRP | 453 mg/l |
| PCT | 27,3 ug/l |
| pH | 7,41 |
| pCO2 | 4,92 kPa |
| pO2 | 6, 59 kPa |
| IGRA test | Negative |
| Autoantibodies | Negative |
| D-Dimers | 3940 ug/l |

Figure 3 *Characteristic clinical and laboratory manifestations of Staphylococcus aureus MRSA/PVL infection that can be used for early diagnosis*1

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| --- |
| 1. Rather young and still healthy people (including infants), with no apparent predisposition, are affected.✅ |
| 2. Disease progresses very rapidly, intensive care is necessary.✅ |
| 3. The clinical picture is dominated by hypotension/septic shock ✅ and/or severe pneumonia with increasing dyspnoea and often haemoptysis. ✅ |
| 4. Despite the severity of the general condition and high CRP and PCT values ✅, the blood leukocyte count remains normal or leukopenia is evident.✅ |
| 5. The chest scan shows multifocal or bilateral involvement ✅of the lung parenchyma, often with pleural effusion or lung tissue cavitation. |
| 6. There are surprisingly few polymorphonuclei in aspirate taken from the lower airways. ✅ |
| 7. In relevant material (haemocultures, tracheal or bronchial aspirate, pleural punctate), S. aureus is demonstrated as the likely aetiological agent (probably by PCR or microscopic findings of gram-positive cocci in clusters).✅ |
| 8. Patients usually come from the community and have no recent history of contact with a healthcare facility.✅ |

CHALLENGE POINT

We have a febrile girl with progressive dyspnoea and a strong suspicion of MRSA/PVL pneumonia.

LEARNING REFLECTION

What will be the key steps to stabilise the patient's condition?

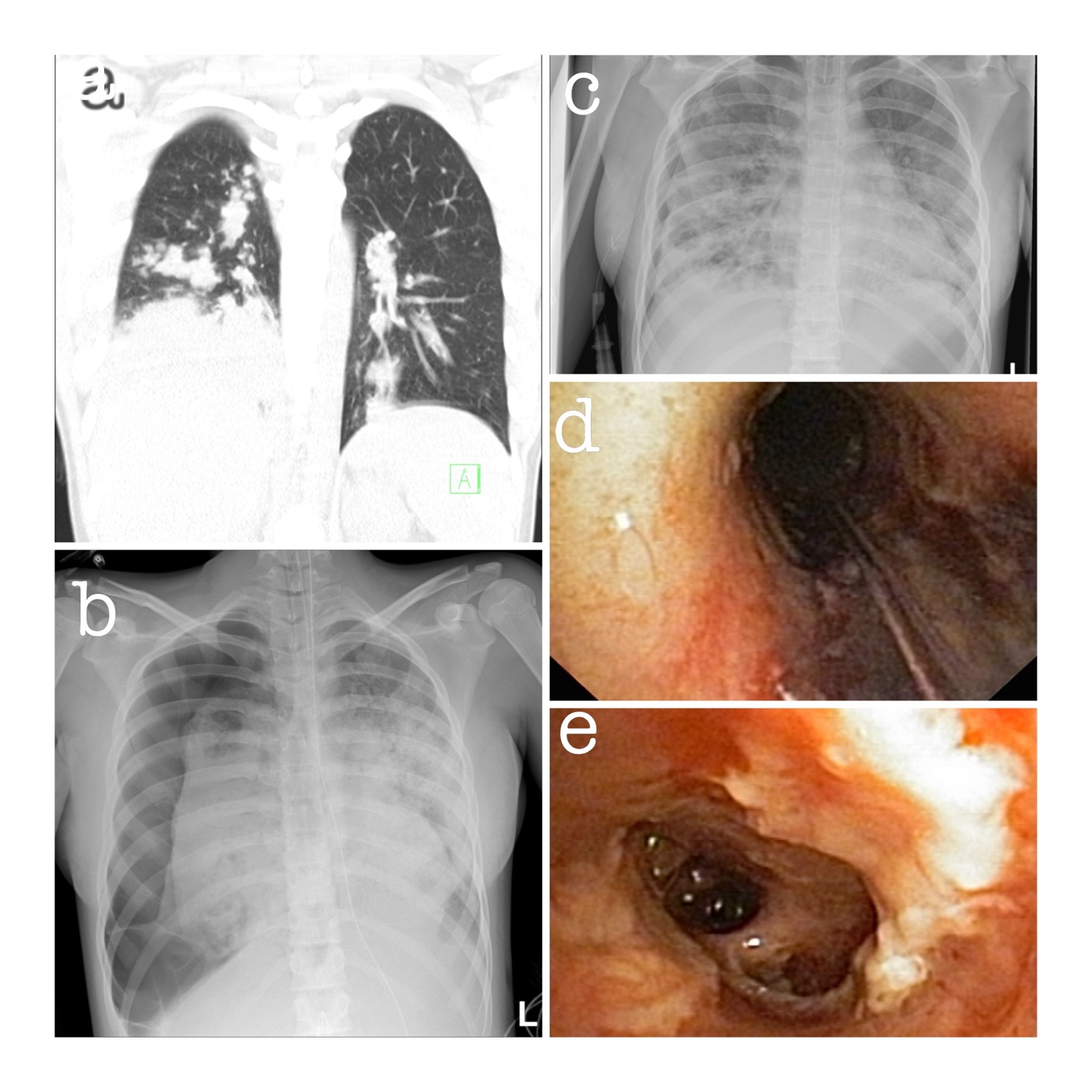
What will be the pharmacological treatment strategy?

*Podcast ICU (intensive care unit) specialist and pneumologist (mp4 – 2)*

*In a child in this condition, we started peripheral venous access, infusion therapy, and blood collection for laboratory testing and samples for microbiological analysis. We then transferred the patient for a chest CT scan. Very quickly we established a working diagnosis of possible staphylococcal pneumonia and combination therapy (combination of antibiotics - cefotaxime, clindamycin, linezolid, antivirals and antifungals) and systemic corticosteroids and intravenous immunoglobulins (IVIG) were started. Non-invasive ventilatory support was initiated soon after admission with a switch to mechanical ventilation when ventilatory failure developed on day 5 of hospitalization (mechanical ventilation modeled to minimize the risk of barotrauma). Repeated monitoring of intrathoracic images and bronchoscopy were performed.*

**Case progression**

The girl was on HFNO (High Flow Nasal Oxygenation) breathing support after admission to ICU. Chest CT showed extensive infiltrates in the right lung (4a). Intensive treatment regimen with antibiotics (cefotaxime, ciprofloxacin, linesolide), antivirotics (oseltamivir), antimycotics (fluconasol) and corticosteroids was established. A positive culture for *Staphylococcus aureus* was obtained from the respiratory tract. Further analysis confirmed MRSA/PVL. Due to the development of acute respiratory insufficiency and worsening of the findings on the chest scan (4b), it was necessary to switch to mechanical ventilation on the 6th day of hospitalization. Bronchoscopy was performed with markedly pathological findings (4d,e). Shortly after the introduction of mechanical ventilation, tension pneumothorax (4c) developed with the need for chest drainage. After 6 days of mechanical ventilation, she was extubated without complications. Bronchoscopic findings were with a significant regression of pathological changes. Thoracoscopy was indicated for persistent pneumothorax with the finding of a fragile and easily bleeding lung and empyema. Empyemectomy performed, source of air-leak objectified, but due to fragility of the tissue, surgical closure was not possible.



*Figure 4 Imaging methods and bronchoscopy. Comments by radiologist and pneumologist.*

a - Computed tomography (CT) of the chest in coronal view shows multifocal consolidations in both lungs, predominantly in the right lung. No pleural effusion.

b- AP chest radiograph showing right-sided tension pneumothorax as a complication of mechanical ventilation with partial collapse of the right lung, slight leftward displacement of the trachea and heart. Compressed right hemidiaphragm, right deep sulcus sign. Extensive consolidation in both lungs. Endotracheal tube and nasogastric probe appropriately placed.

c - Another chest X-ray taken a few days later showed partial resolution of consolidations in both lungs, with a small pneumothorax persisting on the right. There were also small hyperlucent areas in the right lower quadrant suggesting the presence of gas, which was suspected to be necrotizing pneumonia.

d- View of the trachea with a flexible bronchoscope through the intubation cannula. In many places in the trachea there are these livid to black circles. These are haemorrhagic-necrotic lesions, most likely the source of the initial haemoptysis.

e- The right bronchial tree was full of white hard fibrin plaques resistant to suction. In the smaller bronchi, they completely blocked the bronchial lumen.

CHALLENGE POINT

We have a young girl with acute respiratory failure due to an extensive and severe ongoing pneumonia. She no longer needs ventilator support, but her condition is complicated by a large pneumothorax.

LEARNING REFLECTION

What therapeutic methods are available for pneumothorax? What can be done with a mini-invasive approach by in a paediatric ICU?

*Podcast ICU specialist*

*Iatrogenic pneumothorax arising as a complication of mechanical ventilation should always be treated with chest drainage. It is unlikely to resolve spontaneously because of the positive pressure used to create inspiration. The best and safest place to introduce a chest drain is the 5th intercostal space in the ventral axillary line. The drain is then connected to a closed system creating the vacuum needed for excessive air evacuation. On the other hand, a primary spontaneously occurring pneumothorax in a normally breathing child that is not large and progressive can be very well treated with oxygen administered through nasal cannulas. Early chest X-ray and careful monitoring of the patient's vital signs are always necessary.*

**Case progression**

The girl has a chest tube in the chest cavity. She's fully conscious and coughing, afebrile. Auscultation sounds on the right side are still diminished despite intensive respiratory physiotherapy. Combined antibiotic treatment was stopped after 23 days. Her general condition is deteriorated by depression for which she is on psychiatric medication and supportive psychotherapy. The end of intensive care is again complicated by a febrile state with increased inflammatory parameters. Lower respiratory tract cultures were negative. A second chest CT was performed. The chest tube was removed and a positive culture was obtained from the tube with a positive culture for MRSA/PVL. Combined antibiotic treatment (linesolide and ceftaroline) was restarted for another 4 weeks. The girl's physical and mental condition improved significantly and she was discharged to home care with continued antibiotic therapy, respiratory physiotherapy under professional outpatient care.

CHALLENGE POINT

We have a stable patient on ongoing combined antibiotic therapy with persistent pathological changes on chest scan and CT of the thorax.

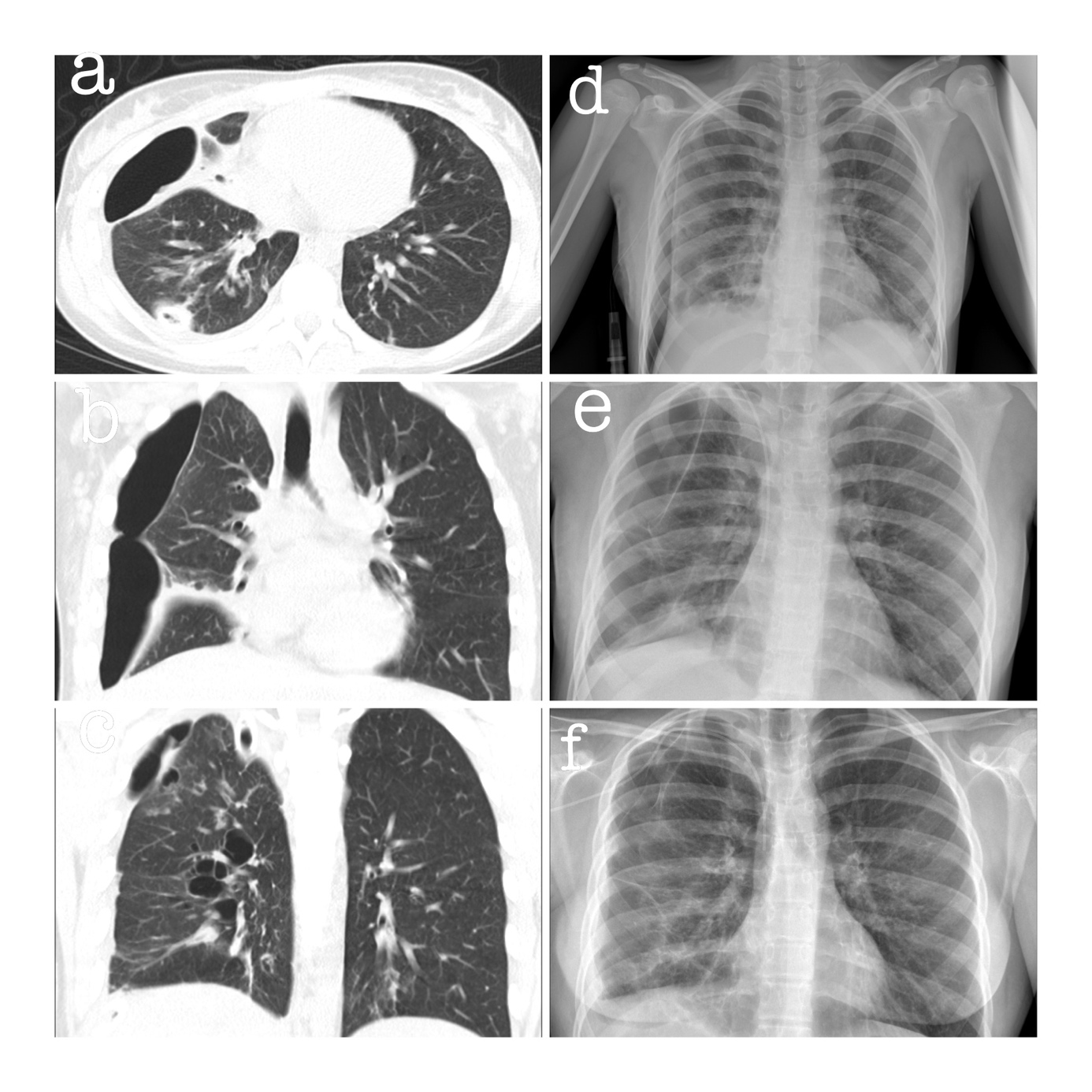
LEARNING REFLECTIONS

What pathological findings do the imaging modalities show?

How should the treatment be continued?

*Podcast pneumologist and ICU and radiologist (mp4- 3)*

*At this stage of treatment, the most important things are time, protection from infection, a nutritious diet and psychological well-being. We continued the antibiotic therapy for 4 weeks to eradicate the MRSA/PVL. We discharged the girl home with frequent outpatient follow-up. She does respiratory physiotherapy at home. Antidepressants were discontinued due to her good mental status. In general, children have a great capacity to heal and it can be assumed that even pneumoceles will resorb over time. No surgery is indicated.*



*Figure 5 Further imaging methods results*

a, b, c - CT scan of the chest, axial and coronal views, showing resolved bilateral pneumonia and the right localised pneumothorax. Multiple thin-walled cavities of different sizes and atelectatic scarring on the right. The right hemidiaphragm is slightly higher than the left. Blunting of the right costophrenic angle is due to mild pleural thickening.

d - Chest x-ray showing almost complete reduction of the infiltrative shadows in both lungs. Small cavities were seen in the right lower zone. Persistent right pneumothorax.

e - Chest x-ray after removal of the lung drain showing a right loculated pneumothorax and atelectatic scarring in the right basal zone.

f - Control chest x-ray showing partial reduction of the right pneumothorax with residual post-inflammatory scarring on the right. The right hemidiaphragm was slightly higher than the left. Blunting of the right costophrenic angle. Left lung was clear.

**DISCUSSION**

Rapidly progressive dyspnoea, cough, haemoptysis and fever have a wide differential diagnosis. All of these conditions are considered emergencies requiring multidisciplinary care. In the first stage, we identified 4 main differential diagnosis routes (pneumonia, vasculitis, TB and pulmonary embolism). By taking a detailed history and ordering the correct laboratory tests, we were able to rule out 3 diagnoses in a short space of time. Acute vasculitic syndromes would be characterised by the presence of autoantibodies, which the girl did not have. For tuberculosis, we would expect a positive epidemiological history of a household TB contact and a positive IGRA test, both of which were negative. A negative family and personal history, absence of risk factors and extensive bilateral radiological findings do not suggest pulmonary embolism. A positive finding of elevated D-dimer is non-specific and may accompany any inflammatory process. With the exclusion of other diagnostic entities, we focused our attention on pneumonia.

The combination of a very severe condition with markedly elevated CRP and PCT in contrast to marked leukopenia, together with the above symptoms, and the fact that we had seen this condition in the past, led us very quickly to suspect an MRSA/PVL aetiology. Panton-Valentine leukocidin (PVL), named after the authors of the 1932 paper 2, is encoded by two genes, luk-S-PV and luk-F-PV, and is transferred between heterologous strains of Staphylococcus aureus by bacteriophages. MRSA/PVL strains have been associated with a particularly virulent form of necrotizing pneumonia, mainly in otherwise healthy children and adolescents, characterised by abscess formation, cavitation, haemorrhage, post-pneumonic pneumatocele and a mortality rate approaching 75 % 3,4. Prompt use of effective antibiotic treatment, IVIG and intensive care is essential for patient survival. For necrotizing pneumonia caused by MRSA, the first-line antibiotic treatment is intravenous vancomycin or linezolid 5,6 To our knowledge, the efficacy of linezolid is superior to that of vancomycin. 7–10In addition to antibiotic treatment, human intravenous immunoglobulin (IVIG) also contributes to treatment success. Diep and colleagues demonstrated in a rabbit model that two specific antibodies can neutralise the toxic effects of α-hemolysin (Hla) and Panton-Valentine leukocidin (PVL). In this preclinical animal model, treatment with IVIG in combination with either vancomycin or linezolid improved survival11. Survival is significantly improved by early treatment with effective antibiotics and IVIG. Post-pneumonic changes, which look frightening in the acute phase of the disease, usually heal spontaneously in surviving patients12.

**CONCLUSION**

The girl in our case report survived, although there were moments when her critical condition and the high mortality in published case series of MRSA/PVL pneumonia did not give us much optimism. We believe that this therapeutic success was due to the early use of linesolide and IVIG. We suspected the aetiology of MRSA/PVL very early. A multidisciplinary team (intensivist, pulmonologist, thoracic surgeon, respiratory physiotherapist, psychiatrist, psychologist, microbiologist) was involved in the girl's care. The aim of this case report is to recall this problem. It highlights the typical clinical symptoms, laboratory findings, radiological presentation and recommended therapy.

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