CASE REPORT

Pulmonary leucostasis syndrome presented by unilateral pulmonary infiltrates

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SUMMARY

A 48-year-old woman presented with suspected acute myelogenous leukaemia with a leucocyte count of $80 \times 10^9/L$. On admission, she had high fever and shortness of breath. Chest X-ray demonstrated unilateral consolidations of right lung suggestive for pneumonia and broad spectrum antibiotics were started. Her condition rapidly deteriorated and despite the clinical diagnosis of pulmonary leucostasis and treatment with leucapheresis the patient died within 2 days after admission from progressive respiratory failure and multiorgan failure. Autopsy showed diffuse leucostasis in the pulmonary capillaries. The present case illustrates that pulmonary leucostasis may be presented by unilateral chest X-ray abnormalities and without clear neurological symptoms (headache and blurred vision). Clinicians should be aware of this since delayed treatment may increase mortality.

At presentation in our hospital she initially experienced minimal shortness of breath. She had no symptoms of headache or blurred vision. Physical examination revealed fever ($39^\circ C$) and an oxygen saturation of 90% with supplementary oxygen without signs of respiratory distress.

INVESTIGATIONS

Laboratory features (table 1) showed anaemia (haemoglobin 4.5 mmol/L), leucocytosis (WCC $80 \times 10^9/L$), thrombocytopenia ($47 \times 10^9/L$), prolonged prothrombin time (17.0 s) and lactate dehydrogenase 726 U/L (normal <250 U/L). Renal function was impaired (creatinine 176 $\mu mol/L$). Morphological evaluation of peripheral blood smear was consistent with AML with monocytic features (monocytes $48.8 \times 10^9/L$, figure 1). Chest X-ray (figure 2) showed blotchy parenchymal infiltrates in the right lung.

TREATMENT

Because pneumonia was suspected, broad spectrum antibiotics were started (amoxicillin/clavulanic acid plus ciprofloxacin). The next day, the patient developed progressive respiratory distress with significant hypoxia (oxygen saturation 60%). A newly performed chest X-ray showed progressive infiltrates in the right lung (figure 3). Laboratory features showed an increasing leucocytosis (WCC $92 \times 10^9/L$). The patient was transferred to the intensive care unit (ICU) for ventilatory support. Initially non-invasive ventilation was started with good clinical result, however, after a few hours the patient's condition deteriorated requiring intubation and mechanical ventilation. After intubation, bronchoalveolar lavage was performed for microbiological diagnosis and antifungal (voriconazole) and antiviral (ganciclovir) therapy were added. CT of the lungs demonstrated severe parenchymal consolidations as well as diffuse ground glass opacities of the right lung, suggestive for infection or leukaemic infiltrates (figure 4). Because of the severe leucocytosis with predominantly (pro) monocytic cells, together with the increase of the pulmonary infiltrates and rapid deterioration of the clinical condition, pulmonary leucostasis syndrome was finally suspected in spite of the atypical unilateral distribution of the infiltrates. Additional fundoscopy was performed, showing retinal abnormalities with signs of leukaemic infiltration, which confirming leucostasis syndrome. Leucapheresis was initiated immediately as well as treatment with hydroxyurea and corticosteroids. Unfortunately, the patient's condition deteriorated progressively in the

BACKGROUND

The leucostasis syndrome is a well-known, life-threatening complication of acute and chronic leukaemia. The syndrome is mostly presented by symptoms involving the central nervous system (CNS), lungs and/or other organ systems. CNS symptoms together with hyperleucocytosis may trigger the diagnosis of the leucostasis syndrome. Pulmonary involvement is typically characterised by respiratory distress together with development of bilateral consolidations on chest X-ray.¹ We report a non-classical case of leucostasis syndrome in a patient with acute (myelo) monocytic leukaemia presented without any CNS symptoms or unilateral abnormalities on X-ray imaging.

CASE PRESENTATION

A 48-year-old woman with a history of essential hypertension and obesity was admitted at our haematology department after referral by a nearby hospital for a suspected diagnosis of acute myeloid leukaemia (AML).

Three days before referral she was admitted in the same nearby hospital because of severe painful haemorrhoids, which were treated by rubber band ligation. Two days after this procedure she experienced shortness of breath together with hypoxaemia (arterial oxygen saturation of 73%). The consulted pulmonologist started treatment with claritromycin. Additional laboratory testing showed severe leucocytosis (white cell count (WCC) $62 \times 10^9/L$) with the presence of Auer rods, indicating AML.

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Table 1 Laboratory results at time of admission

Blood count		
Platelet count ($\times 10^9/L$)	47	(150–400)
Leucocytes ($\times 10^9/L$)	80.4	(4.0–10.0)
Eosinophils ($\times 10^9/L$)	0.0	(<0.5)
Basophils ($\times 10^9/L$)	0.0	(<0.2)
Lymphocytes ($\times 10^9/L$)	10.4	(1.5–3.5)
Monocytes ($\times 10^9/L$)	48.8	(0.1–1.0)
Auer rods	+++	
Haemoglobin (mmol/L)	4.5	(7.5–10.0)
Haematocrit (%)	22	(35–45)
Clotting analysis		
Activated partial thromboplastin time (s)	32	(25–35)
Prothrombin time (s)	17.0	(12.5–14.5)
Chemistry		
BUN (mmol/L)	11.7	(2.5–6.4)
Creatinine ($\mu\text{mol/L}$)	176	(50–90)
Lactate dehydrogenase (U/L)	726	(<250)
C Reactive Protein (mg/L)	157	(<10)
Procalcitonin ($\mu\text{g/L}$)	<0.50	(<0.50)
Arterial blood gas		
pH	7.44	(7.35–7.45)
PCO ₂ (kPa)	5.8	(4.3–6.0)
PO ₂ (kPa)	7.8	(11.0–14.4)
Bicarbonate (mmol/L)	30	(21–29)
Base excess	5.0	(–2.0–3.0)
SO ₂ (mmol/mol)	0.89	(0.94–0.98)

BUN, blood urea nitrogen.

next following hours with development of multiple organ dysfunction syndrome (MODS) and irreversible hypoxaemia. This situation together with the underlying diagnosis of acute leukaemia suggested a very poor prognosis, and further treatment was discontinued and the patient died within 24 h after admission to the ICU. Autopsy of the lungs ([figure 5](#)), spleen and liver demonstrated severe capillar oedema with extensive sequestration of blasts. Postmortum bone marrow smear showed both myeloblastic, monoblastic and monocytic cells (myeloperoxidase positive, [figure 6](#)). Based on the morphological characteristics and available colourings, acute myelomonocytic leukaemia (French–American–British (FAB) classification M4) or acute monocytic leukaemia (FAB classification M5B) was suggested. A more detailed classification could not be given due to the lack of

Figure 1 Peripheral blood smear with a myeloblast. The cytoplasm is filled with Auer Rods (arrow). **Figure 2** Chest X-ray showing blotchy consolidations projecting themselves over the right hemithorax. The left hemithorax is clear, the heart is enlarged.

classifying diagnostics. Microbiological investigation revealed no proof of pulmonary infection ([table 2](#)).

DISCUSSION

Patients diagnosed with acute leukaemia and presenting with fever and pulmonary infiltrates on chest X-ray are primarily suspected of pneumonia, whether or not as a result of opportunistic pathogens. Differential diagnosis includes the pulmonary leucostasis syndrome, in particular when hyperleucocytosis is present. In patients with AML, hyperleucocytosis is present in 10–20% of patients and is more common in patients with myelomonocytic leukaemia, monocytic leukaemia or the microgranular variant of acute promyelocytic leukaemia and should be considered as a medical emergency. Symptoms of leucostasis occur less frequently and typically affect patients with hyperleucocytosis. Hyperleucocytosis is defined as a WCC count greater than $100 \times 10^9/L$ and is associated with increased morbidity and mortality.¹ The threshold of $100 \times 10^9/L$, however, is arbitrary

Figure 3 Chest X-ray showing progressive blotchy consolidations of the right lung.

Figure 4 Chest CT scanning showing massive consolidations of the right lung.

for leucostasis since in AML a leucocyte count of $50 \times 10^9/L$ may already cause severe symptoms, while patients with chronic lymphatic leukaemia (CLL) remain asymptomatic even with WCC counts greater than $500 \times 10^9/L$,² correlated with the size of the malignant cells.

The central nervous system (CNS), retina and lungs are the most common sites for symptomatic vascular obstruction, but effects on other organ systems may occur. CNS symptoms may vary from headache, confusion and somnolence to coma. Blurred vision may be a sign of impaired retinal perfusion. Respiratory symptoms are non-specific and may include dyspnoea and/or tachypnoea together with confirmed hypoxaemia. Diagnosis of pulmonary leucostasis is suggestive when respiratory distress is present together with pulmonary infiltrates on chest radiographics. In some patients, however, chest X-ray can be normal despite microscopic leucostasis.³ The presence of radiographic abnormalities may be explained by concomitant alveolar oedema, which is probably the result of diffuse endothelial damage from either simple embolic ischaemia aggravated by continuing oxygen consumption of the sludged leukaemic

Figure 5 The histology of the lung shows a normal pattern of alveolar spaces with distended (capillary) vessels filled with leucocytes. There is no evidence of inflammation in the alveolar spaces.

Figure 6 Postmortem bone marrow smear with cytochemical staining for myeloperoxidase showing a hypercellular bone marrow filled with premature white cells.

cells or the release of proteolytic enzymes from those cells and the generation of toxic oxygen compounds.^{1 4 5} In the literature, there is no consensus with regard to diagnostic criteria on chest radiography in patients with pulmonary leucostasis. The pulmonary infiltrates are being described as either diffuse alveolar or interstitial^{3 6 7} and almost exclusively bilateral.^{2 3} Since our patient had no clear clinical symptoms of leucostasis, that is, absence of headache and blurred vision together with initially unilateral pulmonary infiltrates, this syndrome was not directly recognised and treatment was primarily aimed at an infectiological cause. The absence of bilateral pulmonary abnormalities on chest radiographs may be an important pitfall in diagnosing pulmonary leucostasis.

Table 2 Microbiological examination

Urine	
Legionella pneumophila antigen	Negative
Blood, cultures	Negative
Blood, molecular detection	
Herpes Simplex virus 1/2	Negative
Cytomegalovirus	<200 copies/mL
Blood, serology	
Anti Legionella pneumophila IgG/IgM	Negative
Bronchoalveolar fluid	
Cultures (bacterial, moulds/yeasts)	Negative
Galactomannan antigen	<0.5
Molecular detection	
Influenza A	Negative
Influenza B	Negative
Para influenza 1 virus	Negative
Para influenza 2/4 virus	Negative
Para influenza 3 virus	Negative
Adenovirus	Negative
Respiratory syncytial A/B virus	Negative
Rhinovirus	Negative
Human metapneumovirus	Negative
<i>Chlamydia pneumoniae</i>	Negative
<i>Mycoplasma pneumoniae</i>	Negative
Enterovirus	Negative
Herpes simplex virus 1/2	Negative
Cytomegalovirus	Negative
Varicella Zoster virus	Negative
<i>Pneumocystis jiroveci</i>	Negative
<i>Mycobacterium tuberculosis</i> complex	Negative

To achieve cytoreduction, leucapheresis and (induction) chemotherapy should be initiated as soon as possible when the leucostasis syndrome is highly suspected. Some centres use whole-lung⁸ or cranial⁹ irradiation as a part of multimodality therapy. If leucapheresis is not available in an emergent situation, repeated phlebotomies with concurrent blood and/or plasma replacement may be attempted.

To the best of our knowledge, this is the first patient described in the literature with pulmonary leucostasis presenting with predominantly unilateral radiographic abnormalities and without clear CNS symptoms of the leucostasis syndrome. Since this life-threatening syndrome may be reversible and improve short-term outcome if leucapheresis is started without delay, it should be stressed that pulmonary leucostasis syndrome should also be considered if unilateral abnormalities are present on chest radiographs.

Learning points

- Pulmonary leucostasis syndrome is a well-known complication of acute myeloid leukaemia, in particular in acute (myelo) monocytic leukaemia.
- The case illustrates that pulmonary leucostasis may be presented by predominantly unilateral pulmonary infiltrates and without clear central nervous system symptoms (headache, blurred vision).
- Early recognition of the leucostasis syndrome is of great importance since leucapheresis may improve short-term outcome.

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