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Brief report

Diffuse pulmonary infiltrates in immunocompromised patients

J.W. Fijen*, T.S. van der Werf, J.J.M. Ligtenberg, J.E. Tulleken, J.G. Zijlstra

Intensive Care Beademing, Interne Kliniek, Academisch Ziekenhuis Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

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Abstract

The differential diagnosis of bilateral interstitial pulmonary infiltrates in immunocompromised patients is very extensive. We describe two immunocompromised patients with diffuse pulmonary infiltrative changes. Bronchoscopic bronchoalveolar lavage after orotracheal intubation using topical anaesthesia combined with mild sedation in an ICU setting is safe in critically ill patients and often yields a conclusive diagnosis. © 1999 Elsevier Science B.V. All rights reserved.

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Introduction

The differential diagnosis of pulmonary infiltrates in immunocompromised patients is extensive [1-4]. We describe two patients with an interstitial chest-radiographic pattern. We propose the use of flexible bronchoscopic orotracheal intubation using mild sedation combined with topical anaesthesia followed by broncho-alveolar lavage to reach safely at a conclusive diagnosis.

Case reports

Patient A, a 38-year-old woman presented to the emergency unit of our hospital with septic shock.

She had been well until the age of 26 years, when

a caesarian section (CS) was performed because of cephalopelvic disproportion. At the age of 33 years twins were born, again by CS. At the age of 34 years she presented with pyoderma gangrenosum of the wound of the CS. A myelodysplastic syndrome (refractory anaemia with an excess of blasts) was diagnosed. One and a half year later, acute myeloblastic leukaemia with cytogenetic abnormalities (del 5q) was diagnosed. She was treated with two cycles of high dose ARA-C and idarubicin. After induction of complete remission, consolidation was achieved with etoposid and mitoxantrone, followed by ablative chemotherapy, total body irradiation and allogeneic bone marrow transplantation (allo-BMT, 32 months before admission). No major complications occurred. A moderate graft versus host disease (GVHD) of the skin was subsequently diagnosed. Polyvalent pneumococcal vaccine (23 types) was administered. Three months before the present episode, she was treated for relapsing leukaemia with an infusion of donor lymphocytes (DLI).

*Corresponding author. Tel.: +31-50-361-6161; fax: +31-50-361-3216.

E-mail address: j.w.fijen@int.azg.nl (J.W. Fijen)

Because of a severe GVHD of the colon, prednisolone (1 mg/kg body weight), cyclosporin (2 mg/kg body weight) followed by high doses of glucocorticoids (1 g methyl prednisolone daily) intravenously were administered. Oral candidiasis and recurrent oropharyngeal herpes simplex virus infections complicated her clinical course. At the time of the present admission, she was in complete remission.

Within 1 week of discharge from hospital, she presented to the emergency room because of severe acute-onset non-radiating pain in both legs, and a cough with production of whitish/yellowish sputum for 1 day. Previous serological analysis for CMV had been negative. Her medication was prednisolone 25 mg bid, aciclovir 400 mg qid, cyclosporin 225 mg bid, fluconazole 50 mg and morphine sulfate 20 mg bid. She was a lifetime non-smoker.

On examination the patient was in shock: blood pressure 60/30 mmHg, pulse 130/min. Axillary temperature was 38.1°C. There was tachypnoea and dyspnoea. Few small inspiratory crackles were noted over the left lower chest. Her extremities were cold, and the pain was localised diffusely over both legs. No further abnormalities were observed. Arterial blood analysis showed pH 7.45, P_{CO_2} 3.6 kPa, P_{O_2} 9.0 kPa, bicarbonate 18.6 mmol/l, BE -5.9 mmol/l, SO_2 0.946 (nasal tube 5 l O_2 /min). The radiographs of the chest showed bilateral basal interstitial pulmonary infiltrates (Fig. 1). The diagnosis 'septic shock and bilateral interstitial pneumonia in an immunocompromised patient after allo-BMT' was made. On admission to our unit, fluid resuscitation was started and resulted in improved haemodynamics. It did not succeed in getting a specimen of sputum. After topical anaesthesia to the oropharynx and trachea using xylocain spray 1% 10 ml in a venturi-system (de Vilbis), and after mild sedation (midazolam, 2.5 mg i.v.) an orotracheal tube was inserted guided over a flexible bronchoscope. Subsequently, bronchoalveolar lavage (BAL) was performed. She was initially started on a broad spectrum antimicrobial regime (ceftazidime, vancomycin and fluconazole) and norepinephrine was initiated. The direct stain of the BAL fluid recovered Gram-positive diplococci while silver stains, auramin-rhodamine stains, and toluidine-blue stains were negative for fungi (including *P. carinii*) and mycobacteria. Blood

cultures remained negative. The antibiotics were switched to benzylpenicillin on the day of admission. She made a fast and uneventful recovery, and the following day, she could be disconnected from the ventilator and discharged to the hematological ward.

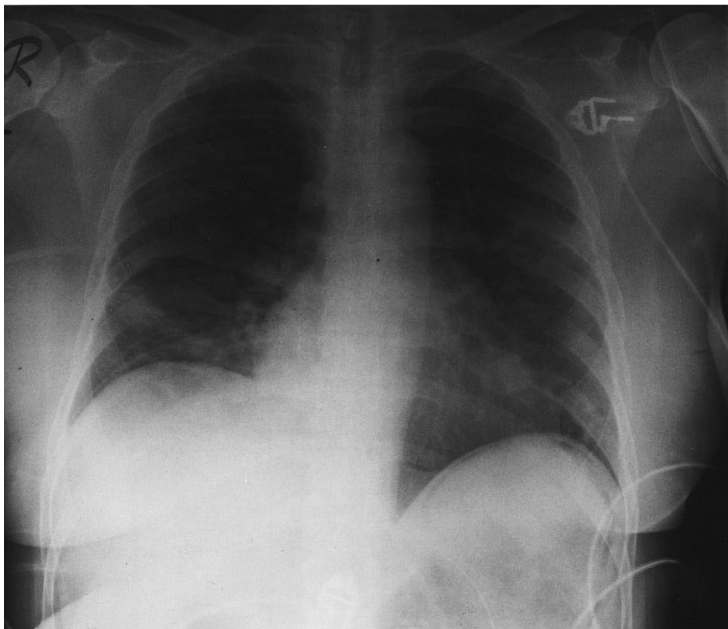
Patient B, a 69-year-old man was admitted to our unit because of respiratory failure.

At age 20 right upper lobe resection was performed because of tuberculosis. At age 62 he was treated for syphilis, paroxysmal atrial fibrillations and pulmonary embolism. One month before the present admission he was admitted to a neurological department because of dizziness and recurrent collapse with amnesia. The patient had lost 5 kg of body weight. On examination he was confused and spoke incoherently. CT scan showed a hypodense zone in the right parietal hemisphere suggesting infarction. After some clinical improvement there was a progressive paralysis of the left arm. Another CT scan and MRI was performed and showed a larger hypodense zone with signs of local pressure and contrast enhancement suggesting infection or metastatic tumor. The patient was treated with dexamethasone 4 mg tid, acenocoumarol and omeprazole 40 mg. He was transferred to our hospital. On further questioning and examination he appeared to have risk factors for HIV and tested positive with a very low CD4 count (<1%). IgG antibodies directed against *Toxoplasma gondii* were positive (136.2 IU/ml) but IgM antibodies were negative. In the following 2 days the patient suffered seizures and developed respiratory failure with bilateral interstitial infiltrates.

On examination his blood pressure was 100/60 mmHg and pulse 90/min. His temperature was 38.5°C. There was tachypnoea (40/min) and dyspnoea. Few small inspiratory crackles were noted over both lower zones of the chest. No lymphadenopathy was detected. No further abnormalities were observed. Arterial blood analysis showed pH 7.48, P_{CO_2} 2.3 kPa, P_{O_2} 5.2 kPa, bicarbonate 13 mmol/l, SO_2 0.760 (ventimask FiO_2 0.45). He required mechanical ventilation. Bronchoscopy showed normal airways and lavage was performed. The direct stain of the BAL fluid recovered Gram-positive diplococci while silver stains, auramin-rhodamine stains, and toluidine-blue stains were negative for fungi (including *P. carinii*), and mycobacteria. PCR of *M. tuber-*



(a)



(b)

Fig. 1. Bilateral interstitial pulmonary infiltrates in mid and lower zones of the lungs on the day of admission (A) and 2 days later (B) in patient A.

culosis complex was negative. Blood cultures remained negative. The patient was treated with coamoxicillin-clavulanic acid. Congestive heart failure complicated the course. Echocardiography showed akinesia of all parts of the heart except for the inferoposterior region without evidence of valvular insufficiency or pericardial effusion. Thrombocytopenia and renal failure developed. Microscopy did not reveal fragmentocytes. The patient died 4 days after admission. Postmortem examination showed sequelae of pneumococcal pneumonia complicated with thrombotic thrombocytopenic purpura (presumably HIV associated) with diffuse myocardial localization of thrombi and necrosis. The cerebral lesion appeared to be due to an ischemic infarction without evidence of lymphoma or toxoplasmosis.

Discussion

The differential diagnosis of diffuse pulmonary infiltrates in immunocompromised patients (after allo-BMT or in AIDS) is extensive. Multiple pathogens and pathologies are possible [2–4]. In an immune-compromised host, bilateral interstitial pulmonary infiltrates are frequently associated with lung infections by opportunistic microorganisms. Table 1 lists diagnoses of pulmonary infiltrates in immunocompromised patients, e.g. after allo-BMT [5]. A

well planned and individually tailored diagnostic work-up is warranted to achieve high diagnostic certainty at the lowest possible health risks for the patient. This work-up should cover the possibility of common causes and common pathogens like pneumococcus [6].

Flexible fiberoptic bronchoscopy has made bronchoscopic examinations possible in ICU patients undergoing mechanical ventilation [7,8]. The number of such procedures has greatly increased in recent years. Bronchoscopy may aid with difficult and/or hazardous intubations, management of atelectasis, and diagnosis of nosocomial pneumonia in ventilated patients [5,9,10]. Diagnostic yield of BAL is greatly increased if no previous antimicrobial agents have been administered in the 48 h preceding the diagnostic procedure [11]. The addition of bronchoscopic lung biopsies increases the health risk for the patient substantially, and although haemorrhage and pneumothorax are uncommon events, biopsies should not be taken routinely. If histological examination is warranted – as is often the case in patients like allo-BMT recipients presenting with diffuse pulmonary disease – a transpleural biopsy ('open' surgical, or video-assisted thoracoscopic surgical; VATS) procedure may be preferred. By classic surgical biopsy or VATS, larger tissue samples can be obtained, and control of bleeding is better compared to bronchoscopic tissue sampling, especially in patients with bleeding and clotting disorders. In our patients, lung

Table 1
Differential diagnosis of pulmonary infiltrates in immunocompromised patients

Infection	Bacteria Viruses (CMV, HSV, RSV) Mycobacteria (tuberculosis or NTM) Fungi or mycoses Others e.g. <i>Nocardia</i> , toxoplasmosis, <i>Pneumocystis carinii</i>
Edema	Fluid overload Congestive heart disease ARDS
Hemorrhage	
Embolism	Trombotic or fat
Malignant	Solid tumor Lymphoma or leukaemia
Pneumonitis	Drug-induced Radiation

tissue biopsy was not necessary for the initially considered pathogens.

Intubation for mechanical ventilation requires deep sedation and muscle paralysis and can be performed in haemodynamically stable patients. However, in haemodynamically unstable spontaneously breathing patients a bronchoscopic BAL procedure is hazardous and we prefer an ICU setting with mechanical ventilation 'stand-by'. During the bronchoscopic procedure, the lavage fluid can cause an increase in venous admixture in the lung volume sampled, but accidentally worsen gas exchange, leading to larger drops in p_{aO_2} than usually observed (1–3 kPa) [12]. Mild sedation and topical anaesthesia precludes the risks of anaesthesia-induced hypotension, with the chance to shift to spontaneous breathing and extubation soon after the procedure.

The radiological pattern of pneumococcal (*Streptococcus pneumoniae*) pneumonia has been classically described as lobar parenchymal consolidation, but other patterns (bronchopneumonic type or interstitial type) occur occasionally [13,14].

There are few reports in the literature on diffuse chest radiographic changes caused by *Streptococcus pneumoniae*. In patients in the early stages of HIV/AIDS who have a similarly impaired cellular immune response, severe chest infections with capsulated microorganisms have been recognized [15,16]. These infections appear to be significantly more common than in HIV-negative controls [17], and an increased incidence of diffuse pulmonary shadowing has been reported in these patients [18]. We hypothesize that the radiologic pattern is changed because of an altered (generally diminished) immunological response of the host to infection. Interestingly, no reports were found about diffuse pulmonary infiltrates caused by common pathogens in the immunocompromised host after allo-BMT.

Conclusion

The differential diagnosis of diffuse bilateral interstitial pulmonary infiltrates in immunocompromised patients is very extensive but a common microorganism with a diffuse pattern of community-

acquired pneumonia should be considered. Bronchoalveolar lavage can safely be performed without the use of deep sedation and muscle relaxants, as orotracheal intubation by flexible bronchoscopy can easily be performed using mild sedation combined with topical anaesthesia. The ICU setting helps to make the procedure safe for these critically ill patients, as complications such as hypotension, shock, and respiratory failure can be diagnosed and treated promptly.

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