

CASE STUDY

***Pneumocystis carinii* pneumonia in a HIV-seronegative patient with untreated rheumatoid arthritis and CD4+ T-lymphocytopenia**

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Pneumocystis carinii pneumonia in a HIV-seronegative patient with untreated rheumatoid arthritis and CD4+ T-lymphocytopenia. A. Prekates, T. Kyprianou, O. Paniara, C. Roussos. ©ERS Journals Ltd 1997.

ABSTRACT: *Pneumocystis carinii* pneumonia (PCP) usually occurs in immunocompromised patients, and it is a life-threatening infection. We report the case of a human immunodeficiency virus (HIV)-seronegative patient with untreated rheumatoid arthritis (RA), who developed fatal PCP related to uncommon CD4+ T-lymphocytopenia.

Although extremely rare and of uncertain aetiology, suppression of cellular immunity and subsequent opportunistic infections should be suspected in such patients.

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Pneumocystis carinii pneumonia (PCP) is an opportunistic infection, encountered in immunocompromised patients. The occurrence of PCP in patients with connective tissue disorders (CTD) is well-documented, and is usually attributed to corticosteroid or other immunosuppressive treatment [1]. We report the case of a human immunodeficiency virus (HIV)-seronegative patient with untreated rheumatoid arthritis (RA) and CD4+ lymphocytopenia, who was admitted to the intensive care unit (ICU) with bilateral pulmonary infiltrates and respiratory failure. Bronchoalveolar lavage (BAL) specimens revealed *Pneumocystis carinii*. The combination of RA, CD4+ T-lymphocytopenia unrelated to any treatment and PCP is unusual, and has interesting implications.

Case Report

A 68 year old female peasant was admitted to hospital because of a month's history of persistent low-grade fever, which did not respond to broad spectrum antibiotics. Fever was preceded by nonproductive cough, anorexia, weakness and night sweats. She also reported polyarthralgias and morning stiffness, lasting 1–2 h, for approximately 5 months before admission. Her past medical history was unremarkable. Her family history revealed a sibling suffering from Sjögren's syndrome (diagnosis was made by the following: keratoconjunctivitis sicca, positive lip biopsy and positive Schirmer test). There was no history of smoking or alcohol abuse. She took no medication, including nonsteroidal anti-inflammatory drugs (NSAIDs).

Physical examination revealed a temperature of 38.8°C, pulse rate 105 beats·min⁻¹, blood pressure 115/74 mmHg,

and respiratory rate 25 breaths·min⁻¹. Fine diffuse inspiratory, bilateral rales were audible, predominantly in the middle and lower chest. Abdominal examination was unremarkable: no lymphadenopathy, hepatomegaly or splenomegaly was found. Soft tissue swelling of both knee joints, right foot, second and third metacarpophalangeal joints bilaterally, third and fourth proximal interphalangeal joints on the left hand, and second, third and fourth interphalangeal joints of the right hand were noted. The patient confirmed that swelling had been present for more than 2 months and it had been noted by another physician (her general practitioner). She also had a Herberden's node on the extensor surface of the right middle finger. The patient fulfilled American College of Rheumatology (ACR) criteria for diagnosis of rheumatoid arthritis [2].

The results of the initial diagnostic work-up were: haemoglobin 11.8 g·dl⁻¹; white blood cell count: 5.230 cells·mm⁻³ (70% neutrophils, 14% lymphocytes, 9% monocytes and 7% eosinophils); erythrocyte sedimentation rate (ESR) 55 mm·h⁻¹; and C-reactive protein (CRP) 3.28 mg·dl⁻¹ (normal value <0.5 mg·dl⁻¹). Values of urea nitrogen, creatinine, glucose, transaminase, bilirubin, alkaline phosphatase, protein, albumin, total serum globulins, amylase, calcium, phosphorus, electrolytes, and protein electrophoresis were within normal limits. Lactate dehydrogenase (LDH) was elevated to 622 U·L⁻¹ (normal range 100–200 U·L⁻¹). Rheumatoid factor was negative. Antinuclear antibody was positive (titre 1:80, speckled pattern). A tuberculin test was negative.

Chest radiography showed diffuse reticulonodular opacities with a predominant bilateral reticular pattern (fig. 1). Radiographic images of bones showed periarticular

osteopenia and narrowing of intra-articular spaces of the affected joints. Five days after admission, the patient developed profound dyspnoea, tachypnoea, tachycardia and confusion, whilst her temperature was consistently above 38.5°C. Arterial blood gas values were arterial oxygen tension (P_{a,O_2}) 5.7 kPa (43 Torr), arterial carbon dioxide tension (P_{a,CO_2}) 4.3 kPa (32 Torr), pH=7.47, and bicarbonates (HCO_3^-) = 24 $mE \cdot L^{-1}$, with fraction of inspired oxygen (F_{I,O_2}) = 0.6. At that time the patient was treated empirically with trimethoprim-sulphamethoxazole (20 $mg \cdot kg^{-1}$ daily of trimethoprim and 100 $mg \cdot kg^{-1}$ daily of sulphamethoxazole, in four doses) and cefepime 2 g daily *i.v.* Serial chest radiographs showed a progressively worsening, and a mixed alveolar and reticular pattern (fig. 2).

The patient was intubated and transferred to the ICU. BAL, *via* a fiberoptic bronchoscope, revealed *Pneumocystis carinii* (methamine silver stain method). Cultures for mycobacteria were negative, and cytological studies were negative for malignancy. Western blot for human immunodeficiency virus (HIV)-I and -II was negative. A subsequent diagnostic work-up revealed: total lymphocytes 672 $cells \cdot mm^{-3}$ (normal range 1,500–4,000 $cells \cdot mm^{-3}$); T-cells 380 $cells \cdot mm^{-3}$ (normal range 680–1,810 $cells \cdot mm^{-3}$); CD4+ T-cells 188 $cells \cdot mm^{-3}$ (normal range 420–1260 $cells \cdot mm^{-3}$); and CD8+ T-cells 192 $cells \cdot mm^{-3}$ (normal range 180–650 $cells \cdot mm^{-3}$). The CD4/CD8 ratio was 0.98. C3 and C4 levels were within normal limits. Immunoglobulins G and M (IgG and IgM), antibodies for adenovirus, cytomegalovirus (CMV), *Mycoplasma pneumoniae*, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), influenza virus type A and B, *Coxiella burnetii*, *Chlamydia psittaci* and *Chlamydia pneumoniae*, were within normal limits. Complement levels, anti-deoxyribonucleic acid (DNA) antibodies, antibodies against cytoplasmic antigens SSA/Ro and SSB/La, and nuclear ribonucleoprotein (RNP) were all negative. Serum angiotensin-converting enzyme (SACE) and ovarian tumour antigen (CA-125) were normal. Both, perinuclear antineutrophil antibodies (P-ANCA) and cytoplasmic antineutrophil antibodies (C-ANCA) were negative. Haemodynamic monitoring during 24 h before death revealed: a cardiac output of 11 $L \cdot min^{-1}$, central



Fig. 1. – Chest radiograph showing diffuse reticulonodular opacities with predominant reticular pattern bilaterally.



Fig. 2. – Chest radiograph showing progressively worsening, mixed alveolar and reticular pattern.

venous pressure of 8 mmHg; a pulmonary artery pressure of 26/9 mmHg; and a wedge pressure of 9 mmHg (without vasopressors). The arteriovenous oxygen difference ($a-vD,O_2$) was 25 $mL \cdot L^{-1}$, and the mixed venous oxygen tension ($P_{\bar{v},O_2}$) 37 mmHg. Blood lactate concentration was 12 $mM \cdot L^{-1}$.

Immediately after diagnosis of PCP, prednisolone was initiated at 25 $mg \cdot i.v.$ *t.i.d.* In spite of all therapeutic efforts the patient's condition deteriorated. A second BAL *via* fiberoptic bronchoscope was not attempted because of severe hypoxaemia ($P_{a,O_2}/F_{I,O_2} < 50$). The patient died four days later from severe hypoxaemia (acute respiratory distress syndrome (ARDS)). Blood cultures obtained within 48 h prior to death were negative. Relatives did not give consent for autopsy, according to local policy.

Discussion

Pneumocystis carinii pneumonia (PCP) was first diagnosed during the 1950s as a clinical entity in patients with deficient cellular immunity [3]. Today, PCP is typically associated with HIV infection, and various primary and secondary immunodeficiencies [4]. A mortality rate of 58% was reported in patients with severe PCP requiring mechanical ventilation, irrespective of corticosteroid adjunctive treatment [5]. More recent data in patients with acute respiratory failure revealed an 83% survival rate in those where high doses of corticosteroids (methylprednisolone 60–125 $mg \cdot i.v.$ every 6 h) were added within 72 h of the initiation of conventional therapy [6]. PCP with various forms of connective tissue disorder (CTD) is rare [1], and case reports among rheumatoid arthritis (RA) patients are even fewer, and almost always attributed to corticosteroid or methotrexate treatment [1].

We believe that the present case is the second report of PCP related to lymphocytopenia in a patient with untreated RA and in the absence of HIV infection. The first case, recently reported by OIEN *et al.* [7], was a patient with long-standing RA, who had received several cytotoxic second-line drugs until three months before admission. The presentation of PCP in this patient

was rather insidious (3–4 weeks) and similar to that observed in HIV-positive patients. On the contrary, immunocompromised subjects with CTD or cancer tend to have more acute disease [8]. A possible explanation is that the initial symptoms and chest radiographic findings could have been attributed to rheumatoid disease. However, interstitial pneumonitis exclusively attributed to RA occurs in 1.6% of RA patients [9].

Differential diagnosis of CD4+ T-lymphocytopenia in HIV-seronegative patients includes: 1) occult HIV infection, and other infectious diseases (pulmonary tuberculosis, rickettsial infections, *Legionella pneumophila* pneumonia, histoplasmosis, brucellosis, adenovirus, varicella zoster and cytomegalovirus infection, hepatitis B, bacterial oesophagitis and staphylococcal enteritis); 2) autoimmune disorders; 3) malignancies, such as lymphoproliferative diseases and bronchogenic cancer; 4) uraemia; 5) idiopathic CD4+ T-lymphocytopenia and common variable immunodeficiency; and 6) old age [10]. The patient studied had received no transfusion in the previous 5 yrs, and clinical history, physical examination and laboratory investigation revealed none of the aforementioned diseases. As only one determination of lymphocyte subsets was available, idiopathic CD4+ T-lymphocytopenia could not be diagnosed. Centers for Disease Control (CDC) diagnostic requirements for this condition are: 1) low CD4+ T-cell level (<300 cell·mm⁻³ or <20% of total lymphocytes) on more than one determination, at least two months apart; 2) negative laboratory evidence of HIV infection; and 3) no defined immunodeficiency or therapy associated with depression of CD4+ T-cells levels [11]. Similarly, common variable immunodeficiency could not be diagnosed since γ globulin levels were within the normal range.

It is well-established both from *in vitro* and *in vivo* immunopathogenetic studies, that patients with RA exhibit dysregulation of serum CD4+ and CD8+ lymphocyte production and distribution [12]. Furthermore, patients with RA usually have abnormally high levels of "primed" CD45RO (+) lymphocytes [13], as well as increased distribution and adherence of CD4+ to articular tissue. Furthermore, recent studies have reported that RA patients who developed lymphocytopenia as a disease manifestation had marked depletion of CD8+ T-lymphocytes, depletion of CD45RO+ cells, and elevated soluble granule membrane protein-140 (s-GMP-140) and soluble endothelial leucocyte adhesion molecule-1 (s-ELAM-1) [13]. This phenomenon was particularly evident in patients who revealed low rheumatoid factor (RF) titres (similar to the profile of this patient). Thus, the most likely explanations for CD4+ T-lymphocytopenia in this patient with RA and PCP, were: 1) RA-induced lymphocytopenia; and 2) old age.

In conclusion, this report could provide the impetus to consider opportunistic infections in patients with rheumatoid arthritis presenting with diffuse pulmonary infiltrates even in early stages, without corticosteroid or

other treatment. Heightened awareness of the possibility of concomitant lymphocytopenia may be warranted, though its nature is unclear and subject to future research.

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