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Pneumocystis carinii Pneumonia in HIV-Negative Patients with Haematologic Disease

Summary: Since 1990, *Pneumocystis carinii* pneumonia (PCP) was diagnosed in 15 adult HIV-negative haematologic patients in our hospital. None of them had received PCP prophylaxis. All except one had been treated with prednisone. Symptoms usually started after stopping or tapering. In six patients the diagnosis of PCP was delayed because of confounding bacterial isolates from blood, sputum or urine leading to unsuccessful antibiotic treatment. PCP was diagnosed by demonstrating pneumocysts in bronchoalveolar lavage fluid. In four patients additional fungal or viral pathogens were identified. The infections were not clustered. The patients were treated with co-trimoxazole and, in case of a $pO_2 < 60$ mmHg, with prednisone. Three patients died (20%); they all had a coinfection with cytomegalovirus and/or aspergillus. The others recovered completely. There were no relapses. Primary PCP prophylaxis should be considered in patients with lympho-proliferative disease and exposure to prednisone.

Introduction

Pneumocystis carinii pneumonia (PCP) is an opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS), in premature babies [1] and in patients treated with immunosuppressive and/or antineoplastic therapy [2–12]. It causes considerable morbidity and mortality, but in patients at high risk it can be prevented effectively by prophylaxis with co-trimoxazole [13]. Before 1990, no documented cases of PCP in HIV-negative adult haematologic patients occurred in our centre. With the exception of bone marrow transplantation patients, who start co-trimoxazole at the time of bone marrow recovery, we had therefore used no PCP prophylaxis. However, we have diagnosed 15 cases since 1990. Such an increase has also been noted in centres in Switzerland [9], Belgium [10], the Netherlands [11], and Finland [12]. The aims of our retrospective analysis were to study the possible risk factors in order to obtain guidelines for PCP prophylaxis, to determine the clinical characterization of the infection, such as presenting symptoms, diagnostic procedures required and treatment outcome and to examine whether there was any evidence for patient-to-patient transmission, as this might have implications for nursing practices in patients at risk.

Patients and Methods

The Academic Medical Centre of the University of Amsterdam is a large referral hospital for haematology. It is also a centre for AIDS care. Since 1990 we have diagnosed PCP in 15 adult patients with a haematologic disease. All underwent a fibre optic bronchoscopy with bronchoalveolar lavage (BAL). The diagnosis was established by demonstrating pneumocysts in the lavage fluid using toluidine blue and Giemsa staining. Six patients also underwent transbronchial lung biopsies using Grocott-Gomori silver staining to find pneumocysts (Department of Pathology,

Academic Medical Centre). All BAL fluids were also routinely examined for bacteria, fungi and viruses.

All patients were treated the same way according to our protocol for the treatment of PCP in AIDS patients. They received co-trimoxazole 1,920 mg t.i.d. starting intravenously and after response, continued orally for a total of 14 days. Subsequently an oral dose of 480–960 mg was given for a variable period of time. Patients with a $pO_2 < 60$ mmHg received further treatment with prednisone in a starting dose of 40 mg twice daily, tapering in 7 to 10 days. One patient received intravenous methylprednisolone pulse therapy 1,000 mg for 3 days. Additional oxygen was supplied in cases of hypoxemia.

Results

Patient Characteristics

Ten patients were male, five female and the median age was 48 years (range 25–72). The underlying diseases are shown in Table 1. The duration of these diseases varied from 3 to 180 months (median 5 months). Eight patients were in the first treatment phase of their haematologic disease, the others had had relapses and had already received multiple treatments. One patient had been treated with myeloablative chemotherapy followed by autologous bone marrow transplantation. The infection occurred before the start of PCP prophylaxis. The others had received conventional chemotherapy. The one patient with a mye-

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Table 1: Diagnoses in HIV-negative haematologic patients with *Pneumocystis carinii* pneumonia.

Non-Hodgkin's lymphoma	4
Chronic lymphocytic leukaemia (CLL)	3
CLL with autoimmune disorder	2
Acute lymphoblastic leukaemia	3
Hodgkin's disease	2
Lymphoblastic crisis of chronic myeloid leukaemia	1
Thymoma	1
Myelodysplastic syndrome	1
Total	15

Table 2: Pathogens found in bronchoalveolar lavage fluid; outcome of disease.

Pathogens in bronchoalveolar lavage fluid	Number of patients	Fatal outcome
<i>Pneumocystis carinii</i> only	11	0
<i>Pneumocystis carinii</i> and <i>Aspergillus flavus</i>	1	1
<i>Pneumocystis carinii</i> , <i>Aspergillus fumigatus</i> and cytomegalovirus	1	1
<i>Pneumocystis carinii</i> , cytomegalovirus and herpes simplex virus	1	1
<i>Pneumocystis carinii</i> and herpes simplex virus	1	0

Myelodysplastic syndrome had a prolonged bone marrow hypoplasia of 7 weeks' duration after intensive chemotherapy. He was the only one who had not received prednisone. All others had a lymphoproliferative disease treated with a variety of chemotherapeutic regimens, all of which included prednisone. The median duration of prednisone treatment in these patients was 42 days (range 20–70 days); the median dose was 3,150 mg (range 840–9,500 mg).

Figure 1: Incidence of *Pneumocystis carinii* in HIV-negative haematologic patients.

Four patients (two with chronic lymphocytic leukemia, one with Hodgkin's disease and one with thymoma) had a prolonged exposure to prednisone because of an autoimmune blood disorder. At the time that PCP was diagnosed, six patients were off prednisone and in seven the dose had been tapered. Only four of the patients had a neutrophil count below $1.0 \times 10^9/l$. Six patients acquired the PCP as outpatients, the others were hospitalized for a median of 23 days (range 7–57 days) when they developed symptoms. All patients were tested HIV-seronegative. None had received PCP prophylaxis. Both in the clinic and in the outpatient department they may have been in contact with AIDS patients. The infections were not clustered (Figure 1).

Symptoms and Diagnosis

The first symptoms of PCP were fever, a non-productive dry cough (both in 12 patients) and dyspnea (nine patients). The median time from the first symptoms until diagnosis was rather long: 10 days (range 4–42 days). One of the main reasons for this delay was a confounding positive bacterial isolate from sputum or other material leading to a specific, but unsuccessful antibiotic treatment. This was the case in six patients: two of them were treated because of *Haemophilus influenzae* in the sputum, one for a bacteraemia with *Staphylococcus epidermidis*, two for a urinary tract infection (*Xanthomonas (Stenotrophomonas) maltophilia* and *Escherichia coli*), and one because of *Staphylococcus aureus* in skin infiltrates.

Hypoxemia (pO_2 below 60 mmHg) was found in eight patients. The median pO_2 was 60 mmHg (range 30–96 mmHg), PCO_2 33 mmHg (range 19–38 mmHg), pH 7.40 (range 7.36–7.51), bicarbonate 25 mmol/l (range 16–28 mmol/l). One patient had unilateral, the others bilateral interstitial infiltrates on the chest X-ray. In all except two patients the number of pneumocysts found in the BAL fluid was low, usually not more than 10–20 cysts in the slide. Pneumocysts were detected in only three of the six available transbronchial lung biopsy specimens. *Pneumocystis carinii* was the only pathogen found in 11 BAL fluids, various co-pathogens were found in four: *Aspergillus* spp., cytomegalovirus (CMV) and human herpes simplex virus (HSV) (Table 2).

Treatment and Outcome

Three of the 15 patients (20%) died of infection. All had a coinfection with fungal and/or viral co-pathogens (Table 2). The fourth patient with a co-pathogen (HSV) remained febrile during treatment with co-trimoxazole, but recovered when after 2 weeks acyclovir was added to the treatment.

Twelve patients made a complete recovery. Two of them had required artificial ventilation for 3 and 10 days respectively. Most other patients recovered quickly with a period until defervescence of a median of 4 days (range 0–16 days). There were no relapses. The eight patients who had

to continue cytostatic treatment did so under co-trimoxazole prophylaxis.

Discussion

We describe 15 cases of *Pneumocystis carinii* pneumonia in adult HIV-negative haematologic patients, all diagnosed during the last 6 years. There are several possible explanations for this apparent increase. Firstly, the AIDS epidemic has led to a high number of PCP in HIV-infected individuals. It has been suggested that, as a result of an increased exposure to pneumocysts, this may lead to more PCP infections in immunocompromised HIV-negative patients [14]. That HIV-infected patients may be a potential infectious source of *P. carinii* is supported by the finding of increased serum titres of anti-*Pneumocystis carinii* antibodies in health-care workers caring for AIDS patients [15]. Chave et al. [16] describe a cluster of PCP infections in renal transplant recipients who had clinic encounters with AIDS patients in the outpatient department. Clusters of PCP cases have also been described in other renal transplant [17] and in haematologic patients [18], suggesting the possibility of person-to-person transmission or acquisition from the environment. From our retrospective study, a patient-to-patient transmission cannot be excluded, but there was no clustering (Figure 1).

Another possibility is that the PCP in HIV-negative patients results from an reactivation of a latent infection as an effect of the immunosuppression. The increased incidence may be the result of the more intensive treatment regimens used nowadays.

A third possibility is that experience in diagnosing PCP in AIDS patients and the increased clinical awareness of this infection has led to more accurate diagnostic procedures in haematologic patients with pulmonary symptoms.

The most important risk factor for PCP in HIV-negative patients is the prolonged use of corticosteroids: 14 of our 15 patients were or had been using prednisone. In 13 of them the symptoms of infection became apparent after stopping or tapering the dose of prednisone, an observation also made by others [8, 11]. Apparently the infection is at first suppressed or masked by the use of corticosteroids. Most of our patients had a lymphoproliferative disease (Table 1). Immunodeficiency associated with the lymphoproliferation may be an additional risk factor for

PCP. Neutropenia is a less prominent risk factor: it was present in only four of our patients. The phase of the underlying disease did not seem to play an important role: PCP occurred both early and late in the disease.

Dry cough, dyspnea and fever in a patient with lymphoproliferative disease who is or has been treated with prednisone should raise suspicion of PCP. Absence of fever does not exclude PCP: three of our patients had no fever at diagnosis. In some of our patients there was a delay in making the diagnosis. This was mainly caused by confounding bacterial isolates leading to unsuccessful treatment. Bilateral interstitial infiltrates on the chest X-ray and excessive arterial hypoxemia are clues to the diagnosis. The diagnosis is made by demonstrating pneumocysts in the bronchoalveolar lavage fluid. In 12 of our 14 patients the number of pneumocysts was low compared to those found in AIDS patients, an observation also made by others [19, 20]. Examination of BAL fluid should be performed on fresh material. We use two staining techniques to recognize *Pneumocystis carinii* either by the presence of trophozoites and sporozoites or by the presence of cyst walls. Because of the low number of *Pneumocystis carinii* in BAL fluid, we do not consider an examination of induced sputum an appropriate diagnostic procedure. In our series the sensitivity of transbronchial biopsies was low: in three of the six patients with a positive lavage fluid who were biopsied no pneumocysts could be detected in the biopsy specimen.

In four patients, additional viral and or fungal pathogens were found in the BAL fluid (Table 2). Three of them died, a coexisting pulmonary infection therefore appears to be the major negative prognostic factor, which is an observation also made by others [11, 20].

The patients with a pO_2 at diagnosis below 60 mmHg were treated with corticosteroids, which has been shown to be beneficial in AIDS patients with PCP [21]. Whether this was also the case in our patients can not be concluded from our study, but the mortality rate of 20% compares favourably with that in several other studies.

We conclude that in our centre PCP has emerged as a serious and not infrequent infection in patients with lymphoproliferative disease treated with prednisone. We therefore decided to protect such patients with co-trimoxazole as primary PCP prophylaxis. This should also protect them against possible person-to-person transmission.

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