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Fatal pneumocystis jiroveci pneumonia in ABVD-treated Hodgkin lymphoma patients

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Dear Editor,

Lung infections are serious complications in patients with hematological malignancies [1–4]. *Pneumocystis jiroveci* is an important causative organism. T cell deficiency and preceding corticosteroid therapy are important risk factors for *Pneumocystis jiroveci* pneumonia (PCP). The course of PCP may be fulminant and in patients who require mechanical ventilation, the prognosis is poor.

When PCP was identified as one of the most important severe infections in children aggressively treated for acute lymphoblastic leukemia in the 1970s, cotrimoxazole was introduced as the drug of choice for therapy as well as for prophylaxis [5]. However, the precise degree of immunosuppression at which PCP may occur is still not fully elucidated. Thus, we are still not able to identify patients who would benefit from prophylaxis with a satisfactory accuracy [1, 3, 6].

We identified several patients with severe PCP belonging to patient categories not generally recommended to be treated with prophylactic cotrimoxazole. Based on this observation, we decided to investigate PCP among a spectrum of patients with hematological malignancies at

our center during an 8-year period. The main objective was to further characterize patients who would have benefited from prophylaxis.

At the Department of Hematology, Karolinska University Hospital Solna, all categories of hematological malignancies/disorders are treated. Patients with new or increasing pulmonary infiltrates are usually examined by both thoracic computerized tomography and bronchoscopy with extensive sampling for possible causative microbial pathogens. Bronchoscopy is avoided in patients who are considered not to tolerate this procedure due to comorbidity, hypoxemia or severe thrombocytopenia.

All results from *P.jiroveci* testing during the years 1999–2006 were retrospectively retrieved from the Swedish Institute for Infectious Disease Control. The specimens have been examined by immunofluorescence (IFL) by use of monoclonal antibodies [7]. Patients with a positive result by IFL treated at our center were identified and their clinical charts reviewed. The study was approved by the local ethics committee.

P.jiroveci was identified by IFL on bronchoscopically obtained secretions in 31 patients, and by IFL on sputum or nasopharyngeal secretions in nine and one patient, respectively. All patients had abnormal findings on chest X-ray (36/38) or CT (26/26).

A total of 41 patients (40 with a hematological malignancy and one with a severe autoimmune hemolytic anemia) with PCP were identified during the 8 year-period. Their median age was 62 years (range 23–83 years; Table 1). None of the patients had received PCP prophylaxis. The large majority of patients (95%) had a lymphoproliferative malignancy (Table 1). Twenty-three patients (56%) had progressive disease and four of the eight Hodgkin lymphoma patients, including one patient with a concomitant myeloma, succumbed to PCP.

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Table 1 Patient and disease characteristics

Variable	All patients (<i>n</i> =41)	Patients surviving PCP (<i>n</i> =31)	Patients who died of PCP (<i>n</i> =10)
Gender (males/females)	24/17	18/13	6/4
Median age (years; range)	62 (23-83)	60 (23-83)	65 (56-82)
Underlying hematological disease ^a			
NHL	12	11	1
CLL	10	9	1
Hodgkin lymphoma	8	4	3+1
Myeloma	7	3	3+1
ALL	2	2	0
AML	1	0	1
CMMML	1	1	0
AIHA	1	1	0
Status of disease			
Complete remission	3	2	1
Partial remission	9	8	1
Progressive disease	23	17	6
Stable disease	6	4	2
Chemotherapy	37	29	8
Corticosteroids	25	18	7
No corticosteroids ^b	16	13	3
Purine analogs	6	6	0
Allogeneic SCT	1		1
Autologous SCT	2		2
HTLV-1 positive	1	1	
Monoclonal antibodies	3	3	0
Hodgkin lymphoma	6	4	2

NHL nonHodgkin lymphoma, *CLL* chronic lymphocytic lymphoma, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CMMML* chronic myelomonocytic leukemia, *AIHA* autoimmune hemolytic anemia, *SCT* stem cell transplantation

^a One patient with Hodgkin lymphoma had a concomitant multiple myeloma

^b Number more than 41 because of overlapping therapies

Only 25 (61%) patients had received corticosteroid therapy prior to their PCP episode, and three of ten patients with a fatal course had not been treated with steroids (Table 1). Two of these patients had Hodgkin lymphoma and had been treated with four more cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [8].

ABVD was also given to additional three HL patients who survived their PCP.

Most patients presented with fever, cough, and dyspnoea (Table 2). Half of the patients had lymphopenia. C-reactive protein (CRP) was elevated in most patients and was significantly higher in patients with a fatal outcome than in

Table 2 Symptoms and laboratory values at presentation

	All patients, (<i>n</i> =41)	Patients surviving PCP (<i>n</i> =31)	Patients who died of PCP (<i>n</i> =10)	<i>P</i> value
Fever; <i>n</i> (%)	30 (73)	23 (74)	7 (70)	0.67
Cough; <i>n</i> (%)	21 (51)	18 (58)	3 (30)	0.08
Dyspnoea; <i>n</i> (%)	26 (63)	18 (58)	8 (80)	0.26
Hypoxia; <i>n</i> (%)	22 (54)	14 (45)	8 (80)	0.18
Laboratory values				
Mean (range)				
Hemoglobin (g/l)	101 (73-159)	105	111	0.45
WBC count (10 ⁹ /l)	5.9 (0.1-293)	26.6	9.7	0.37
Neutrophil count (10 ⁹ /l)	3.6 (0.1-36.0)	4.2	5.1	0.70
Lymphocyte count <1.0×10 ⁹ /l; <i>n</i> (%)	19 (46%)	13 (42)	6 (60)	0.29
CRP (mg/l)	83 (4-545)	94	213	0.008

those surviving the infection (Table 2; $p=0.008$). Assisted ventilation was required given in seven of the ten patients who eventually succumbed from PCP, but in only one of those who eventually recovered from their PCP ($p<0.001$).

PCP can be anticipated to increase in frequency in nonHIV-infected patients due to the increased use of immunosuppressive therapy affecting T cells. In hematological patients, more aggressive therapy is continuously evaluated to combat the underlying disease. Cotrimoxazole prophylaxis has been shown to be very effective [4, 5], but there is no perfectly apt means to select exactly which patients should be given prophylaxis [1, 3]. In HIV patients, a CD4-level below 200 cells/microliter is the accepted criterion, but in nonHIV patients, this limit is not valid enough and there is no other adequate marker of the degree of T cell suppression [6]. Most patients in previous reports have received steroids [2–4], but severe infection in nonsteroid-treated patients have also been reported [1, 6]. Thus, clinical data are necessary to identify which patients should be considered for prophylaxis. Among our 41 PCP patients, five had been treated with ABVD and no steroids for Hodgkin lymphoma. None of these five patients had received prophylaxis, and two of them died of *P. jiroveci* infection. Hodgkin lymphoma patients can be severely CD4+ cell depleted already before treatment [9]. In spite of this fact, PCP prophylaxis is not generally recommended for Hodgkin lymphoma patients receiving ABVD chemotherapy. In the light of our experience, we believe recommendations should be reconsidered.

In the meantime, it is important to consider PCP in any patient with lung disease and some degree of T cell suppression [4]. Semiquantitative PCR is probably the best method for diagnosis and can be applied on induced sputum specimens. Without quantification PCR will identify both colonized and infected patients [10], but a negative PCR

result virtually excludes PCP. The prognosis is generally good if therapy is initiated before respiratory capacity is affected. High CRP predicted a poor prognosis in this as well as in a previous study [3], probably reflecting the vigorous inflammation that seems to contribute to the lung injury and respiratory failure in more advanced disease [4].

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