shortly before or concomitantly to a bone marrow relapse, although in some cases it is apparent at the diagnosis or late in the course of the disease, up to ten years from the initial diagnosis. The skin or the CNS are the sites most frequently involved. Although the prognostic significance of extramedullary involvement in APL has not been formally assessed, from a review of the literature (see Table 1), it appears that about one third of patients may achieve a complete and in some cases sustained remission of the disease. Whether the incidence of this complication is increasing is a matter of debate, as it is its potential relationship with ATRA therapy.[1-4] A number of reasons could account for the increased incidence of extramedullary involvement. Firstly, the longer survival of patients treated with ATRA would increase the number of patients at risk of developing this type of relapse. Secondly, *in vitro* studies have shown that ATRA modulates the expression of adhesion molecules in APL cells enhancing their adhesiveness and motility.[5,6] These mechanisms might explain the efflux of leukemic cells from the bone marrow to the tissues in the ATRA syndrome and might also play a role in extramedullary relapses after ATRA treatment. Nevertheless, extramedullary APL may develop after chemotherapy or at presentation. In conclusion, although rare, extramedullary involvement is possible in patients with APL, a fact that should be considered in the management of these patients. Finally, the actual incidence of this complication and its relationship to new therapies should be prospectively assessed.[7-10]

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Acute promyelocytic leukemia, ATRA, extramedullary involvement, CNS involvement

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Legionella sp pneumonia in patients with hematologic diseases. A study of 10 episodes from a series of 67 cases of pneumonia

Sir,

Legionella pneumophila is a significant pathogen for immunocompromised patients, especially for those with impaired cell-mediated immunity.[1,2] In spite of the fact that patients with malignant hematologic diseases frequently have neutropenia and/or immunosuppression and usually receive glucocorticoids as cytotoxic drugs, information about the prevalence and evolution of pneumonias by *Legionella sp* in these patients is scarce.[2] We summarize the presenting features and response to treatment of 9 patients with hematologic diseases who developed 10 episodes of *Legionella* pneumonia diagnosed in a single institution over a 2.5-year period.

A study of all cases of pneumonia diagnosed in a hematology unit from January 1995 to June 1998 was carried out. One hundred and twenty-seven episodes of pneumonia in 106 patients were diagnosed, 68 were community-acquired and 59 nosocomial. In 67 cases radioimmunoassay for *Legionella pneumophila* serogroup 1 (LPS1) antigen in urine was performed, being positive in 10 (one patient had two episodes of pneumonia). In two cases, *Legionella* was also identified in the culture of bronchoalveolar lavage (performed in 15 cases of pneumonia). In the present study, *Legionella pneumophila* was the most frequently found micro-organism (10 cases, 15%), followed by *Streptococcus pneumoniae* (9 cases, 13%) and *Pseudo-*

Table 1. Clinical features of the ten episodes of *Legionella pneumonia*.

Patient	Age (years)	Hematologic disease	Immunosuppressive drug	Neutropenia*	Acquisition of pneumonia	Respiratory failure	Erythromycin	Death
1	84	NHL	None	No	Nosocomial	Yes	Yes	No
2	26	NHL	Dexamethasone	No	Nosocomial	No	Yes	No
2°	26	NHL	Dexamethasone	No	Nosocomial	No	Yes	No
3	57	NHL	Methyl-prednisolone	No	Nosocomial	No	Yes	No
4	75	ATP	Methyl-prednisolone	No	Nosocomial	No	Yes	No
5	63	NHL	Methyl-prednisolone	No	Nosocomial	Yes	Yes	No
6	16	AML	None	Yes	Community	Yes	Yes	No
7	83	SAA	Methyl-prednisolone	Yes	Community	Yes	No	Yes
8	35	ALL	None	Yes	Nosocomial	No	Yes	No
9	52	ALL	Methyl-prednisolone	Yes	Nosocomial	Yes	Yes	No

*°Recurrent pneumonia; *granulocyte count of < 1×10⁹/L; NHL: non-Hodgkin's lymphoma; ATP: acute thrombocytopenic purpura; AML: acute myelogenous leukemia; SAA: severe aplastic anemia; ALL: acute lymphocytic leukemia.*

monas aeruginosa (5 cases, 7%). Table 1 summarizes the main clinical characteristics associated with the 10 episodes of *Legionella* pneumonia. The median age of the patients was 57 years (range 16-84). Eight of the ten episodes of pneumonia were nosocomial. Fever, cough and dyspnea occurred in all patients and five complained of chest pain. Pneumonia was bilateral in two cases. Five patients developed respiratory failure but none required mechanical ventilation. The median time of disappearance of fever after the initiation of erythromycin (1 g/6 hours i.v.) was 96 hours (range 24-168). The median number of days of treatment with erythromycin was 21 (range 15-90). Recurrence of *Legionella* pneumonia was seen in one patient with lymphoma treated with dexamethasone for a long time. In this case, the pneumonia was cured with ofloxacin (400 mg/12 hours p.o.) for six weeks. Only one patient died.

The high prevalence of *Legionella* pneumonia found in this series can be explained by the fact that legionellosis is a prevalent nosocomial infection in our hospital,[3,4] despite several attempts at eradication (heating and hyperchloration of water). Although there are more than 14 serogroups of *Legionella pneumophila*, the predominant ones are 1, 4 and 6. Urinary antigen detection of LPS1 by ELISA is a good diagnostic tool, with a specificity of 100% and sensitivity of between 70 and 100%.[5,6]

All our patients were immunocompromised. Chemotherapy, treatment with steroids and other situations of immunosuppression such as organ transplants predispose to this infection, suggesting that cell-mediated immunity is the most important defensive mechanism against *Legionella*.[1,2,7-9] The evolution of *Legionella* pneumonia is worse in these patients, mainly depending on the setting in which the pneumonia is acquired (community or nosocomial), the virulence of the *Legionella sp* and the prompt initiation of treatment with erythromycin. All our patients except one received erythromycin at the time of the diagnosis of pneumonia, which probably explains the good evolution of all but one of the cases.

Recurrent *Legionella* pneumonia in patients treated with erythromycin for less than three weeks has been reported in chronically ill and immunocompromised hosts.[1,9] *Legionella* may survive for weeks within alveolar macrophages if an effective cellular immune response is absent. The best treatment for recurrent *Legionella* pneumonia, therefore, probably includes drugs that kill intracellular bacteria or inhibit their growth for prolonged periods of time such as azithromycin or fluoroquinolones,[10] which we gave to one patient in our series.

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Key words

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Prediction of blood cyclosporine concentrations in non-obese and obese hematologic patients with multidrug resistance using total, lean and different adipose factor dosing body weights

Sir,

Cyclosporine (CsA) is a highly lipophilic cyclic polypeptide drug,[1] thus better predictions of blood CsA concentrations would be expected from using *total body weight* (TBW) rather than *lean body weight* (LBW) or *adipose factor dosing body weight* (AFDBW). However, several studies show that CsA distribution correlates better with LBW in obese patients and suggest that CsA steady-state concentrations mainly depend on LBW.[2,3] This leads to difficulty in choosing which body weight to use to optimize CsA dosage regimens and predict blood CsA concentrations in non-obese and obese patients.

Thirteen female and twenty-eight male hematologic patients with multidrug resistance were treated by continuous intravenous CsA infusion (Table 1). Blood CsA concentrations were monitored about 4 times a day during infusion and 11 times after infusion (0, 0.5, 1, 2, 3, 5, 7, 9, 12, 24, and 36 hours after infusion), and were immediately analyzed using a fluorescence polarization immunoassay method (TDx, Abbott Laboratories, Diagnostic Division, Irving, TX, USA).[5]

The PKS program (Abbottbase Pharmacokinetic System, version 1.10, Abbott Laboratories, IL, USA, 1992) was used to predict blood CsA concentration using LBW, 25% AFDBW, 50% AFDBW, 75% AFDBW and TBW with a two-compartment model with volume of distribution in the central compartment (V_c=0.70±0.26 L/kg), clearance (CL=0.25±0.08 L/h/kg) and intercompartment rate constants (k_{12}=0.52±0.31 and k_{21}=0.07±0.02/h).[6,7] LBW = –111.621 + (3.636× height in inches) for adult females and LBW = –130.736 + (4.064×height in inches) for adult males. Dosing body weight = LBW + adipose factor × (TBW – LBW)/100, where adipose factor is set at 25%, 50% and 75%, respectively.

The measured and predicted concentrations were used to calculate percentage prediction errors [100× (predicted concentration – measured concentration)/ (measured concentration)][8] and absolute/relative performances.[9]

Blood CsA concentrations were divided into pre-steady-state, steady-state (infusion rate/clearance)[10] and post-steady-state. Table 2 shows the percentage prediction errors. The Friedman ANOVA test indicates that the medians among five dosing body weights at each kinetic state are not equal at $p<0.001$

Table 1. Patients demographics and CsA dosage.

Patients	*Obese situation*	*Numbers*	*Age (years)*	*Height (cm)*	*TBW (kg)*	*LBW (kg)*	*Obesity index (kg/m²)*	*TBW Dose (mg/kg/day)*	*LBW Dose (mg/kg/day)*	*IVT (days)*
Female	non-obese	6	60±6	165±7	64±9	56.6±4.9	23.4±1.2	9.6±2.7	10.8±2.8	3.7±1.0
	moderately obese	7	58±4	160±3	67±5	53.3±2.0	26.1±1.0	9.9±1.2	12.4±1.4	3.6±1.2
Male	non-obese	12	38±15	172±7	70±5	66.7±5.2	23.7±0.7	11.3±1.8	12.0±2.1	3.4±1.2
	moderately obese	14	44±12	172±3	78±5	65.7±2.2	26.5±1.5	10.4±2.3	12.3±2.6	4.2±0.4
	seriously obese	2	51±17	178±11	103±19	69.7±7.7	32.3±2.2	10.5±0.9	15.4±2.4	2.3±2.2

The data are expressed as mean±SD. Non-obese, moderately obese and seriously obese are defined as obesity indices <25 kg/m², 25-29.9 kg/m² and 30-39.9 kg/m², respectively.[4] IVT, the duration of the continuous intravenous infusion. The average time interval between two courses is 77±73 days (mean±SD). Statistical differences were found between TBW and LBW, between TBW and LBW doses at p<0.05 level (the paired Student's t-test). TBW and LBW doses were calculated by dividing the daily dose by TBW and LBW, respectively.