Table 1. Patient Characteristics.

Characteristic	*No.*	*%*	*Range*
Total no. of patients	13	100	
Sex			
male	6	46	
female	7	54	
Histology			
Diffuse large B-cell	7	54	
B-cell small lymphocytic*	2	15	
Peripheral large T-cell	2	15	
Angioimmunoblastic T-cell	1	8	
Anaplastic large-cell CD30+	1	8	
IPI at diagnosis†			
low or low-intermediate	7	54	
high-intermediate or high	6	38	
IPI at CsA+EPOCH initiation			
low or low-int	5	38	
high-int or high	8	54	
Type of recurrence			
Primary refractory	6	46	
First relapse	6	46	
Second relapse	1	8	
Previous therapies received			
Conventional chemotherapy			
median no. of regimens	2		1-6
median no. of drugs#	11		8-13
median no. of cycles	8		2-27
High dose chemotherapy			
no	8	62	
yes	5	38	
Radiotherapy			
no	7	54	
yes	6	46	

**Histologic progression was present in both cases at the initiation of CsA+EPOCH. †IPI: International Prognostic Index. #Different corticosteroids are considered as one drug.*

mary chemotherapy regimen. The remission rate in patients with a relapse from a complete remission was six out of seven (86% ; 95% C.I.: 42.1 to 99.6%). Of interest, five of them had previously received high dose chemotherapy treatment as they had had high risk lymphomas at the time of diagnosis. Actuarial survival was 18%, median survival was 7 months (95% C.I.: 0.5 to 13) and event-free survival was 8%. Patients with primary refractory lymphoma had significantly worse overall survival than patients in relapse (median survival 2.3 vs 11.3 months; p=0.01).

In conclusion, this novel approach combines two different strategies to overcome multidrug resistance. In this pilot study, CsA+EPOCH obtained high response rates in patients with heavily pretreated relapsed lymphomas. However, we found no responses in patients with primary refractory lymphoma, suggesting that the resistance found in these tumors involves different resistance mechanisms.[2] A better understanding of these mechanisms is necessary to design treatments which will be able to overcome multidrug resistance and to improve the survival in patients with refractory lymphoma.

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Key words

Lymphoma, Cyclosporin A, relapse, resistance

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Subacute spinal cord infarction due to zygomycotic thrombosis in a patient with myelodysplastic syndrome

A 58-year old man with myelodysplastic syndrome developed subacute-onset myelopathy, which did not respond to local irradiation. He finally died of pneumonia. The post-mortem examination revealed disseminated zygomycosis in the lung and the spinal vasculature, causing transverse spinal infarction. Disseminated zygomycosis can be responsible for myelopathy in patients with a hematologic malignancy.

Sir,

Myelopathy is rare complication in patients with a hematologic malignancy. Leukemic infiltration, infection, hemorrhages and cytotoxic agents can be responsible for this complication.[1] We recently cared for a patient who developed myelopathy caused by

Figure 1: Cross-section of the anterior spinal artery, totally occluded by a lot of filamentous fungi (Grocott stain, x200)

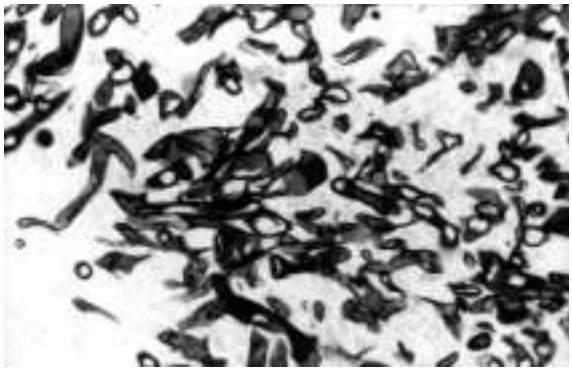

Figure 2: The hyphae are twisted, woven, and very broad, and lack regular septations. Branching of the hyphae with right-angle are commonly observed. (Grocott stain, x400)

zygomycotic thrombosis.

A 58-year old man was diagnosed as having acute myelocytic leukemia transformed from myelodysplastic syndrome in 1995. He did not respond to the conventional chemotherapy and required frequent blood transfusions. He was admitted to our hospital with high-grade fever in 1998. The chest X-ray showed bilateral pneumonia, and computed tomographic scanning of the thorax revealed a large consolidation contiguous with the posterior pleura in the right lower lobe and bilateral multiple nodules. We immediately initiated empirical administration of broad-spectrum antibiotics, but the high-grade fever persisted. We started administration of amphotericin-B on day 5 after admission and the dosage was increased to 1.5 mg/kg/day.

On day 10 after admission, the patient suddenly developed weakness and sensory disturbance of the right leg and urinary incontinence. The weakness of the right leg progressed rapidly to complete paraplegia, and Babinski sign showed a bilateral extensor response. T2-weighted magnetic resonance imaging (MRI) of the spine showed a high intensity signal from the T12 to L1 region, which was not enhanced upon administration of a paramagnetic contrast agent (gadolinium DTPA). Although the MRI findings were not typical of leukemic infiltration, we started local irradiation of this region at 3 Gy/day, but to no avail. The patients' condition rapidly deteriorated and he finally died of respiratory failure 36 days after admission.

At autopsy, the spine was swollen and necrotic along with hemorrhage between T12 and L1 levels. A cross-section of the spinal cord at L1 showed transverse infarction and necrosis. The anterior spinal artery was occluded with an embolus that contained a lot of filamentous fungi (Figure 1). The hyphae were twisted, woven, and very broad without regular septations (Figure 2). Branching of the hyphae with right-angles were observed frequently, but this case did not demonstrate the regular dichotomous bifurcation usually seen in *Aspergillus* infections.[2] Based on the characteristic morphology these organisms were identified as *Zygomycetes*. Large numbers of hyphae were also observed in the alveoli, bronchus and vessel walls. The dissemination of *Zygomycetes* was restricted to the lung and spine. Because the intercostal artery terminates in the anterior spinal artery, the fungi, intruding via the intercostal artery, might have been carried directly to the anterior spinal artery and then occluded it.

Few reports on filamentous fungal infection of the spinal cord have been published.[3-6] However, we should consider that disseminated zygomycosis is an important cause of myelopathy in patients with a hematologic malignancy.

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Key words

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Systemic sarcoidosis associated with interferon-α treatment for chronic myelogenous leukemia

We describe a patient with chronic myeloid leukemia (CML) on low-dose treatment with interferon (IFN) who developed systemic sarcoidosis, a rare IFN-related side effect, while in complete cytogenetic remission. We chose to continue IFN and to treat the sarcoidosis with prednisone. After eight months, the CML is still in complete cytogenetic remission and the sarcoidosis is almost completely resolved.

Sir,

Sarcoidosis is a systemic non-caseating granulomatous disorder of unknown etiology.[1] Sarcoidosis can develop as a consequence of IFN-α therapy.[2,3] The role that IFN plays in the pathogenesis of sarcoidosis is not known. Probably, it stimulates T-cells and macrophages, which produce interleukins, promoting a cascade of inflammation culminating in a granuloma.

A 49-year old female was diagnosed as having CML Ph+ in early chronic phase. The patient was started on IFN-α 3 MU/daily in August 1996. The dosage was not increased because of lack of tolerance. The patient achieved a complete hematologic remission with minor cytogenetic improvement in February 1997. The cytogenetic response was complete in May 1999. In July 1999 the patient developed cough, dyspnea on exertion and some 1-2 cm subcutaneous nodules on her right knee (Figure 1). Skin biopsy revealed non-caseous epithelioid granulomas. Chest X-ray and CT of the thorax showed non-caseous epithelioid granulomas. Cultures for fungi and *tuberculosis Mycobacteria,* performed on broncoalveolar lavage, were negative. A bone marrow biopsy showed epithelioid granulomas (Figure 2).

These findings led us to the conclusion that the patient was suffering from symptomatic sarcoidosis and we started oral prednisone without interrupting the IFN therapy. At the last follow-up visit, after eight months of prednisone therapy, CML was still in complete cytogenetic remission. The skin nodules were reduced, chest X-ray and marrow biopsy showed, respectively, disappearance of hilar opacities and epithelioid granulomas.

Pulmonary or cutaneous sarcoidosis that resolved after oral cortisone or after IFN-α dose reduction has been reported in patients treated with IFN-α for hepatitis C and non-Hodgkin's lymphoma,[4,5] There have been only three cases of sarcoidosis developing during IFN-α therapy in CML patients.[2,3,6] In all three patients sarcoidosis resolved after discontinuation of IFN therapy. Four other cases of sarcoidosis with CML are reported; three patients had underlying sarcoidosis when CML was diagnosed,[7-9] in the fourth both diseases were diagnosed simultaneously.[10]

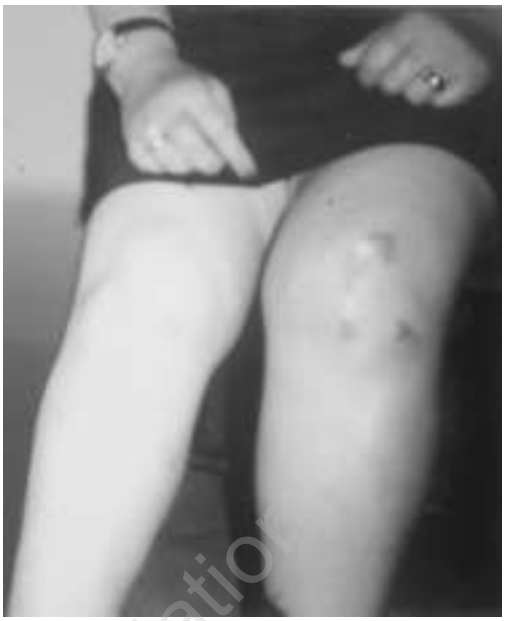

Figure 1: Red subcutaneous nodules on right knee.

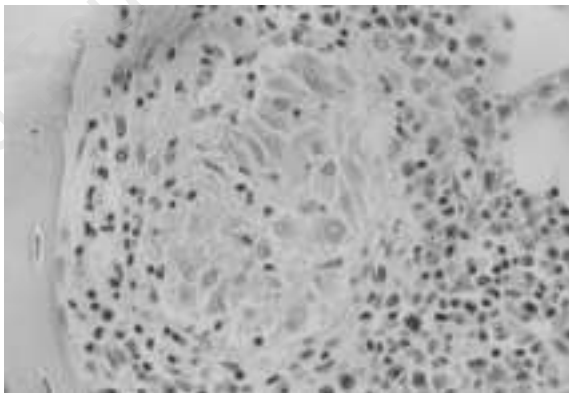

Figure 2: Bone marrow biopsy: isolated epithelioid granulomas. E.E. 400x

Our patient developed cutaneous, pulmonary and bone marrow sarcoidosis. This type of involvement was not described in the previously reported cases. Considering that the 5-year survival rate of CML patients in complete cytogenetic remission is 90%, we chose to continue IFN treatment and to treat the sarcoidosis with oral corticosteroids. The IFN dose could not be reduced because it was already very low, near to the minimum value necessary to maintain complete cytogenetic remission.

We would like to emphasize there is no evidence of the impact of cortisone on cytogenetic response of CML. In the other three patients who developed sarcoidosis during IFN therapy, the drug was interrupted or reduced with clinical resolution of the sarcoidosis. For only one of the three patients is infor-