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Hodgkin's Disease as Pyrexia of Unknown Origin in a Patient with Chronic Lymphocytic Leukaemia

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AS HYPOGAMMAGLOBULINAEMIA and neutropenia develop eventually in almost all patients with chronic lymphocytic leukaemia (CLL), infections become the most common and important complication [1]. For this reason and also because fever is rarely produced by the disease itself, the presence of fever in CLL is usually considered as manifestation of infection and is treated as such even if there are no clinical signs of infection.

In this report we present the case of a patient with CLL who developed fever of unknown origin which finally proved to be due to Hodgkin's disease (HD).

A 54-year-old man, with past history of pulmonary tuberculosis and diabetes mellitus, presented in September 1989 with peripheral lymphadenopathy, enlarged spleen (12 cm), liver (7 cm), white blood cell count of 320 × 10^9/l (96% mature-looking lymphocytes), haemoglobin of 10.6 g/dl, platelets of 148 × 10^9/l and heavily infiltrated bone marrow with small lymphocytes. He was diagnosed as CLL, stage B. He started treatment with chlorabucil/prednisolone with good clinical and laboratory response. In March 1990, while still on the same treatment, he developed fever, anorexia and weight loss. He presented 1 month later, febrile and in poor general condition, but CLL seemed to be under control. On examination he was found with minimal peripheral lymphadenopathy, liver and spleen both palpable 2 cm. His blood count was quite good with haemoglobin of 12.1 g/dl, white blood cell count of 5.8 × 10^9/l (lymphocytes 29%), platelets of 195 × 10^9/l. There was no sign of infection and the investigation disclosed nothing helpful. Computed tomography of the abdomen showed small retroperitonial lymph nodes and spleen and liver enlargement. Chest X-ray was normal. Empirical treatment with common antibiotics had no effect. Subsequently, there was no improvement with antituberculous treatment but a small lymph node in the right axilla started becoming bigger. This lymph node biopsy revealed HD. He was started on doxorubicin-bleomycin-vinblastin-dicarbazine with excellent response.

Searching the literature we found at least 20 cases [2–4] with firm diagnosis of HD in CLL patients. In conclusion we can say that fever unrelated to infection in CLL patients has not only the grave prognosis of higher malignancy transformation, but could represent B symptoms of HD.

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The Prophylactic Use of Fluconazole 50 vs. 100 mg Daily in Haematological Malignancies

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SUPERFICIAL AND invasive fungal infections are common and often life-threatening complications during treatment for haematological malignancies. In many studies oral antifungal drugs like amphotericin B, nystatin and ketoconazole decrease the frequency of oral candidiasis but a reduction of invasive infections has not been documented [1, 2, 3]. These agents are usually poorly tolerated because of their taste, quantity and/or hepatotoxicity.

Fluconazole is one of the new azoles which has been shown to be effective in the treatment of oral candidiasis in HIV infected or neutropenic patients using daily doses of 50 to 400 mg [4–9]. It is not clear whether the higher doses add to the prevention of oral candidiasis a decrease of the frequency of invasive fungal infections. We choose to compare two low dose regimens [3, 9] to see whether there is a relevant clinical difference in efficacy for the prevention of oral candidiasis and whether there is any difference in the occurrence of invasive fungal infections and/or the need for empirical intravenous antifungal therapy.

In a pilot study, we entered 60 consecutive patients with acute leukaemia or malignant lymphoma needing chemotherapy which would lead to granulocytopenia (granulocytes <0.5. 10^9/l) for at least 15 days. Patients were excluded if life expectance was less than 30 days, age was over 80 years, of if severe liver function disturbances were present. Patients were randomised to receive 50 or 100 mg fluconazole daily in identical appearing capsules from the start of chemotherapy throughout the whole period of

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Table 1. Patients' characteristics and results

	Fluconazole daily dose	
	50 mg	100 mg
Number of patients	30	30
Age (years)		
Median	48	40
Range	20–75	16–75
Diagnosis		
AML	18	17
ALL	6	4
NHL/HD	6	9
Mucositis WHO scale		
0	17	18
I	9	4
II	3	6
III	1	2
Patients receiving corticosteroids	7	5
Neutropenia (days)		
Median	31	32
Range	19–61	23–43
Clinical oropharyngeal candidiasis	2	1
Patients with febrile episodes	21	20
Fever of unknown origin	6	12
Clinically documented infection	6	3
Microbiologically documented infection	9	5
Bacterial septicaemia	6	4
Pulmonary aspergillosis	2	1
Others	1	0
Time to fever (days)		
Median	18	16
Range	3–35	1–26
Fever (days)		
Median	5	3
Range	0–33	0–10
Antibiotics (days)		
Median	14	17
Range	0–37	0–42
Patients receiving intravenous amphotericin-B	9	4
Patients dying of infection	3	1
Patients dying of malignancy	1	0
Patients with persisent colonisation		
C. albicans	5	3
Other yeasts	3	2
Gram negative bacteria	3	1
Patients with acquired colonisation		
C. albicans	1	0
Other yeasts	2	7
Gram negative bacteria	1	2

AML, Acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease.

granulocytopenia. Concurrently, ciprofloxacin 500 mg twice a day was administered. Surveillance cultures were taken two times weekly from the oral cavity (mouth washes of 10 ml sterile normal saline) and faeces. Yeasts were identified by the use of API—20 C Aux (Bio Merieux, France). Drug resistance of isolated yeasts was not tested. Colonisation was defined as persistent if a given species was present before therapy and persisted thereafter in any culture. Colonisation was defined as acquired if a species showed up in at least two cultures after starting therapy. Types of infection were defined as previously described [10].

When presenting with fever (temperature >38.5°C), patients were treated with intravenous imipenem-cilastatin 2 g daily. Only if signs of a progressive or new infection developed was antibiotic treatment changed to intravenous vancomycin 2 g and aztreonam 4 g daily. If, in so treated patients, signs of a new or progressive infection appeared, intravenous amphotericin-B was added [10].

Patients characteristics and results are given in Table 1. In the 50 mg group the five isolated non-*Candida albicans* yeasts were (number of patients with mouth, faeces or mouth and faeces isolations, respectively): *Candida glabrata* (1,0,2), *Sacharomyces cerevisiae* 1 (0,0,1), and non-specified (1,0,0). Of these, *C. glabrata* represented persistent colonisation in 2 patients and *S. cerevisiae* in 1 patient. In the 100 mg group the nine isolated non-*C. albicans* yeasts were: *C. glabrata* (0,2,1), *C. inconspicua* (0,1,0), *Geotrichum penicillatum* (0,1,0) and non-specified (2,1, 1). Of these, *C. inconspicua* and a non-specified yeast represented persistent colonisation each in 1 patient. There were no differences in duration of neutropenia, number of febrile episodes, time to fever, use of antibiotics and number of clinical oral candidiasis. No clinically or microbiologically documented invasive infection could be attributed to yeasts. There was a trend to a lower need for empiric amphotericin-B in the 100 mg group. All 3 patients with pulmonary aspergillosis died despite proper therapy, together with 1 patient with *Ps. maltophilia* septicaemia for a total of four infectious deaths.

In these highly immunocompromised patients fluconazole was effective in preventing clinical oral candidiasis, 50 mg daily being a cost-effective dose.

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