

Richter's Transformation; the Cause of Fever of Unknown Origin in a Case with Chronic Lymphocytic Leukemia

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is the most common leukemia in many countries. Infections are the most common causes of morbidity and mortality; lymphoid cell dysfunction and neutropenia associated with chemotherapy are main predisposing conditions for infection. For this reason infectious conditions must be excluded in a case with CLL and fever. Richter's transformation (RT) is a kind of lymphoma that is a rare condition in CLL cases. Fever of unknown origin is a rare finding in Richter's transformation (RT) but it has been reported as anecdotal reports. Here a case with RT as the cause of fever in a case with CLL was reported and literature was reviewed.

Key Words: Chronic lymphocytic leukemia (CLL), Fever of unknown origin (FUO), Richter transformation (RT)

ÖZET

Kronik Lenfositik Lösemisi Olan Bir Olguda Orijini Bilinmeyen Ateş Nedeni: Richter Transformasyonu

Kronik lenfositik lösemi (KLL) pek çok ülkede en sık karşılaşılan lösemi grubunu oluşturmaktadır. Enfeksiyonlar bu hastalık grubunda morbidite ve mortalitenin en sık sebebidir ve kemoterapi ile ilişkili lenfoid hücre disfonksiyonu ve nötropeni, enfeksiyonlara yatkınlığın başlıca nedenlerini oluştururlar. Bu neden ile ateşi olan KLL'li olgularda enfeksiyöz durumlar mutlaka dışlanmalıdır. Richter transformasyonu (RT) KLL olgularında nadir görülen bir lenfoma türüdür ve orijini bilinmeyen ateşlerin de nadir sebebini oluşturmaktadır. RT ilişkili orijini bilinmeyen ateş olguları anekdotal raporlar şeklinde bildirilmiştir. Burada KLL tanısı olan ve ateş nedeni olarak RT saptanan bir olgu sunulmuş ve literatür gözden geçirilmiştir.

Anahtar Kelimeler: Kronik lenfositik lösemi (KLL), Orijini bilinmeyen ateş, Richter transformasyonu

INTRODUCTION

FUO is not a rare condition in daily practice; infections, malignant diseases and collagen vascular disorders are the most common causes of FUO. Lymphoreticular malignancies invading liver, spleen and bone marrow are the most common causes of FUO among malignancies.^{1,2}

Chronic lymphocytic leukemia (CLL) is the most common leukemia in western countries and 95% of them are of B cell origin.³ Infections are the most common causes of morbidity and/or mortality; T and especially B cell dysfunction and neutropenia associated with chemotherapy are main predisposing conditions for infection. For this reason infectious conditions must be excluded in a case with CLL and fever.⁴ Here a case with Richter's transformation (RT) as the cause of fever in a case with CLL was reported and literature was reviewed.

CASE REPORT

Fifty-six year-old-man was diagnosed as Stage-I CLL on August 2004. He was asymptomatic and he was followed without therapy for one and half year. On February 2006, progressive disease developed and he was treated by 2 cycles of Cyclophosphamide and Fludarabine (CF). However this therapy was changed with Cyclophosphamide-Vincristine-Prednisolone (CVP) due to infectious complications. At the end of 10 cycles peripheral blood findings were within normal limits. His condition and peripheral blood findings were well until April 2007. At this time, he admitted to the hospital with diarrhea and WBC was found as $248 \times 10^9/L$. p53 analysis was found to be negative. Fludarabine-Mitoxantrone-Dexamethason (FND) regimen was started. However repeated infectious complications developed and they were treated by antibiotics. On June 2007, he admitted with fever ($39^{\circ}C$) again and there was herpetic lesions on the lip, monilial aphthous ulcers on the tongue, anterior cervical and right axillary lymphadenopathy and hepatosplenomegaly in physical examination. Laboratory findings have been summarized in Table 1. Abdominal US and CT scans showed intraperitoneal and retroperitoneal lymph nodes and hepatosplenomegaly. Vegetation was not detected echocardiographically. Piperacillin-tazobactam, fluconazole and

acyclovir were started. Blood cultures taken for 5 times were found to be negative. Urine culture showed *Enterococcus faecalis* (300.000 cfu/ml). After anti-infective therapy, urine culture was negative and herpetic and aphthous lesions regressed completely. Brucella agglutination and CMV-PCR were found to be negative. Three induced sputum samples and 3 urine samples did not show ARB. Stool samples were negative for parasites and leukocytes.

Clinical outcome: After anti-infective therapy all the cultures were repeated and they were found to be negative for 3-4 times. However high grade fever, anemia and thrombocytopenia persisted. Antibiotics were stopped after 2 weeks. RT was thought clinically. Lymph node and bone marrow biopsies taken to show RT and to rule out other unusual microorganisms. When waiting the biopsy results naproxen was given to the patient and his fever disappeared with this drug.

Bone marrow biopsy showed small lymphocytic leukemia with focal prolymphocytic proliferation. Lymph node biopsy showed small lymphocytic lymphoma morphology. CyclinD1 was negative and p53 was found to be positive. R-CHOP chemotherapy was given for RT but fever developed at the forth day of chemotherapy. Blood culture at this time showed ESBL (+) *E. Coli*. Carbapenem was prescribed, however his general condition deteriorated. He was intubated in intensive care unit but he died after 24 hours. *M. tuberculosis* was not shown in none of the samples.

DISCUSSION

RT is a rare condition in CLL cases and is seen in about 3% to 10% of these cases. Median survival time after RT is 6 months. The most important findings of this entity are poor response to usual CLL therapies, progression in lymphadenopathy and/or organomegaly and high grade morphology in peripheral blood and/or pathological specimens taken from lymph node or bone marrow.^{4,7} Predisposing conditions for RT are p53 mutations and fludarabine containing regimens. p53 mutation, which was negative at the beginning, is an important property of RT in our case

Table 1. Patient's laboratory findings when admission and follow up

Laboratory Findings	22.06.2007	30.07.2007
Wbc	132.500/mm ³	140.600/mm ³
Hb	7.5 g/dl	7.0 g/dl
Hct	23.7%	22.5%
Platelet	57.000/mm ³	25.000/mm ³
AST	43 U/L	176 U/L
ALT	62 U/L	166 U/L
Glucose	104 mg/dl	114 mg/dl
BUN/creatinin	11/0.9 mg/dl	9/0.7 mg/dl
CRP	104 mg/L	129 mg/L
Procalcitonin	0.05 ng/ml	11.3 ng/ml

Fludarabine using probably contributed to RT development in our case. But in one study RT incidence was not higher in patients receiving nucleoside analog, like fludarabine or chlorodeoxyadenosine. In this study it has been found that patients at all stages and in complete response were at risk for RT.⁸

Fludarabine treated patients with CLL also may be associated with infections involving T-cell dysfunction, such as listeriosis, pneumocystosis, mycobacterial infections, and opportunistic fungal and viral infections.⁹ For this reason recurring and long lasting fever and infections are not rare in fludarabine users. But in our patient we did not show evidence of bacteremia, viral infection except herpes labialis (i.e., cytomegalovirus or varicella-zoster virus), mycobacterial and parasite infection. Our patient's spiking fevers (39°C) continued for long time before and after hospital admission for diagnostic evaluation and no response to antibiotic therapy. His fever responded to naproxen test. The response to naproxen suggests that the etiology of the patient's fever was in neoplastic origin and not infectious.^{4,10}

FUO is a rare finding in RT but it has been reported as anecdotal reports.^{8,11-12} As mentioned before, infection and fever are very frequently seen findings in CLL cases. For this reason fever in a case with CLL requires exclusion of an infectious episode. The diagnosis of unusual infections may be diffi-

cult and sometimes requires long term and detailed explorations and examinations. In clinical practice, when we see a case with CLL and fever, the first step is diagnostic procedures for infection and second step is to start wide spectrum antibiotics. Although it is rare, fever may not be due to the infection in CLL. RT must be diagnostic challenge in a case with CLL and fever (especially which prolonged and high-spiking fever).

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