Chronic Lymphocytic Leukemia With Central Nervous Involvement In The Form of Localized Mass Responding to Therapy With Fludarabine

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ABSTRACT
We report a extremely rare case of involvement of the central nervous system (CNS) in the form of a localized mass by chronic lymphocytic leukemia (CLL). A 69-year-old man was admitted to our hospital with dysartria. Cranial computed tomography (CT) revealed a left frontal mass. He had generalized lymphadenopathy and hepatosplenomegaly. Examination of peripheral blood smear and finding of immunophenotyping of peripheral blood mononuclear cells were consistent with the diagnosis of B-cell CLL. His disease had a agrresive outcome. Cranial RT was applied and then fludarabine plus cyclophosphamide (FC) were begun. After this treatment, peripheral blood lymphocytosis and all the palpable lymph nodes disappeared. Three months after diagnosis, there was nearly complete regression of the mass on cranial magnetic resonance imaging. After six courses of FC, the patient is still alive and he is in complete remission two years after diagnosis. This case shows that CLL might be complicated by brain involvement in the form of a localized mass. Fludarabine seems effective in controlling this form of CLL.
Keywords: chronic lymphocytic leukemia, CNS involvement, fludarabine

ÖZET
Kitle Tarzında Santral Sinir Sistemi Tutulumu ile Karakterize, Fludarabin'e Cevap Veren Kronik Lenfositer Lösemi
Bu sunumumuzda, santral sinir sisteminde kitle tarzında tutulum olan, çok nadir görülen bir kronik lenfositer lösemi (KLL) olgusu bildirdik. 69 yaşında erkek hasta disartri şikayeti ile hastanemize başvurdu. Kranial bilgisayarlı tomografisi ile beyninin frontal kısmına yerleşik bir kitle tespit edildi. Fizik muayenesinde yaygın lenfadenomegali ve hepatosplenomegali mevcuttu. Çevresel kan yaymasının incelenmesi ve çevresel kanın mononukleer hücrelerinin immünfenotipleme bulguları B-hücreli KLL tanısı ile uyumluydu. Hasta hızlı bir klinik seyre sahipti. Kranial radyoterapi uygulandı ve daha sonra fludarabin/siklofosfomid kemoterapi protokolü başlandı. Bu tedaviden sonra, çevresel kan lenfositozu ve bütün palbe edilebilen lenf bezleri geriledi. Tanıdan 3 ay sonra çekilen kranial MRI'de kitlede tama yakın gerileme mevcuttu. 6 kür FC kemoterapi küründen sonra hasta halen hayatta idi ve tanıdan 2 yıl sonra tam remisyondaydı. Bu olgu KLL'nin kitle tarzında beyin tutulumu ile komplike olabileceğini göstermektedir. Fludarabin, KLL'nin bu formunun kontrolünde etkili gözükmektedir.
Anahtar Kelimeler: kronik lenfositik lösemi, MSS tutulması, fludabarin

INTRODUCTION

Chronic lymphocytic leukemia [CLL] is an indolent disease characterized by the insidious accumulation of small mature-appearing lymphocytes in the peripheral blood, bone marrow, and lymphoid tissues (Rozman and Montserrat 1995). Involvement of central nervous system [CNS] is extremely rare in CLL. In a retrospective study, only eight cases of direct CNS involvement by leukemic cells among 962 patients (0.8%) was found (Bower et al. 1997). Moreover, most documented cases have been of leptomeningeal and cranial nerve infiltration (Elliott et al. 1999). Cerebral mass due to CLL is exceedingly rare.

In the present report, we describe a CLL patient who presented with neurological impairment secondary to a cerebral mass.

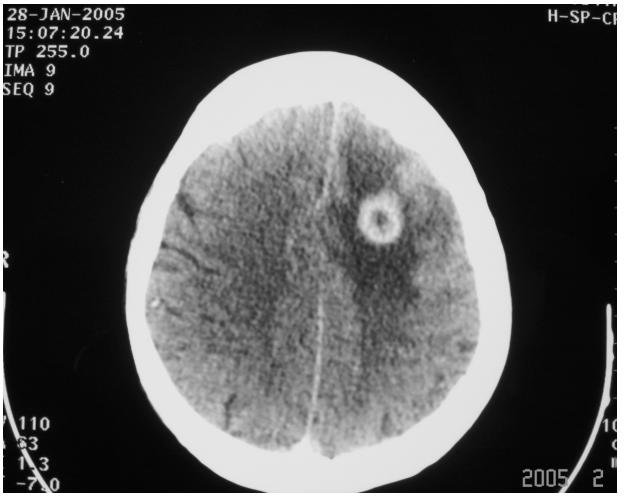

Figure 1

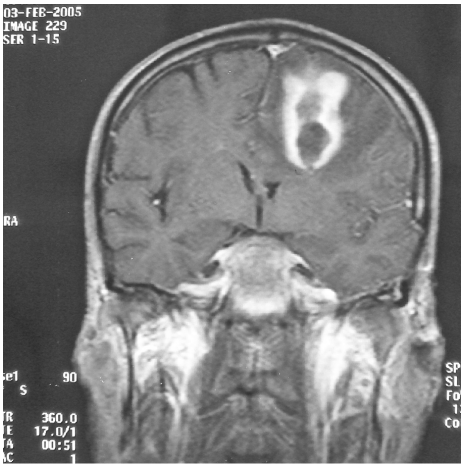

Figure 2

CASE REPORT

A 69-year-old man was admitted to our hospital with dysartria beginning one day before his admission. The patient noticed bilateral multiple cervical masses six months ago but did not seek medical attention. On physical examination, he had generalized lymphadenopathy and hepatosplenomegaly. Neurological examination revealed dsyarthria and right central facial paralysis. Laboratory data showed: hemoglobin, 9,9 gr/dl; hematocrit, 28,9%; leucocytes, 11800/µL [87% lymphocytes]; platelets, 128000/µL; β-2 microglobin, 4228ng/dl; LDH, 204 U/L [N<192]. The peripheral blood smear showed many mature lymphocytes and also a few large cells with prominent nucleoli. Flow cytometric analysis of the peripheral blood mononuclear cells showed that the majority expressed B-cell markers CD19, CD20, and CD23, co-expressed CD5 (dim) with kappa immunoglobulin light chain restriction. These cells were negative for CD2, CD7, CD10, and FMC7. These findings were consistent with the diagnosis of B-cell CLL. The clinical stage was III according to Rai classification.

Pathological examination of a cervical lymph node biopsy revealed a diffuse infiltration with round, mildly pleomorphic atypical lymphocytes with hyperchromatic nuclei. Cranial computed tomography (CT) revealed a left frontal mass 2x2,5 cm in diameter with a large area of oedema around and it caused minimal frontal subfalcine shift [Figure 1].

Anti-oedema treatment with dexamethasone was started to be administered; and the patient's dysarthria quickly improved. The lymphocyte count increased up to 50.000/µL on the eighth day after admission. In the meanwhile, on the eighth day of admission a left limb paralysis and dysarthria developed. Cranial magnetic resonance imaging [MRI] showed that the mass was larger with a 4,5x3,5x3 cm dimension [Figure 2]. The dose of dexamethasone was increased and one course of COP was given. Furthermore, the patient was put on cranial radiotherapy on the thirteenth day of admission. Neurological signs regressed; but, increase in the lymphocyte count continued and it was 75 000/µL on the thirtieth day of admission. Cranial MRI on the fortieth day of admission showed partial regression of the mass [Figure 3]. Fludarabine [25mg/d, 3 days] and cyclophosphamide [200 mg/d, 3 days] were begun on the fiftieth day of admission. After this treatment, peripheral blood lymphocytosis and all the palpable lymph nodes disappeared. Three months after diagnosis, there was nearly complete regression of the mass on cranial MRI [Figure 4]. After six courses of FC, the patient is still alive and he is in complete remission two years after diagnosis.

DISCUSSION

Although CLL is the most common form of leukemia, involvement of the CNS in CLL is uncommon (Bower et al 1997, Cramer et al 1996). CNS involvement in CLL is usually leptomeningial (Elliott et al 1999) and cerebral mass due to CLL is extremely rare. Patton et al (1992) reported a patient with a 3-year history of CLL who had a progressive decline in mental status and he had an enhancing lesion in the frontoparietal region of the brain on CT. Moreover, one case presenting as a mass involving the hypothalamus and two cases with pituitary masses have been reported

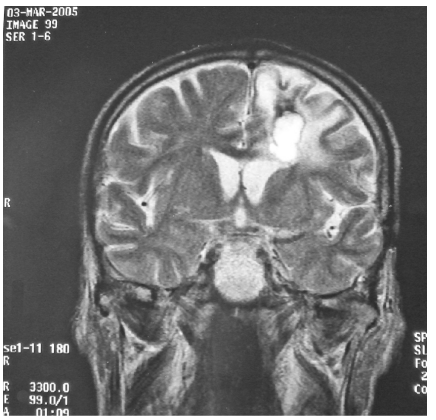

Figure 3

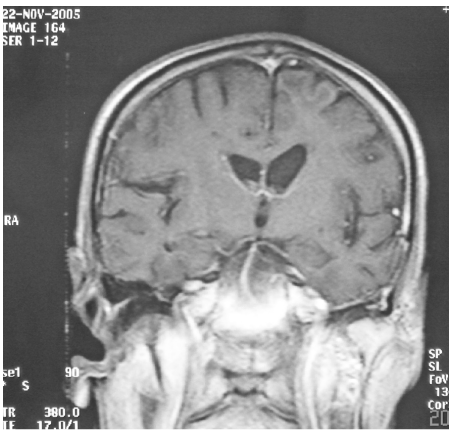

Figure 4

(Garofalo 1989, Fain 1992). O'Neill et al (1989) reported that 2 patients with CLL subsequently had parenchymal CNS non-Hodkgin's lymphoma. However, they proposed that their cases were primary brain lymphoma, suggesting a new form of Richter's syndrome; since neither any evidence for systemic lymphoma nor of progression of the leukemia was found. Although our case resembles the cases reported by O'Neill, our patient had progressive leukemia together with rapidly growing cerebral mass.

Leukemic involvement of the CNS may be associated with a number of symptoms including motor deficits, confused state, optic neuropathy, cerebellar dysfunction, cranial nerve palsies, headache, and fever (Brick et al. 2002). Our patient had cranial nerve palsies and signs of cerebral oedema. These neurological findings are not specific for CLL involvement of the brain and might be seen many clinical conditions associated with cerebral disorders. Given the extremely rare occurrence of invasion of the CNS by CLL, verification of this diagnosis and a thorough analysis to exclude more likely diagnoses are essential. As our patient had progressive disease and the localization of the mass was difficult to reach, biopsy for pathological evaluation could not be performed. However, near complete resolution of the mass after radio-chemotherapy and the 2 year duration of remission after treatment with fludarabine and cyclophosfamide combination strongly suggested that the mass in the brain was associated with CLL.

Because of its rarity, there are few data on the treatment of CLL which invades the CNS. The cases with meningial involvement successfully have been treated using various combinations of steroids, intrathecal administration of methotrexate or cytosine arabinoside [or both], and cranial irradiation (Liepman and Votaw 1981, Steinberg et al 1985, Singh and Thompson 1986, Cash et al 1987, Stagg and Gumbart 1987, Cramer et al 1996, Currie et al 1988). However, in cases which caused a mass in the brain, intrathecal chemotherapy alone would not be adequate, and the addition of cranial irradiation appears necessary for optimal disease control. Elliott et al (1999) reported a CLL case with parenchymal infiltration of cerebrum who achieved a complete clinical remission with fludarabine treatment. As mentioned, we observed that the combination of fludarabine with cyclophosphamide was highly effective and provided durable remission after cranial RT.

CONCLUSION

This case shows that CLL might be complicated by brain involvement in the form of a localized mass. Fludarabine seems effective in controlling this form of CLL.

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