Cryptococcal Meningitis in Chronic Lymphocytic Leukemia Patients

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KEY WORDS: chronic lymphocytic leukemia, *Cryptococcus neoformans*, meningitis

IMAJ 2009;11:437–439

Cryptococcal meningoencephalitis is caused by the encapsulated yeast *Cryptococcus neoformans*. Most affected patients have T cell dysfunction; 90% of them today are AIDS patients, the remaining 10% having profound immune suppression following organ transplantation, lymphatic malignancies (especially Hodgkin's lymphoma) and sarcoidosis.

Chronic lymphocytic leukemia is associated with impaired immunity. The main immune defect is humoral, which is present in one-quarter of the patients, and carries an increased risk of bacterial infection. However, the neutrophil count may be low following chemotherapy or bone marrow infiltration by leukemic cells. Furthermore, immune cellular impairment is also recognized in CLL, including decreased T helper activity, increased T suppressor activity, reversal of CD4/CD8 ratio, and defects in natural killer cells and in complement function [1]. Also, CLL is more prevalent in older people, a population already in humoral and cellular immune decline [2].

Chemotherapy in CLL patients causes neutropenia and T cell dysfunction. Alkylating agents are associated mainly with bacterial infections and to a lesser degree viral and fungal infections. Fludarabine decreases the CD4 and monocyte counts as well as natural killer cell count and function. CD4 counts decrease within 2–3 months and stay low for a prolonged time, thus making patients susceptible to opportunistic infections in the absence of neutropenia or concurrent steroid treatment.

We present two rare cases of cryptococcal meningitis in CLL patients, emphasizing the diagnostic and therapeutic dilemmas.

PATIENT DESCRIPTIONS

PATIENT 1

A 78 year old woman was admitted because of disorientation accompanied by euphoric and somnolent episodes over the previous few weeks. She also complained of dysuria, urgency and frequency in urination without fever for 2 weeks prior to admission.

CLL had been diagnosed 6 years earlier, accompanied by recurrent episodes of severe Coombs positive hemolytic anemia. Treatment consisted of a combination of cyclophosphamide, oncovine and prednisone, and for the previous 6 months intravenous cyclophosphamide (1000 mg) every 4 weeks and prednisone 10 mg a day.

On physical examination the patient appeared sick. Body temperature was 36.4°C, blood pressure was 135/80 mmHg and pulse rate 100 beats per minutes and regular. Examination of the heart, lungs and abdomen was normal and there was no lymphadenopathy. Neurological examination revealed an alert, oriented woman without nuchal rigidity or any focal neurological deficits. Hemoglobin level was 12.2 g/dl, white blood cell count 12,400/ml^3 (45% lymphocytes) and platelet count 140,000/ml^3. Serum glucose, electrolytes, liver and kidney function tests as well as thyroid function tests, blood gases and vitamin B_{12} levels were all within the normal range. Urinalysis was positive for leukocytes, erythrocytes, protein and nitrite, while culture yielded *Enterococcus fecalis*.

During the first 3 days of hospitalization the patient was treated intravenously with vancomycin. The urinary complaints resolved; however, she became intermittently stuporotic, disoriented and confused. Brain computed tomography scan revealed brain atrophy compatible with age alone. Lumbar puncture showed 175 leukocytes/ml^3 with 10% segments and 90% mononuclear cells, 75 erythrocytes/ml^3, and protein and glucose levels of 161 mg/dl and 40 mg/dl respectively. Cerebral spinal fluid smear showed a large amount of cryotococci. *C. neoformans* grew in the CSF culture. Blood cultures were sterile but cryptococcal antigen titer was 1:512. The patient was treated with IV amphotericin B (1 mg/kg) for 2 weeks. During the treatment she was extremely weak and her consciousness fluctuated from fully alert to sleepy. A second lumbar puncture (on day 14) yielded 200 leukocytes/ml^3 with 2% segments and 98% mononuclear cells,

CLL = chronic lymphocytic leukemia

CSF = cerebrospinal fluid

310 erythrocytes/ml^3, and protein and glucose levels of 175 mg/dl and 52 mg/dl respectively. CSF smear demonstrated *C. neoformans* again but to a lesser degree and the yeast still grew in culture. The antigen titers were 1:2048 in the CSF and 1:1024 in the blood. The treatment was changed to fluconazole 400 mg/day.

Gradually the patient's mental status and comprehension improved. In view of the risk of current infection versus previous life-threatening episodes of hemolysis, the patient was treated with another course of cyclophosphamide and was discharged to a rehabilitation center. A month later she was fully coherent, without neurological deficits. She continued treatment with fluconazole, low dose prednisone and a course of cyclophosphamide every 4 weeks. The blood cryptococcal antigen titer gradually declined to 1:64 after 7 months of treatment when the fluconazole dose was reduced to 200 mg/day. The titer declined further to 1:6 after 10 months treatment. The patient died because of acute respiratory failure 5 months later while on fluconazole 200 mg/day.

PATIENT 2

An 82 year old man was admitted because of headache and low grade fever during the previous month. CLL was diagnosed 13 years earlier and he was treated over the years with leukeran.

For the year prior to admission his disease has been considered in remission and he received no treatment. In addition he had mild chronic renal failure, hypercholesterolemia and well-controlled hypertension. During the previous month he was treated with levofloxacin for maxillary sinusitis. In the week preceding his admission he suffered headache and dizziness when walking, followed by short episodes of absence. Temporal arteritis was suspected, prednisone was added, and temporal artery biopsy was scheduled. On the day of admission syncope occurred, without convulsions.

Upon admission the patient was fully alert and his vital signs were normal. No tenderness over his temporal arteries, lymphadenopathy or neurological deficit was noted. A complete blood count disclosed leukocytosis of 24,310/ml^3 (79% lymphocytes); hemoglobin level was 11.8 g/dl and platelet count 114,000/ml^3. The serum creatinine and urea levels were 1.3 mg/dl and 42 mg/dl respectively. Glucose, electrolytes, and liver function tests were within the normal range. Urinalysis was negative for cells, protein or nitrites. Brain CT scan revealed no abnormalities, except for fluid and mucosal thickening in the maxillary sinuses. Lumbar puncture was remarkable for an elevated opening pressure (260 mmH_2O), very low glucose level (7 mg/dl), high protein level (186 mg/dl), and 36 cells/ml^3 (mostly polymorphonuclears). Gram stain was negative for bacteria. The working diagnosis was partially treated meningitis. Treatment with ceftriaxone and trimethoprim-sulfamethoxazole (because of allergy to penicillin) was started, and prednisone was stopped. After 3 days, as the patient's condition did not change and blood cultures were sterile, a second lumbar puncture was performed. CSF characteristics were similar to the previous examination, but the titer for cryptococcal antigen was 1:1024 .The antibiotics were discontinued and amphotericin B was started. Later on *Cryptococcus neoformans* was isolated from CSF cultures.

The patient's hospitalization was complicated by worsening of kidney function attributed to the amphotericin treatment. Serum creatinine level rose to 2.6 mg/dl, followed by severe hypokalemia and hypomagnesemia secondary to amphotericin-induced renal tubulopathy. The amphotericin was switched first to the liposomal formulation and later to fluconazole. Some time later severe hyponatremia (serum sodium level 115 mEq/ml) compatible with SIADH (syndrome of inappropriate antidiuretic hormone) occurred, with recurrent short episodes of absence and the development of encephalopathy with the emergence of flapping tremor and stupor. Nevertheless, a clear improvement in the CSF variables on serial lumbar punctures was observed.

The clinical course was further complicated by acute myocardial infarction with recurrent pulmonary edema that required intubation. The patient was transferred to the intensive care unit, where he developed Pseudomonas pneumonia and later succumbed to carbapenem-resistant Klebsiella sepsis.

COMMENT

Review of the literature reveals only a few reports similar to the patients presented here. The largest series consists of 41 patients with different malignancies who were diagnosed with cryptococcosis; 5 of them had CLL of whom at least 3 were treated with high dose steroids [3]. Other case reports described cryptococcal infections in CLL patients who were treated with various chemotherapies.

The diagnosis of cryptococcal meningoencephalitis is based on CSF findings that are characterized by high opening pressure, low glucose and high protein levels, and lymphocytosis. Although the yeasts are seen on india ink stain, growth in culture provides a definite diagnosis. Cryptococcal antigen is found in the CSF, blood or both [1].

Adverse prognostic factors that predict treatment failure are high opening pressure during lumbar puncture, low CSF glucose level, less than 20 leukocytes/ml^3 in CSF, positive CSF smear, evidence of disseminated disease by positive blood cultures or high antigen titers in the blood or CSF, mental changes, age over 60 years, and underlying malignancies. Several series considered steroid treatment, lymphatic malignancies (especially Hodgkin's lymphoma), and absence of cryptococcal antibodies as adverse prognostic factors [4], while others found leukocytosis and mental status to be of prognostic

value [5]. Our patients had almost every known unfavorable prognostic factor: elevated opening pressure on lumbar puncture, very low glucose CSF level, strongly positive smear for cryptococci, and very high antigen titers in blood and CSF. Also the patients' age, their neurological findings and underlying malignancy are considered grave prognostic factors [5].

Our first patient was treated with cyclophosphamide, which is not considered a risk factor for cryptococcal meningitis, and her daily prednisone dose was low. The second patient was treated only briefly with prednisone after the emergence of his symptoms. Similar to almost half of the non-AIDS or organ-transplanted patients with cryptococcal meningitis, no obvious risk factor could be found, with the exception of inherent immunological impairment secondary to CLL.

The therapeutic approach was complicated and challenging. The first patient demonstrated remarkable clinical improvement but no change in the CSF findings after 2 weeks of amphotericin B treatment. She was then switched to oral fluconazole, which is known to be an effective fungocidic agent. Another dilemma was the risk-benefit ratio of renewing the chemotherapy while she was actively infected and facing fulminant meningitis versus the risk of life-threatening hemolysis that she faced in the past. We decided to treat her with reduced doses of cyclophosphamide, anticipating control of hemolysis without aggravating the cryptococcal infection. The last unresolved dilemma was the length of fluconazole treatment. Treatment duration is not clear .While most non-AIDS patients require 8–10 weeks of consolidation therapy with fluconazole, immunosuppressed individuals may need more prolonged treatment. Nevertheless, specific guidelines regarding the length of antifungal treatment, especially in patients who continue immunosuppressive treatment for underlying diseases, are lacking. Of note, a relapse after discontinuation of fluconazole therapy is rare [1]. Notably, the first patient had quite a remarkable recovery from the cryptococcal meningitis despite having to continue immunosuppressive therapy. The second patient succumbed to infectious and medical complications, and not to uncontrolled cryptococcal disease, as illustrated by his repeated lumbar puncture results. He exemplified the wide range of medical complications that can obstruct the treatment of cryptococcal meningitis. The patients' complications were either secondary to the disease itself (hyponatremia, absence, and encephalopathy) or to the treatment (worsening kidney function, hypokalemia and hypomagnesemia), and finally because of his frailty (myocardial infarction, pulmonary edema, hospital-acquired infections).

In conclusion, we present two CLL patients who developed cryptococcal meningitis even though they were not treated with fludarabine. The therapeutic dilemmas are presented and discussed considering the lack of sound evidence due to the rare occurrence of cryptococcal meningitis during the course of CLL.

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