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Case Report

Leukemic and cryptococcal meningitis in an alemtuzumab-treated chronic lymphocytic leukemia patient - a case report

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Abstract. Patients with chronic lymphocytic leukemia (CLL) have very heterogeneous evolution and clinical manifestations. Although the presence of leukemic infiltration in isolated organs is common in CLL, central nervous system involvement is extremely rarely seen. The impaired immune system due to the disease and to the immunosuppressive treatments makes CLL patients susceptible to opportunistic infections. We here report the case of a 52 year-old man with CLL, treated with multiple therapeutic lines including significantly immunosuppressant drugs fludarabine and alemtuzumab, who developed simultaneous leukemic and cryptococcal meningitis. Both conditions are rarely seen and to our knowledge their simultaneous occurrence has not been previously reported.

Key Words: *Cryptococcus neoformans*, chronic lymphocytic leukemia, meningitis.

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Introduction

Chronic lymphocytic leukemia (CLL) is a heterogeneous disease, with a large array of clinical behaviors, ranging from fortuitously discovered asymptomatic disease, to a rapidly progressive course, with enlarged lymph nodes, severe infections and ultimately, bone marrow failure. Central nervous system (CNS) involvement, however, is exceedingly rare, with only 89 previous reported patients in the literature (de Souza et al 2014). Impaired immune response occurs mainly through lymphocyte dysfunction, hypogammaglobulinemia, and neutropenia, related to the primary disease, but also to the therapy. These inherent immune defects make infections with encapsulated bacteria a common complication (Tsiodras et al 2000).

Cryptococcus neoformans is an encapsulated fungus responsible for cryptococcal meningoencephalitis, one of the most important HIV-related opportunistic infections, resulting in more than 600000 deaths per year (Park et al 2009). An adequate quantity and quality of T-cells is required to mount a proper defense against *C. neoformans* (Crowe et al 1991), which makes CLL a much less-likely independent risk-factor, when compared to AIDS.

Alemtuzumab is a humanized IgG1 monoclonal antibody that targets the human CD52 surface antigen. Alemtuzumab was approved in 2001 for use in patients with fludarabine-refractory CLL. Side effects include profound cellular immune dysfunction, with CD4 cell depletion, resulting in opportunistic infections similar to those seen in AIDS patients. Cytomegalovirus (CMV) reactivation appears to be the most common such complication, but cases of cryptococcal infections, affecting either lung or CNS, have been reported in both CLL and organ-transplant patients undergoing alemtuzumab treatment (Alinari et al 2007; Nosari 2012; Silveira et al 2007).

We here present the case of a CLL patient, treated with multiple lines including fludarabine and alemtuzumab, who developed simultaneous leukemic and cryptococcal meningitis. All patients of our Institute sign a comprehensive informed consent form including their agreement for the use of anonymised data or biological samples for research purposes.

Case description

A 54 year-old man, living in precarious hygiene conditions in the countryside, pigeon farmer and dog owner, with no relevant medical history, was referred by his general practitioner to the Oncology Institute Cluj because of generalized (i.e, bilateral axillary, laterocervical and inguinal) lymphadenopathy of 2-3 cm, of recent discovery. A left laterocervical node biopsy was performed and pathologic examination described a pattern typical of CLL/Small lymphocytic lymphoma, with diffuse infiltration with mature-looking lymphoid cells, positive for kappa chains, LCA, CD20, dim for CD79, and negative for lambda chains, CD25 and bcl-2. The patient did not return to the institute until 4 months later, and was since followed in the hematology department of the of the Oncology Institute Cluj. He was complaining of fatigue and clinical examination was similar to the one at diagnosis, with generalized lymphadenopathy of 1-2 cm. No hepatosplenomegaly was noted at that point. Full blood count

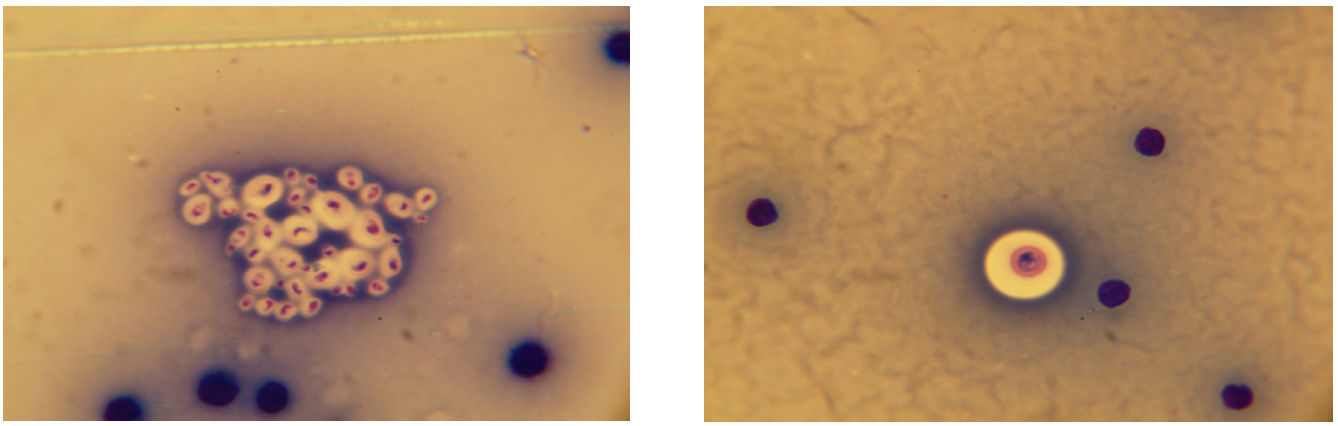

Fig. 1 – May Grunwald Giemsa stained cytology preparations of cerebrospinal fluid showing the presence of *C. neoformans* as encapsulated yeast and small mononuclear cells. Magnification 100x. Laboratory of hematology and cytology, Oncology Institute Cluj

(FBC) showed markedly elevated white cell count (WCC) at 229 G/L, of which 4% neutrophils and 96% lymphocytes (5% prolymphocytes), hemoglobin was slightly decreased at 11.8 g/dl, and platelet count was normal at 203 G/L. Erythrocyte sedimentation rate was slightly elevated at 31 mm/h. Also, elevated lactate dehydrogenases (LDH) and slight hyperuricaemia were noted. Liver function tests, as well as renal function, were normal. Monotherapy with chlorambucil 10 mg per day, continuously, was started. Five months later, clinical remission of peripheral lymphadenopathy was noted, WCC dropped to 18 G/L with 80% lymphocytes, 15% neutrophils, 4% monocytes and 1% blast cells. Hemoglobin became normal at 15,1g/dl, and platelets were normal at 179 G/L. Chlorambucil was recommended to be continued at the same dose, but, after a year of stable FBC, the WBC started to rise again to more than 100 G/L, obviously due to poor adherence of the patient to treatment. Restarting the treatment with chlorambucil led to a new hematologic response, with almost normal WCC.

It subsequently became obvious that the patient was only intermittently adhering to his treatment, with tumoral syndrome and lymphocyte counts varying from almost normal to more than 200 G/L, over the next 3 years. It also became obvious the disease exhibited a very rapid lymphocyte doubling time, with only short interruptions in treatment leading to steep increase in peripheral blood lymphocytes.

However, disease progressed overall, with the appearance of anemia, intermittently treated with erythropoiesis-stimulating agents. Almost four years after the initial diagnosis, fludarabine became an available treatment option, and the patient was put on single agent oral fludarabine at a dose of 7 mg daily for 5 consecutive days every month. At this point, the patient had generalized lymphadenopathy of up to 3 cm diameter, and a spleen 2 cm below the left costal margin. FBC showed a WCC at 36 G/L with 90% lymphocytes, hemoglobin of 9.5 g/dl, and 176 G/L platelets, equivalent to a progression to stage Rai 3 from a Rai 1 at diagnosis.

After 8 months of oral fludarabine, the patient presented progressive disease, with slightly increasing lymphadenopathy up to 3 cm diameter, but an evolving splenomegaly at 12 cm under the left costal margin, prompting the application for alemtuzumab treatment, which was obtained two months later (and four and a half years after the initial diagnosis). At the start of alemtuzumab treatment, the FBC showed 114 G/L white blood cells (WBC), with 90% lymphocytes, a slight anemia with a hemoglobin of 11.2 g/dl, and a normal platelet count of 183 G/L. LDH were elevated at 1011 U/L. Liver function tests were normal. Alemtuzumab was administered according to the standard schedule, starting with three progressive doses on alternate days during the first week, to reach the standard dose of 30 mg per day, which is then maintained 3 times a week over the next weeks. Antipnemocystis and antiviral prophylaxis were administered (co-trimoxazole 800 mg per day, 3 days a week, and acyclovir 400 mg twice daily).

Treatment was well tolerated, but clinical response in terms of tumoral syndrome was not noted, and WBC and lymphocyte count were increasing progressively, prompting re-introduction of chlorambucil and stopping alemtuzumab.

Ten weeks later, and 5 years after the initial diagnosis of CLL, the patient was admitted with malaise, night sweats, headache, vomiting, lethargy, confusion, personality changes, restlessness, prompting a lumbar puncture, which revealed the presence of lymphocytes and an encapsulated fungus. The cerebrospinal fluid (CSF) cytology preparation was performed in the ctytology laboratory of the Oncology Institute Cluj, according to a classical method involving smears of CSF sediments obtained by centrifugation, and fixed using eggwhite (Fig. 1).

Immunophenotypic analysis of lymphocytes from cerebrospinal fluid (CSF) identified the same CLL immunophenotype, matching findings from circulating lymphocytes. Rapid latex identification was performed by the microbiology laboratory of the Infectious Diseases Clinical Hospital, as well as subsequent CSF cultures, identifying *C. neoformans* as the aforementioned encapsulated fungus. Antifungal susceptibility test showed susceptibility to fluconazole and posaconazole. The patient was HIV-negative. Antifungal therapy with high dose intravenous fluconazole 800 mg daily was promptly started, according to international treatment guidelines for cryptococcal meningoencephalitis (Chen et al 2014), on an inpatient basis. CSF was sterile 6 weeks later and 50 mg of intrathecal cytarabine administration was initiated to manage the leukemic meningitis. The patient was discharged with oral fluconazole, 400 mg daily. The patient returned one month later to our hospital with severely altered general state and shortly died in microbiologically undocumented, presumed septic shock. No hematological workup was performed. At the family request, a post mortem was not performed.

Discussion

CLL seldom affects the CNS or leptomeninges, and even more rarely neurological manifestations are present. Although

meningeal invasion by B-cell CLL was discovered in 20% of cases by a large autopsy series, clinical syndromes remain exceedingly rare, which shows that neurological infiltration with CLL B cells is underdiagnosed (Barcos et al 1987; Marmont 2000; Weizsaecker et al 1979). CNS lymphocytic invasion, when symptomatic, typically leads to altered mental status, cranial nerve abnormalities, optic neuropathy and cerebellar dysfunction. Long term survival may be related to the stage of disease when CNS involvement is detected and intrathecal chemotherapy may be required (Weizsaecker et al 1979).

It remains difficult to prove beyond any doubt whether our patient's clinical syndrome was caused by the leukemic or the infectious component of meningitis. However, considering the rarity of clinically manifest CLL meningitis, it seems more likely that *C. neoformans* was responsible for this complication becoming symptomatic. Thus, it stands to reason that, if the opportunistic infection had not occurred, diagnosis of leukemic meningitis would have been delayed.

C. neoformans and *C. gatii* are the two pathogenic species of the Cryptococcus genus of encapsulated yeasts. It has significantly risen to attention, during the last half-century, from being very rare human pathogens, with barely more than 300 cases of cryptococcosis reported before 1955, to becoming a common world-wide opportunistic pathogen, as immunocompromised human populations have increased dramatically over the past two decades (Park et al 2009).

Of these immunocompromised populations, it is the T-cell deficient which bears the brunt of cryptococcoses world-wide, most notably HIV-patients. Cryptococcal infection, be it lung, CNS or any other less common site, seldom appears as a complication of CLL, because it is primarily humoral immunity that is impaired in this disease. The largest case series published consists of 41 patients with cryptococcal meningoencephalitis and neoplastic disease in which the majority consisted of CLL patients (Kaplan et al 1977), of note, at a time when profoundly immunosuppressive therapy like fludarabine and alemtuzumab was not available.

In our patient's case, immunity was compromised not only due to his underlying disease, but also because of the treatment. Alemtuzumab, an anti-CD52 monoclonal antibody used both in fludarabine-resistant CLL patients and as an immunosuppressant in transplant patients, is known to potentially deplete CD4 lymphocytes, making these patients susceptible to HIV-specific opportunists (Alinari et al 2007). Cryptococcosis in alemtuzumab-treated patients has already been described, in CLL (Henn et al 2013), but more often in alemtuzumab-treated solid organ transplant recipients (Silveira et al 2007). This studies show an association between cryptococcosis cumulative incidence and the number of alemtuzumab doses received. However, our patient received also fludarabine, a significantly immunosuppressant drug, which may also have contributed to the serious infectious disease.

We here reported a rare association of crypococcal meningoencephalitis with CLL meningeal involvement, which, to our knowledge, has not been reported before. We reckon the rarity of this condition might be in part attributable to underdiagnosing. Moreover, with the prospects of even more intensive and immunosuppressive hematologic and oncologic therapy, the incidence of both conditions is likely to increase.

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