Case Study

Tuberculous Meningoencephalitis in a Patient with Hairy Cell Leukemia in Complete Remission

Girardi K,¹⁾ Paviglianiti A,¹⁾ Cirillo M,²⁾ Bianchi A,²⁾ Gherardi G,³⁾ Annibali O,¹⁾ Cerchiara E,¹⁾ Marchesi F,¹⁾ Tomarchio V,¹⁾ Miglio C,⁴⁾ Tirindelli MC,¹⁾ Onetti Muda A,²⁾ and Avvisati G¹⁾

Tuberculous meningoencephalitis is a rare disease associated with high morbidity and mortality. We report a patient with hairy cell leukemia in complete remission who, after a single cycle of chemotherapy with cladribine, presented fever and neurological deficits. Laboratory diagnosis of tuberculous meningoencephalitis was made by polymerase chain reaction testing for *Mycobacterium tuberculosis* in cerebrospinal fluid. Despite the prompt institution of antitubercular-therapy, patient's general condition did not improve and he died. Mycobacterial infection should be considered in patients with intra-cranial lesions, affected by hematological malignancies and persistent immunosuppression. [*J Clin Exp Hematopathol* 52(1) : 31-34, 2012]

Keywords: tuberculosis, meningoencephalitis, mycobacterium, hairy cell leukemia, cladribine

INTRODUCTION

Tuberculosis (TBC) meningoencephalitis represents 1.3% of all TBC cases and 6.3% of extrapulmonary TBC.¹ It may be observed in patients with hematological malignancies or after stem cell transplantation, because of a severely impaired host immunity.²⁻⁶ We describe a patient with hairy cell leukemia who, after a single cycle of chemotherapy with cladribine, despite the achievement of complete remission (CR), experienced central nervous system (CNS) TBC and died.

CASE REPORT

A 57-year-old Caucasian man was diagnosed and treated for hairy cell leukaemia (HCL) on March 2009. The patient received a single course of chemotherapy consisting of a five-days administration of cladribine at the dose of 0.14 mg/Kg/day achieving a CR of disease. Antiviral prophylaxis with

acyclovir was started at the initiation of chemotherapy and antibacterial prophylaxis with fluoroquinolones was also administered during neutropenia, lasting four weeks. The patient did not have a history of pulmonary TBC and there was no evidence of pneumonia during the treatment. Two months after the achievement of CR, he was re-admitted to the hospital, because of the appearance of syncope with urinary and fecal incontinence, high fever and confusion. Neurological examination revealed confusion, spatiotemporal disorientation, dysarthria, bilateral dysmetria and a positive result at 'finger to nose test'.

The laboratory evaluation revealed: hemoglobin 11.6 g/dL, white blood cells 7,460/ μ L with neutrophils 7,060/ μ L, lymphocytes 230/ μ L, and platelets 166,000/ μ L. The others laboratory findings were in the normal range except for: serum sodium 125 mmol/L, hyper- α_2 -globulinemia with hypo- γ -globulinemia at serum electrophoresis and hypoalbuminemia (serum albumin 2.5 g/dL). Cytomegalovirus, toxoplasma, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus 1 and 2 and parvovirus B19 serum IgM were all negative. Tuberculin skin test or QuantiFERON (R)-TB test were not performed because of the low sensitivity in immunocompromised patients.⁷ A first lumbar puncture revealed proteinorrachia (2.780 mg/dL) and hypoglycorrachia (17 mg/dL). The cerebrospinal fluid (CSF) examination showed the presence of white blood cells represented by 100% of lymphocytes and no neutrophils; no bacterial or fungal infec-

Received : June 23, 2011

Revised : October 21, 2011

Accepted : November 1, 2011

¹⁾Department of Hematology, Transfusion Medicine and Cellular Therapy, ²⁾Department of Pathology, ³⁾Department of Laboratory Medicine, and ⁴⁾Department of Radiology, University Campus Biomedico, Rome, Italy

Address correspondence and reprint request to Girardi Katia, M.D., Department of Hematology, Transfusion Medicine and Cellular Therapy, University Campus Biomedico, Rome, Italy

E-mail : k.girardi@unicampus.it

tious pathogens were found in CSF culture and research of pathogen viruses in CSF performed by polymerase chain reaction (PCR) techniques was negative. Despite computed tomography scan of the brain showed no alterations, electroencephalogram showed diffuse aspecific abnormalities.

The patient was treated with meropenem and acyclovir at standard dose with no improvement. Therefore, a second lumbar puncture was performed and proteinorrachia with lymphocytosis was confirmed. CSF culture for the research of *Mycobacterium tuberculosis* (MTB) was negative, while PCR performed in the CSF revealed the presence of MTB.

As a consequence, a combination therapy for CNS TBC consisting in isoniazide, rifampicin, pyrazinamide and ethambutole was initiated; however, patient's general condition did not improve. A cranial magnetic resonance imaging scan was performed, revealing the presence of numerous small enhancing lesions in both cerebral and cerebellar hemispheres (Fig. 1). Despite the anti-TBC therapy, the patient's general conditions rapidly deteriorated and he died after 23 days from the admission in hospital.

The autopsy revealed bilateral pulmonary edema that was considered the immediate cause of death. The leptomeninges were thickened around cranial vault, and characterized by white and gelatinous membranes, due to an inflammatory infiltrate. In addition, there was cerebral softening in the right temporo-parietal and frontal lobes. The histological examination documented an inflammatory infiltrate in meninges and choroid plexus (Fig. 2A): immunohistochemistry revealed that the majority of the infiltrating lymphocytes were of the T origin (Fig. 2B). The cerebral softening was determined by caseating necrosis containing acid-fast bacilli. No

disseminated foci of TBC in other regions were observed. Histologic examination of spleen, liver and bone marrow of several vertebrae, was repeatedly negative for hairy cell leukemic cells, confirming the CR of the disease after a single course of cladribine.

DISCUSSION

TBC occurring after chemotherapy causes a more severe infection with a high mortality rate. The case reported here is, to the best of our knowledge, the first example of TBC with exclusive cerebral involvement in a patient affected by hairy cell leukemia treated with cladribine, although TBC *per se* is not a rare event in such patients.

In fact, several cases of pulmonary and disseminated TBC are described in literature⁸⁻¹² while a few reports of isolated extrapulmonary cases are documented suggesting that this event is rare. However, no case of isolated CNS TBC, to date, is described in literature.^{13,14} MTB is able to hijack the intracellular mechanisms of pathogen killing in macrophages creating an ideal environment for replication and growth.¹⁵ Memory cells will be present until the death of the infected subject. The T cells' repertoire will form the main response leading to granuloma formation and infection containment, influencing susceptibility to or protection from the disease. Immunosuppression and alteration in cell-mediated immunity (i.e. lymphoproliferative disease) by the generalized systemic immunologic impairment and chemotherapy lead to reactivation of TBC later in the course of neoplastic diseases.^{16,17} In fact, the natural history of HCL includes frequent and severe infections. Studies of the immune system of patients with

Fig. 1. Cranial magnetic resonance imaging. (1A) The cranial magnetic resonance imaging revealed the presence of numerous small enhancing lesions in both cerebral and cerebellar hemispheres. (2B) T2-weighted sequences TSE documented meningeal thickening, caused from diffuse leptomeningeal inflammation.

Fig. 2. Histological findings. (2A) Histological examination of brain parenchyma showed an infiltration of lymphocytes that follow the vascular pattern. (2B) Evidence of acid-alcohol fast bacilli by Ziehl-Neelsen stain in brain parenchyma allowed to confirm the diagnosis of tuberculous meningoencephalitis.

HCL identified several potential reasons, including profound neutropenia and monocytopenia.¹⁸ However, Damaj *et al.*¹⁹ demonstrated that the most important risk factor is the absolute lymphocyte count ($< 1 \times 10^9/L$) at diagnosis.¹⁹

In addition, treatment including chemotherapy and splenectomy further compromised the immune system. Cladribine, an adenosine deaminase resistant nucleoside analog, is converted in cells to its active triphosphate, that progressively accumulated resulting in an unbalance in purine pools, which prevents DNA repair and may be the most important mechanism of its antitumor effect in replicating and nonreplicating cells.²⁰ Cladribine is the most myelosuppressive of purine analog and causes a pronounced lymphopenia and lymphocyte dysfunction, which may persist up to 8 months after treatment.^{21,22} In particular, after therapy with cladribine, it has been observed a rapid reduction of CD4 cells, which decrease within 2 to 3 months of therapy to levels similar to those observed in acquired immunodeficiency syndrome.²³ Petzer *et al.*²⁴ incubated human bone marrow cells with cladribine and documented a dose-dependent inhibition of T-lymphocyte colony forming cells. In addition purine analogue therapy causes a transient monocytopenia and reduction in natural killer cells.¹⁸ All these factors increase the risk of opportunistic infections, including TBC.

An early diagnosis and a prompt institution of antitubercular-therapy are important for succeeding in the treatment. Therefore, it is important to have rapid, sensitive, specific, and cost-effective assays to provide results within 24-48 hours.²⁵ Isolation of MTB from CNS samples requires 2-6 weeks and it is insensitive if large amounts of CSF (a

minimum of 6 mL of CSF fluid) are not tested. Current technology includes PCR testing for MTB CSF with sensitivity of 48% and specificity of 100%, respectively, compared to 39% and 100% of culture alone. Very recently the commercial availability of PCR has given even better results as for sensitivity is regarded.²⁶ The PCR test has been found to be a potential test for the diagnosis of cerebral TBC with no involvement of the meninges in human immunodeficiency virus-infected patients. However, these promising findings must be interpreted against a background of false positive and false negative results; therefore, the gold-standard for the diagnosis is histology.

The basic principles that underly the treatment of pulmonary TBC also apply to extrapulmonary forms of the disease. Although relatively few studies have examined treatment of extrapulmonary TBC, increasing evidence suggests that 9-12 months regimens that include isoniazide and rifampicin is recommended for tuberculous meningoencephalitis.¹ Centers for Disease Control recommends the addition of corticosteroids, even though it is controversial: the rationale behind the use of corticosteroids is to reduce the harmful effects of inflammation. On the other hand, by reducing inflammation, steroids can in turn effect the penetration of antitubercular drugs into the CSF and interfere with the interpretation of CSF studies.

The development of multiple intracranial lesions in a patient with hematological disease requires a comprehensive search for unusual opportunistic infections, including MTB. Prompt institution of antitubercular-therapy, within 24-48 hours from the onset of symptoms, is essential to avoid mor-

bidity and mortality, even if the laboratory tests did not demonstrate the presence of alcohol-fast bacillus in samples. Determining which assays will be most useful to the clinician is a challenge. CSF cell count, microscopy, nucleic acid amplification, detection of growth in culture, DNA probes, PCR assays and neuroimaging play an important role in the diagnosis of CNS TBC.

Clinicians and microbiologists must work together in a synergistic network to ensure the most appropriate care for their patients. The case described by us is peculiar because the CNS TBC developed while the patient was in CR and despite the initiation of antitubercular therapy the patient died, indicating that the immunosuppression caused by cladribine was deep and persisting despite the achievement of CR.¹² Interestingly, patients with multidrug-resistant tuberculous meningitis show little or no clinical improvement with standard TBC treatment and their prognosis is poor. Furthermore, at least 10% of patients with tuberculous meningitis have paradoxical deterioration after treatment initiation. Therefore, it remains to be determined whether or not all HCL patients treated with cladribine or other antineoplastic drugs should receive anti-TBC prophylaxis.

REFERENCES

- 1 CDC 2005: Extrapulmonary tuberculosis cases and percentages by site of disease : reporting areas, 2005. Centers for Disease Control and Prevention, Atlanta, GA
- 2 Heath PD, Grant JW: Intracranial infection due to *Mycobacterium bovis* in Hodgkin's disease. *Br Med J* 288:465-466, 1984
- 3 Shet AS, Saba N, Raush D, Belzer M: Intra-cranial lesions in a patient with Hodgkin lymphoma. *Leuk Lymphoma* 45:419-422, 2004
- 4 Campos A, Vaz CP, Campilho F, Morais A, Guimaraes MA, *et al.*: Central nervous system (CNS) tuberculosis following allogeneic stem cell transplantation. *Bone Marrow Transplant* 25:567-569, 2000
- 5 Roy V, Weisdorf D: Mycobacterial infections following bone marrow transplantation : a 20 year retrospective review. *Bone Marrow Transplant* 19:467-470, 1997
- 6 Richeldi L, Losi M, D'Amico R, Luppi M, Ferrari A, *et al.*: Performance of tests for latent tuberculosis in different groups of immunocompromised patients. *Chest* 136:198-204, 2009
- 7 Bennett C, Vardiman J, Golomb H: Disseminated atypical mycobacterial infection in patients with hairy cell leukemia. *Am J Med* 80:891-896, 1986
- 8 Gallo JH, Young GA, Forrest PR, Vincent PC, Jennis F: Disseminated atypical mycobacterial infection in hairy cell leukemia. *Pathology* 15:241-245, 1983
- 9 Au WY, Kwong YL, Ma SK, Mak YK, Wong KF, *et al.*: Hairy cell leukemia in Hong Kong Chinese : a 12-year retrospective survey. *Hematol Oncol* 18:155-159, 2000
- 10 Richeldi L, Luppi M, Losi M, Luppi F, Potenza L, *et al.*: Diagnosis of occult tuberculosis in hematological malignancy by enumeration of antigen-specific T cells. *Leukemia* 20:379-381, 2006
- 11 Alvarez M, Berdonces P, Rojo P, Beltrán de Heredia JM, Zumarraga I, *et al.*: Pulmonary infection caused by *Mycobacterium szulgai* in a patient with hairy-cell leukemia. *Enferm Infecc Microbiol Clin* 10:433-434, 1992 (*in Spanish*)
- 12 Panchovska MS, Solakov PT, Anavi BL, Spasov EA, Tokmakova KP, *et al.*: Wrist tuberculosis in cladribine—induced remission of hairy cell leukosis. *Folia Med (Plodvid)* 42:37-40, 2000
- 13 Thorel JB, Grosbois B, Paris G, Schneebeil S, Goasguen J, *et al.*: Leukocytoclastic vasculitis and hepatic tuberculosis disclosing hairy cell leukemia. *Rev Med Interne* 9:530-533, 1988 (*in French*)
- 14 Salgame P: Host innate and Th1 responses and the bacterial factors that control *Mycobacterium tuberculosis* infection. *Curr Opin Immunol* 17:374-380, 2005
- 15 Boom WH, Canaday DH, Fulton SA, Gehring AJ, Rojas RE, *et al.*: Human immunity to *M. tuberculosis* : T cell subsets and antigen processing. *Tuberculosis* 83:98-106, 2003
- 16 Ferrara G, Losi M, Fabbri LM, Migliori GB, Richeldi L, *et al.*: Exploring the immune response against *Mycobacterium tuberculosis* for a better diagnosis of the infection. *Arch Immunol Ther Exp* 57:425-433, 2009
- 17 Cheson DB: Perspectives on purine analogues. *Hematol Cell Ther* 38 (Suppl 2):S109-116, 1996
- 18 Kraut E: Infectious complications in hairy cell leukemia. *Leuk Lymphoma* 52 (Suppl 2):50-52, 2011
- 19 Damaj G, Kuhnowski F, Marolleau JP, Bauters F, Leleu X, *et al.*: Risk factors for severe infection in patients with hairy cell leukemia : a long-term study of 73 patients. *Eur J Haematol* 83:246-250, 2009
- 20 Betticher DC, Fey MF, von Rohr A, Tobler A, Jenzer H, *et al.*: High incidence of infections after 2-chlorodeoxyadenosine (2-CDA) therapy in patients with malignant lymphomas and chronic and acute leukaemias. *Ann Oncol* 5:57-64, 1994
- 21 Samonis G, Kontoyiannis DP : Infectious complications of purine analog therapy. *Curr Opin Infect Dis* 14:409-413, 2001
- 22 Steis RG, Urba WJ, Kopp WC, Alvord WG, Smith JW 2nd, *et al.*: Kinetics of recovery of CD4⁺ T cells in peripheral blood of deoxycytosine-treated patients. *J Natl Cancer Inst* 83:1678-1679, 1991
- 23 Petzer AL, Bilgeri R, Zilian U, Haun M, Geisen FH, *et al.*: Inhibitory effect of 2-chlorodeoxyadenosine on granulocytic, erythroid, and T-lymphocytic colony growth. *Blood* 78:2583-2587, 1991
- 24 Bhigjee AI, Padayachee R, Paruk H, Hallwirth-Pillay KD, Marais S, *et al.*: Diagnosis of tuberculous meningitis : clinical and laboratory parameters. *Int J Infect Dis* 11:348-354, 2007
- 25 Baker CA, Cartwright CP, Williams DN, Nelson SM, Peterson PK: Early detection of central nervous system tuberculosis with the gen-probe nucleic acid amplification assay : utility in an inner city hospital. *Clin Infect Dis* 35:399-342, 2002