negative at the end of the induction phase. She was still negative 38 months after diagnosis. The BM at the time of relapse showed a positive signal, revealing BM infiltration despite the morphologic negativity. The sequence obtained from the lymph node showed complete homology with the sample taken at diagnosis.

Most relapses occur within four years of diagnosis and involve an extramedullary site other than the CNS and testis in less than 2% of cases. Our case relapsed in 2 extramedullary sites as bulky disease. Even though BM analysis at the time of relapse had a positive PCR signal, according to standard criteria this cannot be considered as a BM relapse. The patient showed early and continuous molecular negativity at consecutive time-points. According to recent studies on MRD in ALL, this pattern should be considered as a positive prognostic factor. There is no satisfactory explanation of this late, unusual relapse. We can hypothesize that the pharmacological treatment did not eradicate the leukemic clone completely, but merely reduced the disease to a level not detectable by the probe. A second hypothesis is that some cells escaped the impact of chemotherapy in a protected site (sanctuary) and became no longer detectable as residual cells in the bone marrow.

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Key words
Leukemia, late relapse, gene rearrangement, T-cell receptor.

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References

Cryptococcal meningitis during front-line chemotherapy for acute lymphoblastic leukaemia

Fungi cause opportunistic infections in immunocompromised patients. In the case of Cryptococcus neoformans infection, diffusion to meninges is a typical occurrence. We report the case of a 13-year-old child who owned a lovebird and who developed cryptococcal meningitis during chemotherapy for intermediate risk acute lymphocytic leukemia.

Sir,
The fungi responsible for the recent increase in mycoses are those causing opportunistic infections, including Cryptococcus neoformans. In children undergoing bone marrow transplantation or chemotherapy for malignancies, prolonged neutropenia (absolute neutrophil count, ANC, <500/m3), mucosal breakdown, impairment of cell-mediated immunity, widespread use of broad-spectrum antibiotics, and central venous catheters are the major causes of fungal opportunistic infections, especially in case of long-term treatment with corticosteroids and/or prolonged hospitalization.1,2 Cryptococcus neoformans is widely diffused.

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encapsulated yeast isolated worldwide from soil, usually in association with bird droppings, primarily of pigeons and parrots. These ejective and asymptomatic hosts are vectors of infections especially if they closely share habitat with men as in the case of lovebirds (Agapornis). Inhalation of fungal spores is usually the initial event of cryptococcosis which is primarily an asymptomatic, pulmonary infection, remaining localized to that site in immunocompetent subjects. In immunocompromised hosts, however, the infection may disseminate and meningitis represents the most typical manifestation.  

We report the case of a 13-year old child who owned a lovebird, and who developed cryptococcal meningitis during the induction phase of AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) ALL-9502 protocol for treatment of intermediate risk acute lymphocytic leukemia (ALL) (prednisone, vincristine, daunomycin, L-asparaginase and triple intrathecal therapy with methotrexate, prednisone and cytosine arabinoside, after 7 days of prednisone at increasing dose). 

Thirty-five days after beginning therapy, in a condition of bone marrow hypoplasia, but not of neutropenia (WBC 3,300/m3, ANC 1,120/m3), the patient developed persistent hyperpyrexia associated with bronchopneumonia. Despite 18 days of empirical antibiotic therapy with ceftriaxone (100 mg/kg/day) alone, followed by ceftriaxone plus amikacin (20 mg/kg/day), teicoplanin (10 mg/kg/day) plus amikacin, and clarithromycin (10 mg/kg/day) plus imipenem (60 mg/kg/day), the fever persisted and patient’s clinical status worsened with onset of headache, nausea, vomiting and psychomotor disturbances up to the appearance of seizures, syndrome of inappropriate secretion of ADH, and isolated deficit of the VI cranial nerve.

On the basis of lumbar puncture results (protein 0.6 g/L, glucose 0.42 g/L and 50 lymphocytes/m3), the ineffectiveness of the antibiotic therapy, and the history of cohabitation with a lovebird, a search for fungal infections was initiated (India ink smear, serum antigen titer assessment, cerebrospinal fluid (CSF) antigen titer assessment and cultures) and was positive for Cryptococcus neoformans. Therapy with liposomal amphotericin B (1 up to 3 mg/kg/day) plus fluconazole (150 mg/kg/day) was promptly initiated and maintained for 7 weeks until complete clinical resolution. At that time reinforced consolidation chemotherapy was restarted, and contemporaneously the patient received fluconazole 10 mg/kg/day. Serum and CSF antigenic titers remained high (1:1024 and 1:32, respectively) during the first 5 months of treatment with fluconazole, then subsequently decreased progressively and after 12 months became negative (1:2 and 1:4, respectively). After 19 months of treatment, fluconazole was stopped.

After 2 years of follow-up, the patient is alive and well in first complete remission and serum and CSF antigenic titers remain negative.

A front-line chemotherapy for leukemia based on long-term steroid treatment may damage cell-mediated immunity, which represents the most important host defence against fungi. For this reason, cryptococcosis should be suspected in every case of hyperpyrexia and persistent headache, especially when associated with bronchopneumonia, in all leukemic patients receiving front-line chemotherapy. Careful enquiries should be made about exposure to birds.

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Key words
Childhood acute lymphoblastic leukemia, meningitis, Cryptococcus neoformans.

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References

Chromosomal instability in chronic myeloid leukemia: Philadelphia breakpoints are independent of spontaneous breakage and fragile sites

Increased frequencies of spontaneous and bromodeoxyuridine induced breakages with a non-random distribution of breakpoints were found in patients with chronic myeloid leukemia.