. Case reports

Listeriosis after fludarabine treatment for chronic lymphocytic leukemia

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Abstract

The authors report a case of *Listeria monocytogenes* septicemia in a patient with advanced CLL after a single course of fludarabine, without any other immunosuppressive therapy e.g. corticosteroids. The immunosuppressive action of fludarabine in patients who are already severely immunosuppressed must be considered from a diagnostic and therapeutic point of view. Listeriosis and other opportunistic infections, like pneumocystis carinii pneumonia, have been reported during and after treatment with purine analogues. Prophylaxis with cotrimoxazole must therefore be discussed in patients with CLL treated with fludarabine.

Various infections have been observed in patients with chronic lymphocytic leukemia (CLL) after treatment with the purine analogue fludarabine [3, 11].
We report the case of a patient with advanced CLL who developed a *Listeria monocytogenes* (LM) infection early after fluradabine therapy.

Case report

A 69-year-old woman with a 15-year history of CLL was hospitalized for disease progression, with multiple lymph nodes and spleen enlargement. The white blood cell count was 150 x 10^9/l (98% lymphocytes, 2% neutrophils), the hemoglobin level was 75 g/l and the platelet count was 75 x 10^9/l (Binet stage C). Her disease proved to be refractory to conventional treatment: daily chlorambucil for several years followed by 4 courses of cyclophosphamide, adriamycin, vincristine and prednisone; the last in March 1995.
In July 1995, she received a first cycle of treatment with fludarabine (25 mg/m^2 daily for 5 days) without any other immunosuppressive therapy such as corticosteroids.
Fifteen days later, she developed fever (39° C). The history and physical examination were unremarkable; specifically there was no headache or nuchal rigidity. Lumbar puncture was not performed. Laboratory data showed neutropenia (WBC: 40 x 10^9/l with 2% neutrophils: 0.8 x 10^9/l), anemia (Hb: 90 g/l) and thrombocytopenia (53 x 10^9/l). Two days later, blood cultures grew *Listeria monocytogenes*.
Because of penicillin allergy, trimethoprim-sulfamethoxazole (TMP-SMZ) was given (320/1600 mg orally for 21 days) the patient became apyrexial within 48 h.
The absolute CD4 lymphocyte count was 1.6 x 10^9/l with a high absolute CD8 count (4.5 x 10^9/l). No other case of listeriosis was noted in the family or in the neighborhood where the patient lived.
Antibacterial prophylaxis with TMP-SMZ was given (160/800 mg orally daily) to prevent infections during and after four further fludarabine cycles.

Discussion

Recently, Anaissie et al [1] reported an increased incidence of listeriosis in patients with CLL treated with fludarabine and prednisone. In this large series, all the patients who had listeriosis after fludarabine treatment (7/248) had also received prednisone. No patient who had received therapy with fludarabine alone (without corticosteroids) developed a LM infection. In contrast, our patient did not receive any corticosteroid during fludarabine therapy before developing listeriosis. One similar case has been described with a listerial brain abscess occurring several months after eight cycles of fludarabine alone [4].

Our patient had been treated with only one cycle of fludarabine before developing listeriosis. However, several features led us to think that fludarabine might be a risk factor for the development of the infection. The patient had never had any infection since the beginning of her malignant disease many years ago nor any infection after several courses of chemotherapy.

Fludarabine has been shown to lower all blood lineages, but the greatest effect concerns the CD4 cells [3, 9]. O'Brien et al reported that the decrease of the CD4 lymphocyte count usually occurs after 3 cycles of fludarabine treatment [9]. Anaissie et al. found a decreased CD4 lymphocyte count in the majority of their patients with listeriosis (4/5) (but the interval between the last course of fludarabine and listeriosis was not specified) and suggested that this low count was a possible pathogenic factor for LM infection [1]. The absolute CD4 lymphocyte count in our case was normal immediately after listeriosis. Another case of listeriosis after fludarabine with a normal CD4 lymphocyte count has been reported [4]. Other opportunistic infections such as pneumocystis carinii pneumonia (PCP) have been described after a single course of fludarabine [2].

The importance of immunodepression exposing the patient to the risk of listeriosis does not seem directly related to the number of CD4 lymphocytes [6]. This suggests that other cell-mediated immune functions, which could be deficient after fludarabine, might play a role in the development of listeriosis. The low prevalence of listeriosis among HIV-infected patients supports this hypothesis. To our knowledge, about thirty cases of listeriosis in patients with the acquired immunodeficiency syndrome have been reported [5]. However, most of these patients had another immunosuppressive condition such as liver cirrhosis, non Hodgkin's lymphoma or were taking corticosteroids. A low CD4 lymphocyte count does not seem sufficient to enhance the development of LM infection. Several authors have suggested that another T-cell subset might provide an alternative antilisterial immune mechanism in humans [7]. The role of each T cell subset, of mononuclear phagocytes and of cytokines in listeriosis has been recently clarified by Milon [8]. In reaction to LM infection, two subsets of sensitized CD4 and CD8 cells elaborate interleukin-12 or alpha -interferon, which activate macrophages, neutrophils or natural killers by several pathways. In addition to the decrease in CD4 lymphocytes, fludarabine might create a deficiency in mediators implicated in this immune response. In our case, we observed an increased CD8 lymphocyte count, the CD4/CD8 ratio was 0.35 and the monocyte count was 2200/mm^3.

To prevent listeriosis after purine analogue therapy, multiple prophylactic options are of interest. Food known to contain LM such as vegetables, dairy products and undercooked meats could be forbidden. The exclusion of steroids from treatment regimens including fludarabine should be considered because fludarabine-therapy combined with corticosteroids leads to an increased risk for listeriosis compared with fludarabine alone and does not provide any advantage for achievement of a remission [9].

Similar features have been observed concerning PCP. TMP-SMZ may be used for prophylaxis of both PCP and listeriosis. Penicillin or ampicillin alone or in combination with an aminoglycoside is the gold standard for the treatment of serious infections caused by LM. TMP-SMZ has been used for the treatment of listeriosis in both immunosuppressed and immunocompetent hosts. The advantages of TMP-SMZ over other antilisterial agents include its bactericidal activity which contrasts with the bacteriostatic action of ampicillin and its high concentrations in CSF [10]. PCP and listeriosis in patients with CLL have been reported early after fludarabine treatment or later, several months after the end of purine analogue therapy [6]. Therefore, the length of the risk period for these infections can not be predicted. This supports antilisterial and antipneumocystis prophylaxis with TMP-SMZ in patients with CLL treated by fludarabine from the beginning of treatment.

From a diagnostic point of view, listeriosis must be considered in patients treated by purine analogue therapy and who develop fever or neurological signs.

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