PACT WITH THE DEVIL: ALEMTUZUMAB THERAPY, IMMUNE SUPPRESSION AND INFECTIOUS COMPLICATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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PACT WITH THE DEVIL: ALEMTUZUMAB THERAPY, IMMUNE SUPPRESSION AND INFECTIOUS COMPLICATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA (Abstract).
Infectious complications are an important cause of hospitalization in patients diagnosed with chronic lymphocytic leukemia. The pathogenesis of infection is complex, involving both disease-induced and treatment-related immune depression. During the last decade, the management of chronic lymphocytic leukemia (CLL) has been redefined by the approval of monoclonal antibody-based treatment, which resulted in improved therapeutic responses. Nonetheless, the profound lymphopenia induced by monoclonal agents was accompanied by increased incidence of infections caused by a new spectrum of opportunistic microorganisms. We report the case of a patient with hypercellular CLL who received Alemtuzumab as first line therapy and obtained a satisfactory therapeutic response, but developed subsequent atypical infectious complications. Keywords: CHRONIC LYMPHOCYTIC LEUKEMIA, ALEMTUZUMAB, IMMUNE SUPPRESSION, MYCOBACTERIUM TUBERCULOSIS, ATYPICAL INFECTION.

Infectious complications represent a significant cause of morbidity and mortality in patients diagnosed with chronic lymphocytic leukemia (CLL), infection-related mortality ranging between 30-50% (1).

The pathogenesis of infection is complex, involving both disease-induced and treatment-related immune depression. Immune depression determined by the natural course of the disease features hypogammaglobulinemia, T-cell subpopulations abnormalities, B-cell and neutrophil defects, as well as neutropenia through bone marrow involvement (2, 3). In addition to these preexisting abnormalities, specific therapy further increases the risk of infection by agent-specific effects on the immune system. Monoclonal antibodies represent a novel and innovative treatment approach in CLL, in combination with standard chemotherapy or in single-agent regimens. Alemtuzumab is a monoclonal antibody directed against CD 52, expressed on tumor cells, and normal B and T cells, and macrophages (4). Its introduction in CLL therapy has been linked to an in-
creased risk of viral infection, notably cytomegalovirus (CMV), opportunistic infections, prolonged lymphopenia and neutropenia, especially in pretreated patients or refractory disease (5,6). We report the case of a patient with hypercellular CLL who received Alemtuzumab as first line therapy with a satisfactory therapeutic response, but developed subsequent atypical infectious complications.

CASE REPORT

We present the case of a 41-year-old male patient with low socioeconomic status admitted to our hospital for general fatigue, night sweats and abdominal swelling experienced over the previous 3 months. Family and personal history were not significant. Physical examination revealed ECOG (Eastern Cooperative Oncology Group) performance status 2, splenomegaly 25 cm below the left costal margin, hepatomegaly 9 cm, and generalized adenopathy of 3 cm maximum diameter. The complete blood count revealed extreme hyperleukocytosis 934,000/mm³, lymphocytes 919,000/mm³, Hb 7.5 g/dl, and platelets 30,000/mm³. Biochemical analysis showed elevated LDH, uric acid, and erythrocyte sedimentation rate, with the rest of the parameters within normal range. Pulmonary radiography was normal. Flow cytometry identified a lymphoid population with specific CLL phenotype, CD 38 negative. Risk assessment at diagnosis was based on hyperleukocytosis, large tumor mass, elevated LDH, CD 38 negativity, and absence of deletion 17 p. Due to the large circulating tumor mass, the patient was considered high risk. Alemtuzumab was started in standard regimen of weekly administration for 12 weeks, inducing a partial response: normalized lymphocyte count, persistent spleno-megaly (24cm), hepatomegaly (8 cm), anemia and thrombocytopenia. In the eleventh week of treatment the patient developed a prolonged febrile syndrome. Alemtuzumab therapy was discontinued. The etiologic spectrum of febrile splenomegaly in this case included infection or CLL transformation to aggressive B-cell proliferation (Richter syndrome). Alemtuzumab therapy included the patient in the highest risk class for infection (grade 4 neutropenia (250/mm³) and lymphopenia). Cytomegalovirus (CMV) infection was ruled out by successive PCR determinations. Hepatitis viruses were absent, and empirical antiviral therapy with acyclovir and valaciclovir was ineffective. Repeated blood cultures remained negative throughout the 2 months of persistent fever. Broad spectrum antibiotics were unsuccessful. Invasive hepatosplenic fungal disease was highly unlikely due to normal ultrasound appearance, normal liver function tests and unresponsiveness to empirical antifungal therapy. Serology for leishmaniosis was negative. We considered the possibility of a mycobacterial infection. Diagnostic splenectomy and hepatic biopsy were performed to rule out the probability of Richter syndrome. Histopathologic examination and tissue cultures certified the presence of Mycobacterium tuberculosis. The general health status of the patient declined immediately after splenectomy, with persistence of the febrile syndrome and cholestasis. The pulmonary radiography revealed features of disseminated miliary tuberculosis. The patient was referred to the pulmonology department where standard tuberculostatic therapy was initiated (isoniazid, pyrazinamide, ethambutol, rifampicin) with prompt resolution of the febrile syndrome. Tuberculostatic treatment was continued for 9 months. The patient maintained the partial
therapeutic response for 2 years before disease recurrence through hyperleukocytosis and thrombocytopenia.

**DISCUSSION**

The major determinants of infection in CLL patients are tumor-associated immune deficiency and immunochemotherapy-related immunosuppression (3).

CLL specific immune deficiency features defects in humoral and cellular effector mechanisms, complement and neutrophil function. Hypogammaglobulinemia is a common finding (7).

Defects in cell-mediated immunity are mainly linked to T-cell dysfunction. Apart from purine analogue and alemtuzumab therapy, CD4+ and CD8+ T-cell defects are the direct effect of the malignant clone or cytokine secretion and include impaired intracellular signaling and cytoskeleton dysfunction reflected in modified motility, chemotaxis and deficient immune synapses (8, 9). Aberrant populations of suppressor T cells and Th2 responses have also been reported (3).

NK cell and monocyte dysfunction are being cited (10). Finally, neutrophils exhibit migration and phagocytic defects, while neutropenia becomes more prominent in the late stages of the disease through extensive bone marrow infiltration (2,3,7).

During the last decade the management of CLL has been redefined by the approval of monoclonal antibody-based treatment, which resulted in improved therapeutic responses. Nonetheless, the profound lymphopenia induced by monoclonal agents was accompanied by a corresponding increase in the incidence of infections caused by a new spectrum of opportunistic microorganisms (5).

Alemtuzumab is a humanized monoclonal antibody directed against the CD52 antigen expressed on both normal and malignant B CLL lymphocytes, NK cells, monocytes, macrophages and eosinophils. It is currently indicated as first line therapy in high risk patients associating 17p deletion and as salvage therapy for fludarabine-resistant disease (5, 6). Its mechanism of action is both complement and cellular-dependent. Alemtuzumab treated patients develop profound and prolonged (up to a year) lymphopenia, resulting in the increasing incidence of low CD4 count-associated infections. The degree of therapy-induced immunosuppression is also determined by CLL stage, previous chemotherapy regimens and treatment response. The spectrum of Alemtuzumab-associated infections ranges from banal bacterial infections, CMV reactivation (10-25%), varicella zoster virus, parovirus, herpes simplex infection, *Pneumocystis carinii* pneumonia to more atypical pathogens: *Cryptococcus, Histoplasma*, invasive fungal infections (*Aspergillus, Candida, Rhizopus, Fusarium), Rhodococcus* and mycobacterial infection (7). Mycobacterial infection in CLL patients has been documented less frequently, with an incidence of 88/10000 cases, and is correlated with steroid use and autoimmune phenomena (11).

We present a case of splenic mycobacterial infection developed 12 weeks after Alemtuzumab therapy, presenting as a prolonged febrile syndrome associating treatment-resistant splenomegaly. Alemtuzumab-associated immunosuppression raised a high suspicion of CMV or atypical infection but, as the febrile syndrome persisted, the presence of a large tumor mass was considered suggestive for transformation to a higher grade lymphoproliferation. The cardinal diagnostic procedure that offered
the correct diagnosis was splenectomy. It is debatable whether splenic tuberculosis was already present at the time of diagnosis and progressed with the onset of Alemtuzumab-induced lymphopenia or developed during treatment. We hypothesize that the defects in CD8+ mediated immunity and the predominant Th2 response determined the activation of a preexisting infection, while subsequent treatment-induced T-cell depletion permitted its progression and extension.

The high incidence of infection in Alemtuzumab treated CLL patients resulted in the development of guidelines for antiviral, Pneumocystis and antifungal prophylaxis. There are no current recommendations for preemptive mycobacterial therapy in high risk febrile patients.

**CONCLUSION**

We presented an atypical and rare case of splenic tuberculosis developed under mixed Alemtuzumab and CLL-related immune deficiency. Although Alemtuzumab treated patients are at high risk for CMV reactivation, the clinician should consider atypical micobacterial infection in the presence of prolonged febrile syndrome, especially in patients with poor socioeconomic status. It remains to be seen whether the low incidence of mycobacterial infection in high risk febrile patients will result in specific guidelines for diagnosis and monitoring.

**REFERENCES**