Fludarabine induced Immune Thrombocytopenia in a patient with CD5 Positive B Cell Chronic Lymphocytic Leukemia

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Introduction

Fludarabine is a purine nucleoside analogue, which inhibits DNA synthesis by inhibiting DNA polymerase and ribonucleoside reductase.[1] It affects both dividing and non- dividing cells.[2] Fludarabine possesses proven efficacy in the treatment of a variety of indolent B cell lymphoproliferative disorders including chronic lymphocytic leukemia[3], low-grade non-Hodgkin's lymphoma[4] and Waldenstrom macroglobulinemia.[5] It is also a part of conditioning regimes in non-myeloablative bone marrow transplantation.[6] The common side effects include myelosuppression, immunosuppression, and neurologic toxicity.[7] The rare side effects are immune mediated hemolytic anemia[8] and thrombocytopenia.[9] Here we describe a case of a middle-aged lady who was diagnosed as B cell chronic lymphocytic leukemia and developed immune mediated thrombocytopenia following oral Fludarabine.

Case Report

Fifty years old female presented to the hematology outpatient with a history of low-grade fever, weight loss and painless swellings on both sides of neck since one month. She was a known patient of diabetes mellitus and hypertension. There was no previous history of autoimmune diseases. Examination at the time of presentation revealed bilateral cervical and axillary lymphadenopathy. Spleen was palpable 3cm below the left subcostal margin. Rest of the general and systemic examination was unremarkable. Investigations revealed hemoglobin 12.1 gm/dl, white cells count 35,500/cumm and platelets 277,000/cumm. Absolute lymphocyte count was 28,000/cumm. Bone marrow and bone trephine findings were consistent with the diagnosis of lymphoproliferative disorder (chronic lymphocytic leukemia). Immuno-phenotyping revealed positivity against CD5, CD19, CD20 and CD22 and hence consistent with B cell chronic lymphocytic leukemia. Other laboratory investigations were within normal ranges. Serial blood counts subsequently revealed progressive increase in absolute lymphocyte count along with an increase in the percentage of prolymphocytes. On physical examination, there was an increase in the number and size of lymph nodes of cervical region.

Initially she received three cycles of tablet chlorambucil 10mg PO daily for two weeks in a cycle of four weeks with no improvement. She was started on tablet Fludarabine 25mg per meter square for five days every four weeks. She responded well to the treatment. After four cycles of Fludarabine, she developed petechial hemorrhages on both legs, spontaneous epistaxis, bleeding from left ear and malena. She was admitted in the hospital and the complete blood count showed hemoglobin 7.9 gm/dl, white cell count 6100/cumm and platelet count 3000/cumm. Bone marrow aspiration and trephine was done. It was a cellular specimen showing normal maturation of erythroid and myeloid precursors along with plentiful megakaryocytes suggesting immune mediated destruction of platelets. There was clearance of the disease. She was started on Prednisolone 30mg PO bid, but the symptoms persisted with the platelet counts remaining less than 10,000/cumm. She received a course of intravenous immunoglobulin 1gm/kg for two days. Her symptoms improved and the platelet counts gradually increased. Platelets counts stabilized to more than 150,000/cumm in six weeks time.

Discussion

Patients with lymphoproliferative disorders have an increased risk of autoimmune disorders such as autoimmune hemolytic anemia and thrombocytopenia.[10,11] Pathogenesis is obscure, however it has been postulated that leukemic B cells elaborate immune suppressive cytokines, such as transforming growth factor beta, which may account for the reversal in the ratio of CD4 to CD8 T cells.[12] There is also a down regulatory expression of CD154 (CD40-ligand), a surface glycoprotien that is expressed on CD4 + T cells following immune activation. Because CD154 (CD40-ligand) plays a critical role in the development of an immune response, such down modulation may be responsible for an immune deficiency state.[13,14] Fludarabine is a potent suppressor of T lymphocytes and this drug may accelerate the pre existing T cell immune suppression that normally occur during progression of chronic lymphocytic leukemia, exacerbating the underlying tendency to autoimmunity.[11] The pathogenic autoantibodies generally do not appear to be produced by the malignant B cell clone.[15]

This patient developed immune mediated thrombocytopenia after four courses of Fludarabine and recovered completely in six weeks time. As it has been observed that these patients usually recover within ten weeks[9] so the option of splenectomy should be reserved for those patients who are refractory to first line therapy with persistent significant thrombocytopenia for more than ten weeks. Re-exposure to the drug can lead to recurrent thrombocytopenia[9], so it is advisable not to rechallenge the patient who has had an episode of immune mediated thrombocytopenia.

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