Imatinib-induced thyroiditis in Philadelphia chromosome-positive chronic myeloid leukemia

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Abstract:
Here, we present a case of chronic myeloid leukemia for which imatinib therapy was initiated. Triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone was normal, and thyroid microsomal autoantibodies (TMA) were positive and patient was diagnosed as thyroiditis treated with corticosteroids for 1½ months which lead to resolution.

Key words:
Chronic myeloid leukemia, imatinib, thyroiditis

Philadelphia chromosome results from reciprocal translocation of key genes Abelson murine leukemia viral oncogene homolog (ABL1) and breakpoint cluster region (BCR) between chromosome 9 and 22, respectively. The fused ribonucleic acid BCR-ABL transcript encodes a 210 kDa BCR-ABL protein that has constitutive protein tyrosine kinase (TK) activity unlike the normal c-ABL protein (145 kDa) which is usually inactive. This constitutive activity results in uncontrolled growth of the myeloid cells resulting in chronic myeloid leukemia (CML). Imatinib inhibits TK enzyme by competitive inhibition of adenosine triphosphate binding to BCR-ABL, CD-117 (c-Kit), and platelet-derived growth factor receptor. Imatinib is currently recommended as a monotherapy in CML and CD-117 (c-Kit) - positive unresectable or metastatic gastrointestinal stromal tumors.

As compared to interferon-α plus cytarabine combination, imatinib has been shown to have significantly higher complete hematological response, complete cytogenetic response, major cytogenetic response, and estimated freedom from progression of disease. Based on high response rates and good tolerability in clinical trials, imatinib has become the first line treatment and the gold standard for treatment for CML. Imatinib is generally well-tolerated, however, it is associated with cramps and facial/limb swelling in some instances. As with any other recently introduced drug, the toxicity profile of imatinib is evolving. We present a case of imatinib-induced autoimmune thyroiditis.

Case Report
In June 2004, a 58-year-old Asian female presented with anxiety, palpitations and breathlessness. Her blood pressure was 175/110 mm Hg. Laboratory analysis revealed total leukocyte count (TLC) of 56,000. Differential leukocyte count revealed blasts, promyelocytes, myelocytes, and metamyelocytes with decreased leukocytes. Bone marrow revealed hypercellularity with myeloid to erythroid ratio of 9:1. Uric acid was 8.8 mg/dl. Liver function test (LFT) and kidney function test (KFT) were normal. Leukocyte alkaline phosphatase was normal. Rest of the biochemistry was within normal limits. Cytogenetic report confirmed the diagnosis of Philadelphia positive CML.

99Technetium scan revealed irregularly increased osteoblastic activity in bilateral shoulder and sacroiliac joints. Rest of the skeleton system showed physiologically normal radiotracer distribution. The patient was started on imatinib 400 mg and folic acid 5 mg once daily in August 2004. Peripheral smear remission was seen in 2 months, i.e., TLC returned to normal value and hemoglobin and platelet counts normalized. One year later, the patient presented with bilateral redness of eyes and facial swelling which was treated with antihistamines. Following this, 1 month later, the patient presented with bilateral parotid swelling which was not evaluated. Parotid swelling resolved of its own within a month without any treatment. In August 2005, bone marrow biopsy revealed normocellular

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Discussion

Most common adverse events reported with imatinib are edema, nausea, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and headache.[3] Cardiotoxicity including congestive heart failure has been reported with imatinib.[4] Grade 3 and 4 anemia, thrombocytopenia, and neutropenia have also been reported.[5] This case illustrates a possible occurrence of imatinib-induced autoimmune thyroiditis. In a case of thyroiditis, history is one of the most vital parts of evaluation. The differential diagnosis of thyroid pain includes acute, subacute thyroiditis, chronic thyroiditis, hemorrhage into a cyst, malignancy including lymphoma, and rarely, amiodarone-induced thyroiditis or amyloidosis. The absence of small tender asymmetric goiter, fever, dysphagia, and erythema over thyroid rules out bacterial or fungal causes of thyroiditis. The patient had bilateral parotid swelling 6 months before the presentation which resolved of its own. The absence of fever and presence of TMA ruled out mumps as a cause of thyroiditis. The absence of weight loss and acute presentation ruled out malignancy. Finally, the positive response to treatment with corticosteroids also ruled out infection and malignancy as a cause of pain in thyroid. There was no history of exposure to radiation, I[131], exposure, and trauma. Thus, only possible cause can be autoimmune thyroiditis which responded well to the treatment with corticosteroids.

Imatinib was started in August 2004, and the patient presented with the thyroiditis in November 2005 establishing the temporal association of thyroiditis with imatinib. Use of Naranjo’s probability scale[6] and WHO causality scale assessment indicated imatinib as a possible cause of thyroiditis because the idiopathic cause of autoimmune thyroiditis cannot be ruled out. Sunitinib, a TK inhibitor, a drug of same class has been implicated as a cause of lymphocytic and destructive thyroiditis.[7] A review the literature of studies of thyroid dysfunction induced by TK inhibitors showed that thyroid dysfunction is not a rare entity with the use of TK inhibitors although not so common with the use of imatinib.[8]

As there was possibility of progression of CML when drug is withheld, drug withdrawal was not done to check the possible causation of thyroiditis by imatinib. Second, there was no increase in the thyroid hormone levels and the severity of thyroiditis did not mandate drug withdrawal.

It is possible that the bilateral parotid swelling was also related to imatinib use. Bilateral parotid swelling can be of autoimmune origin like thyroiditis. Hence, a possibility of activation of autoimmune diseases with the use of imatinib cannot be ruled out.

Conclusion

It cannot be excluded that imatinib like sunitinib can cause thyroiditis. Hence, clinicians should be aware of the possibility of thyroiditis with imatinib and should have an eye not to miss the event.

References

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