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CASE REPORT

Human immunodeficiency virus Infection in a patient of chronic myelogenous leukemia

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ABSTRACT

Association of Cancer and HIV infection is seen in practice. Commonly observed cancer in HIV infected patients are Non-Hodgkin's Lymphoma, cervical cancer and Kaposi Sarcoma, Coexistent Chronic Myelogenous Leukemia (CML) and HIV infection are rare. We report a case where these two diseases were found in a patient and were treated with a single agent Hydroxyurea.

Key words: *CML, HIV, Hydroxyurea*

INTRODUCTION

Chronic myelogenous leukemia (CML) is a chronic myeloproliferative disorder which remains in chronic phase for a variable period followed by accelerated phase and later blast crisis. Various drugs have been used in the management of CML and these are busulfan, alpha-interferon, hydroxyurea, and Imatinib, the last mentioned, a tyrosine kinase inhibitor.

In last three decades, the incidence of human immunodeficiency virus (HIV) infection has been on the rise. The immunodeficiency state makes the patient vulnerable to various infections. With the introduction of anti-retroviral therapy and modern antibiotics, the long-term survival of HIV patients has certainly improved[1] and now HIV is considered as chronic infection. However, it is also observed that there has been an increase in the incidence of cancers in HIV afflicted patients. There are few case reports about development of CML in HIV-1 patients in adult and pediatric age groups.[2,3] Clinical course of such patients is significantly altered with chemotherapy and/or antiretroviral therapy.

We report a case here, where CML was diagnosed earlier and while the treatment was ongoing, HIV infection was detected. The patient received a single drug, hydroxyurea, mainly prescribed for CML. It was observed that the patient not only responded favorably to hydroxyurea, as far as CML was concerned, but is maintaining good health in the presence of HIV infection.

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REVIEW OF LITERATURE

Association of CML and HIV infection is rare. The first case where both these conditions were coexisting was reported in 1995.[2] In this patient, HIV infection was first detected and CML was diagnosed later. Setty *et al.* record a case of congenital HIV infection who had CML for more than 10 years. This patient was treated with antiretroviral agent, Zidovudine for HIV and alpha-interferon for coexisting CML[4] Webb studied 10 patients in whom CML and HIV was coexistent. The response to Imatinib and combination Anti-Retroviral Therapy (cART) was excellent.[3] Combination of Imatinib with Highly Active Retroviral Therapy was shown to have a good control of CML and HIV over a period of 69 months.[1] In 1997, complete cytogenetic response was documented with a combination of alpha-interferon and Zidovudine in an asymptomatic patient of CML and HIV.[5]

Before tyrosine-kinase inhibitors appeared on the scene, hydroxyurea was used extensively for two reasons. One, the cost of the drug was affordable and secondly it offered good control of CML. In early 1980s, patients with HIV infection were treated with hydroxyurea alone and later this was combined with didanosine or stavudine as first line therapy.

However, results of monotherapy with hydroxyurea in HIV infection were inferior to that of HAART. In addition peripheral neuropathy was observed in 5.8% when hydroxyurea was used as a single agent. This percentage increased to 20% when it was combined with antiretroviral agents.[6] These patients due to altered immunological status often contracted pulmonary tuberculosis and isoniazid used for treating mycobacterial infection further enhanced the chances of peripheral neuropathy.[7] Therefore, hydroxyurea was later omitted from the anti HIV regimes.

CASE REPORT

A 50-year-old male patient was a known case of diabetes mellitus and was being treated for that since 1989. He was; however, quite irregular with this treatment and his diabetes was often out of control.

In November 2005, he presented with complaints of fever, cough with expectoration and weakness. The fever was low grade and there was no history of hemoptysis, dysuria and hematuria. Routine laboratory investigations showed high White Blood Cell count which was 59,000/mm^3, and there were premature leucocytes on peripheral smear. He also had elevated platelet count which was 726,000/mm^3. His diabetes was out of control with FBS level 264 mg/dl and PPBS value 372 mg/dl.

A provisional diagnosis of CML with uncontrolled diabetes mellitus was made and he was further investigated.

His routine urinalysis showed glycosuria. Renal Function Tests and Liver Function Tests were within normal limits. Test for HIV infection was non-reactive. Chest X-ray did not reveal any abnormality. Bone marrow aspiration study was consistent with the diagnosis of CML. Test for Philadelphia chromosome was not carried out.

He was given hydroxyurea 500 mg 3 times a day and subsequently the doses were titrated with reference to WBC count.

During the follow-up that spanned over next several months, he experienced occasional seasonal attacks of respiratory infection. For this, he was treated with antibiotics and insulin which controlled the infection promptly.

In October 2010, he complained of occasional fever, cough with slight expectoration and loss of appetite, weakness and weight loss. He was diagnosed to have pulmonary tuberculosis on the basis of his clinical picture and positive TB ELISA test (IgM) for which he received anti tubercular treatment for next 10 months.

In February 2011, he complained of retrosternal burning sensation while walking which was relieved by rest. He also experienced tightness around the chest. The pain did not radiate but was associated with the mild breathlessness. ECG did not reveal any abnormality. The Treadmill Test was strongly positive for exercise induced coronary insufficiency.

As his symptoms and stress test suggested coronary heart disease, he was referred to a cardiac center for further evaluation. 2D-echo was carried out which showed echo-concentric LVH, normal resting systolic function, presence of diastolic dysfunction, no regional wall motion abnormalities, and normal PA pressure. Coronary angiography was done on 1st March 2011 which showed LVEF 50% and triple vessel disease. Revascularization was contemplated; however, his routine investigation showed a positive HIV test; hence no further interventional treatment was carried out.

This new development necessitated further investigations. Philadelphia chromosome was tested which showed a positive result. CD3, CD4 and CD8 count results were 2940 cells/mm^3, 393 cells/mm^3 and 2477 cells/mm^3 respectively. Viral load was tested on 5th November 2011and it showed 43356 HIV-1 RNA copies/ml.

He was advised to start anti-retroviral therapy along with Imatinib, however, patient declined to take this treatment due to lack of resources. He was therefore continued on hydroxyurea.

In May 2012, the retroviral disease tests were repeated. The results of both the tests are given in Table 1.

Patient continues to take hydroxyurea regularly and in spite of advanced HIV he has not developed any major complications of HIV or CML during his follow-up period.

Table 1: Virological markers

Date	CD$_4$+count (%)	CD8+count (%)	CD$_4$/CD8 ratio	Viral load
10th September 2011	393 (13.37)	2477 (88.25)	0.16	43,356 copies/ml (4.6 log 10 copies/ml) 5th November 2011
27th May 2012	566 (14.21)	3289 (82.58)	0.17	Less than 20 copies/ml

CD – Cluster Determinant

DISCUSSION

CML is a clonal disorder arising from pluripotent stem cell. Incidence of CML in Western countries is 1/100,000 population. Its incidence in India is recorded from 6 population based cancer registries and varies from 0.8 to 2.2/100,000 for males and from 0.6 to 1.6/100,000 populations for females. This may not reflect the true incidence. Studies based on hospital patients show a higher incidence which ranges from 40% to 82 % of leukemia cases in adults.[8]

The clinical course of CML is in different phases. Majority of patients (90-95 %) present in an initial chronic phase of variable duration (average-5-5½ years). When initial treatment is started in chronic phase of CML, approximately 95% of patients achieve complete hematological response. The chronic phase usually progresses to accelerated phase and eventually culminates in blast crisis.

There are approximately 2.5 million HIV infected patients in India. The incidence of coexisting cancer and HIV is unknown.

HIV associated cancers are broadly classified in two groups. They are:

Acquired immunodeficiency syndrome (AIDS) defining cancers which include non-Hodgkin lymphoma, invasive cervical cancer and Kaposi' sarcoma.

Non-AIDS defining cancers are other malignancies not included in the above group.

This patient of CML with HIV-1 infection shows a different clinical course than either presenting singly. His CML was diagnosed 7 years ago and so far has not shown any evidence of accelerated phase or blast crisis. The presence of HIV infection was detected 5 years after the diagnosis of CML and though he has not received triple drug therapy, he remains clinically stable. If Imatinib was used for CML, he would also need triple drug anti-retroviral therapy because the tyrosine kinase inhibitor does not have any effect on HIV-1. Therefore for CML coexistent with HIV-1 infection, hydroxyurea as a single agent seems to be useful at least in this case.

Hydroxyurea has antiviral and anticancer properties. In fact, before the advent of effective anti-retroviral agents, many HIV patients were treated with a combination of hydroxyurea and didanosine as hydroxyurea has a synergistic effect with reverse transcriptase inhibitors such as didanosine. Hydroxyurea significantly enhances the antiretroviral effects of the adenosine analog reverse transcriptase inhibitor dideoxyinosine by reducing intracellular de-oxyadenosine triphosphate concentrations due to inhibition of ribonucleotide reductase enzyme.[9] As newer antiviral agents such as protease inhibitors, integrase inhibitors, entry blockers and other agents from reverse transcriptase class, were introduced the use of hydroxyurea in the management of HIV-1 became less and less. Though, it was easily available at a lower cost, severe hematological toxicity and associated neuropathy, hydroxyurea was later omitted from the guidelines for the antiretroviral therapy.[7]

This patient shows many atypical features. He is taking only one agent, hydroxyurea since the diagnosis of CML and has good performance status in spite of having a very low CD_4/CD_8 ratio. He did not progress to accelerated phase or blast crisis in last 7 years. He was treated for tubercular infection but did not acquire other opportunistic infections in last several months. He has significant longer survival without an "ideal" treatment for CML or HIV infection.

It is observed that when a single antiretroviral agent is used in the treatment of HIV-1 infection, drug resistance develops in a short time. No opinion, however, can be made regarding the aspect of drug resistance.

This could probably be the first report of a patient who had CML first and later developed HIV. This case does not fit in conventional classification of HIV associated cancers. As per this definition, patients have retroviral infection first and later due to infections such as HHV8, EB virus or other unknown viruses and/or mechanisms develop different types of cancer at a later date.

At the time of preparing this report (December 2012) the patient was taking hydroxyurea and the CML is fairly well controlled. His performance status remains at zero (ECOG score) and he regularly visits for follow-up.

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