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Case Report

Forgotten Dapsone Therapy for HIV Associated Thrombocytopenia

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ABSTRACT

We report a case of a 36-year-old male known to have Diabetes Mellitus. He presented with complaints of fever, cervical lymphadenopathy and hyperpigmented macular and non-pruritic rash over his body associated with generalised weakness. On examination he had non-tender cervical adenopathy. Laboratory evaluation showed thrombocytopenia (18,000/ul). He was found reactive to Human-Immunodeficiency Virus. Cervical lymph node biopsy showed caseating necrotising granuloma suggestive of Tuberculosis. Bone marrow aspiration and biopsy revealed a normocellular marrow with increased and hypolobated giant platelets. Other causes of thrombocytopenia were ruled out. Patient was diagnosed to have cervical lymph node tuberculosis with HIV associated thrombocytopenia and treated with Dapsone and Anti-tubercular drugs. 6 weeks later his platelet count became normal. A Number of treatment options exist including steroids, Rituximab, other immunosuppressive therapy, thrombopoetin receptor agonist as well as splenectomy but these are expensive and have number of side effects. The case highlights the importance of being aware of HIV associated thrombocytopenia so as to facilitate the prompt recognition and treatment of this condition. It is also a review of dapsone as a well-established drug for treatment with a good safety profile. Unfortunately, this treatment option has not been well explored.

Key Words- Human Immunodeficiency Virus (HIV), Thrombocytopenia, Tuberculosis, Dapsone.

INTRODUCTION

Hematological manifestations of human immunodeficiency virus (HIV) infection have abroad spectrum, ranging from mild disturbances to life threatening conditions. Thrombocytopenia is one such clinical manifestation that should alert clinicians. [(1)] It is a common finding in 40% individuals infected with HIV during the course of their illness. [(2)] Thrombocytopenia occurs in 15-60% of patients with AIDS, and is seen in about10% of patients at early stages of HIV infection. According to one report, 1 year prevalence of thrombocytopenia is 8.7% in people with one or more AIDS defining illness, 3.1% in patients with CD4 count >200 but without clinical AIDS. [(3)] The need to create an awareness of ruling out HIV infection in patients presenting with thrombocytopenia has prompted us to document this case and discuss the therapeutic options.

CASE REPORT

A 36-year-old male patient known to have Diabetes Mellitus and was on Insulin therapy for the same. He had complains of low grade fever with cervical adenopathy hyperpigmented macular and non-pruritic rash over his body. He then reported to our out-patient department for further evaluation and management. He was moderately built and nourished and was febrile (99 ^{0}F). He had non-tender, soft to firm cervical adenopathy. His respiratory, cardiovascular and neurological examination was unremarkable. There was no other peripheral stigmata of Tuberculosis. He had hyperpigmented macular and non-pruritic rash over his arms, legs, trunk and back. Complete blood count (Table 1) showed thrombocytopenia (18,000/uL) with giantplatelets; haemoglobin, total and differential leucocyte count and erythrocyte sedimentation rate (ESR) were within normal limits.

Serum aspartate aminotransferase [(AST) 45 U/L] and serum alanine aminotransferase [(ALT) 48U/L] were mildly elevated. Serum bilirubin was 1 mg/dL. Renal parameters were normal. On Further investigations patient was found reactive to Human Immuno-Deficiency virus (HIV) and was subsequently confirmed with Western Blot. HisCD4+ cell count was 241/cu.mm and HIV viral load was 888,806 copies/ml. His peripheral smear was negative for malarial parasites. Dengue serology and A.N.A were negative. Serum A.C.E level was normal. He was not on any drugs to cause thrombocytopenia. All the other causes of thrombocytopenia were ruled out. Chest roentgenogram and Abdominal Ultrasound were normal. Patient had no other opportunistic infections. Bone marrow aspiration and biopsy revealed normocellular marrow with increased and hypolobated megakaryocytes. A G6PD assay performed was normal. Patient was diagnosed as a case of tubercular cervical lympadenitis with HIV associated Thrombocytopenia. Insulin treatment was continued for Diabetes Mellitus. He was started on 4 drug regimen of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide for cervical adenopathy and oral dapsone for the thrombocytopenia. Anti-Retroviral therapy was withheld for 2 months to prevent Immune Reconstitution Inflammatory Syndrome (I.R.I.S). At 6 weeks follow-up, his platelet count increased to 1,94,000/mm3 (Table 1) and he remained free of any hematological symptoms. After 6weeks he was managed with tenofovir, emtricitabine, efavirenz for the HIV infection. He responded well to the Anti-tubercular medications also with near complete resolution of cervical tubercular lymph nodes which was continued for total of 6 months.

TABLE 1: Complete blood picture report at the time of initial presentation and at 6-weeks of follow-up

Variable	At presentation	At 6 weeks follow-up
Haemoglobin (gm%)	12.5	13.6
M.C.V (f L)	84.3	92.6
Total Leucocyte Count (cu/mm)	4800	7600
Platelet count (/mm3)	18,000	1,94,000
Reticulocyte Count (%)	1	0.5
ESR mm (at the end of 1st hour)	28	36

MCV = mean corpuscular volume;
ESR = erythrocyte sedimentation rate

DISSCUSSION

Reduction in all major blood cell lines has been recognized among patients infected with HIV, shortly after the first description of the acquired immunodeficiency syndrome (AIDS). Although various hematological abnormalities have been described in HIV infection, many questions have been raised regarding the pathogenesis and treatment of HIV related thrombocytopenia. When thrombocytopenia occurs in an otherwise HIV infected adult, it is considered to be a diagnostic criterion for the AIDS-related

complex. By the CDC classification isolated thrombocytopenia in an HIV infection would be classified as P-2F. [4] Increasing the complexity of HIV infection, hematological manifestations can be seen, in which HIV-related thrombocytopenia (Tr-HIV) is one of them, often asymptomatic, but may be associated with a variety of bleeding abnormalities and with a high morbidity. Despite of the common prevalence of HIV-induced thrombocyto-penia, profound thrombocyto-penia is totally rare (1.5%). It occurs in patients from all major risk groups and may present at any time during the course of HIV infection, from asymptomatic infection to advanced acquired immunodeficiency Syndrome (AIDS). The incidence of platelet abnormalities appears to increase with progressive immuno-suppression. In the current era of combination antiretroviral therapy, it is more commonly encountered among patients with uncontrolled HIV replication and hepatitis C virus (HCV) co-infection. [5]

The causes of thrombocytopenia in HIV infected patients can be divided into two groups: primary HIV-associated thrombocytopenia (PHAT) and secondary thrombocytopenia. [6] PHAT is the most common cause of low platelet counts encountered in HIV-infected patients. [7] Clinically, PHAT is similar to classic ITP. Platelet counts are often higher in HIV-infected patients, and mild thrombocytopenia occasionally resolves without therapy. The aetiology of thrombocytopenia in PHAT is complex. The combination of normal or increased numbers of megakaryocytes in the face of reduced numbers of circulating platelets in bone marrow examination is seen, as in our case. It suggests the presence of ineffective platelet production and/or increased peripheral destruction. Secondary causes of thrombocytopenia are generally the result of underlying opportunistic infections, hypersplenism, malignancy, drugs and other co-morbid conditions. [8]

After the exclusion of secondary causes of thrombocytopenia and discontinuation of potentially marrow-suppressing medications, there are many therapies available for the management of PHAT. Individual circumstances dictate the necessity and acuity of therapy. Spontaneous remission has been seen in as many as18% of patients who have PHAT. The optimal treatment of HIV associated thrombocytopenia remains uncertain. In those who do not respond, therapy historically has consisted of institution of zidovudine (AZT). Recent studies indicate that highly active anti-retroviral therapy (HAART) is equally effective. Other treatment modalities include glucocorticoids, intravenous IgG (IVIG), intravenous anti-D therapy, splenectomy, danazol, dapsone, interferon and vincristine. In our case we had chosen oral dapsone.

In the present patient, steroids were not considered in view of significant side effects such as flaring up of tuberculosis and uncontrolled diabetes. A.R.T can be used for treatment of thrombocytopenia but in view of risk for development of I.R.I.S it was not started in this case. Oral dapsone was administered in dose of 100mg PO daily. It has been shown to raise platelets with no major toxicity. Oral Dapsone has shown to be effective in some patients with HIV related thrombocytopenia. Dapsone is a drug that has been used long time for various indications. Millions of people have received dapsone for lepromatous leprosy. It is used to both treat and prevent pneumocystis pneumonia (PCP) and prevent toxoplasmosis in people unable to tolerate trimethoprim with sulfamethoxa-zole. [9] The two most notable Hematologic side effects of dapsone are haemolytic anemia and methemoglobinemia. [10] The

rates of hemolysis can be as high as 20% in treated patients, but in most cases it is a mild hemolysis in response to dose reduction. However, hemolysis can be severe in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and patients should ideally be screened for this condition before administration of dapsone.

Agranulocytosis and aplastic anemia can also occur, although rarely, with dapsone therapy. Dapsone can also cause a characteristic hypersensitivity syndrome characterized by fever, eosinophilia and a rash that is responsive to steroid therapy. Other side effects of dapsone include hepatitis, cholestatic jaundice, peripheral neuropathy, nausea, and gastrointestinal disturbances. [11] Trials have shown that dapsone is a safe, inexpensive treatment. The safety profile of dapsone has to be weighed against the side effect profile of alternative therapies, such as splenectomy, rituximab, azathioprine, cyclosporine, and MMF (mycophenolate moefetil). The hazards of immunosuppression (opportunistic infections, malignancies, and reactivation of tuberculosis), nephrotoxicity and bone marrow toxicity are considerably greater with these other options.

Splenectomy carries the operative and perioperative risks of surgery, as well as the lifelong risk of being vulnerable to overwhelming sepsis. Although dapsone therapy may be discontinued in responders after 6–12 months, once splenectomized, patients may have to be on lifelong penicillin prophylaxis. Dapsone is considerably cheaper than its alternatives. The studies have also confirmed the beneficial effect of dapsone in patients with chronic idiopathic autoimmune thrombocytopenic purpura. Dapsone is a useful, but neglected, inexpensive therapeutic option for the treatment of chronic and/or refractory ITP. The use of IVIG is hampered by its high cost and the need for hospitalization.

HIV-related thrombocytopenia is a complex and incompletely understood phenomenon. The ideal treatment for HIV-related thrombocytopenia has not yet been determined. Studies have shown that HAART is equally effective. As far as other treatments are concerned, most of the effects appear to be transient and risks and benefits should be weighed on a case-by-case basis. Treatment should be individualized and it is reasonable to accept chronic thrombocytopenia even with low platelet counts as long as there are no significant bleeding complications. Withholding the treatment may be appropriate in the absence of bleeding even if the platelet count is less than 50,000 per cu mm. In conclusion, it may be stated that individualization of therapy is important in HIV-related thrombocytopenia. With the increasing incidence of AIDS, an emphasis must be laid on the need for testing blood for HIV before transfusion and avoiding blood transfusion unless absolutely indicated. [12]

CONCLUSION

Dapsone is a useful, but neglected, inexpensive therapeutic option for the treatment of chronic and/or refractory ITP in patients who are refractory to or dependent on steroids or in whom steroids are contraindicated before opting for more expensive and more hazardous second-line therapies. Dapsone is a valuable drug in patients with HIV with other opportunistic infections like Tuberculosis where steroids are contraindicated and also useful to both treat and prevent Pneumocystis pneumonia (PCP) and prevent toxoplasmosis in people unable to tolerate trimethoprim with sulfamethoxazole. Dapsone should not be considered in patients requiring a rapid rise in the platelet count, such as in an emergency. G6PD status should be routinely

assessed before dapsone is started, and patients should be closely monitored for hemolysis and methemoglobinemia while on the drug. Further large-scale studies and controlled trials that allow head-to-head comparison of dapsone with other therapeutic options need to be carried out.

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