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CASE REPORT

Tenofovir induced severe thrombocytopenia

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Abstract

Tenofovir disoproxil fumarate is used in the management of hepatitis B and human immunodeficiency virus infection. We present a 50 years old lady, post liver transplant, who was switched over from entecavir to tenofovir, for management of hepatitis B reactivation. She developed bleeding diathesis and severe thrombocytopenia was detected on investigations. Bone marrow examination showed normocellular marrow with megakaryocytes. Tenofovir was stopped and she was started on intravenous immunoglobulin, followed by steroids. There was improvement in platlet counts. The case highlights a rare side effect of tenofovir therapy.

Key words: Tenofovir; Hepatitis; Thrombocytopenia

Core tip: The present case report highlights a rare side effect of tenofovir therapy for hepatitis B infection. As the drug is commonly used in for management of hepatitis B and human immunodeficiency virus infection, the knowledge to this rare side effect would help physicians to be more watchful and improve patient management.

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INTRODUCTION

Tenofovir disoproxil fumarate is often used in management of hepatitis B and human immunodeficiency virus (HIV) infection. Nausea, vomiting, renal dysfunction and abdominal discomfort are the known adverse effects of the drug[1]. We report a case of post liver transplant severe

thrombocytopenia following introduction of prophylactic tenofovir.

CASE REPORT

A 50 years old lady had undergone deceased donor liver transplantation for hepatitis C related cirrhosis in 2013. The donor was anti HBc positive. Post transplant, she was treated for recurrence of hepatitis C virus (HCV) infection at 6 mo with sofosbuvir and simeprevir. For new onset tuberculous pleural effusion she received a complete course of antituberculous medication. She was also initiated on entecavir 0.5 mg once a day as prophylaxis for hepatitis B virus (HBV) infection. The HCV cleared with a sustained viral response at one year. The HBV DNA load which was not detectable in the immediate post transplant period increased to 13665 IU/mL at end of one year and this was attributed to a default in adherence to the treatment. Patient was switched over to Tenofovir 300 mg once a day.

Four weeks later after initiation of tenofovir, she developed bleeding gums, and generalised ecchymoses. Apart from tacrolimus she was not on any other medication or alternative systems of medicine. On evaluation, the platelet count dropped to 3000 cells per cu.mm, haemoglobin was 10.8 g/dL, with a total leukocyte count of 4500/cu.mm. Liver function tests including trasnminases were normal (ALT 27 IU/L, AST 32 IU/L). Serum creatininewas 0.8 mg/dL and blood Tacrolimus trough value was 4.3 ng/mL. She received several platelet transfusions but the levels were not sustainable. Peripheral smear did not show platelet clumping or satellitism. Other investigations included reticulocyte count (4.5%), Lactate dehydrogenase (489 U/L), serum haptoglobin [< 7.30, d-Dimer (negative)], Direct Coombs test (negative) and serum anti-nuclear antibody (negative). Bone marrow aspiration and biopsy showed normocellular marrow with megakaryocytes. The possibility of immune mediated thrombocytopenia was considered and she was started on intravenous immunoglobulins 1 mg/kg per day for 2 d. Her platelet counts improved dramatically to 124000 cells per cu mm and she was started on steroids and folic acid. In absence of any known factor and documentation of thrombocytopenia 4-wk after initiation of tenofovir, the latter was considered as the possible aetiological agent. She was switched over to entecavir. On follow up a month later, her liver function tests were normal and platelets had improved to 131000/cu.mm.

DISCUSSION

Tenofovir is a commonly used drug in management of hepatitis B. It is used in a dose of 300 mg/d. It is mainly metabolised and excreted by the kidneys with a half life of 14-17 h[2]. The common side effects include renal dysfunction, Fanconi's syndrome, pneumonia, pancreatitis, cutaneous lesions and diabetes insipidus[3]. Thrombocytopenia as an adverse effect has been reported with use of interferon, adefovir, lamivudine and entecavir while treating patients with chronic hepatitis B[4,5]. However, tenofovir induced thrombocytopenia, though reported in FDA safety reports, has rarely been described in clinical setting. Though there have been few reports in patients with HIV infection on antiretroviral therapy, the drug induced thrombocytopenia (DITP) following tenofovir monotherapy for hepatitis B is less well described[6,7].

DITP is an increasingly common cause of thrombocytopenia[8]. DITP typically presents 5 to 10 d after beginning daily drug dose, or within hours after re-exposure to a drug that has been taken occasionally for a period of time. It is characterised by rapid onset, bleeding manifestations and platelet counts below 20000/cu.mm. It may mimic primary immune thrombocytopenia (ITP)[9]. It is often reported in patients who are hospitalised, or are on multiple medications with combination of co-morbidities[10].

Many drugs can cause thrombocytopenia either by non-immune or immune mechanisms. Non-ITP results in suppression of platelet production by general myelotoxicity, dose-dependent myelosuppression or interference with specific megakaryocyte function. Immune-mediated thrombocytopenia results in accelerated platelet destruction by drug-dependent platelet antibodies that cause platelet clearance or activation. A thorough clinical and drug history is essential to exclude herbal medicines, food additives and supplements before making a diagnosis of DITP[11]. Despite this, diagnosis is difficult in a handful of cases and is often considered as circumstantial[12,13]. Arnold *et al*[14] have enlisted 16 drugs that met both clinical and laboratory criteria for causing DITP.

Our patient was on long term immunosuppression with tacrolimus and had recent history of exposure to tenofovir. Within 4 wk of initiation of tenofovir, she developed severe thrombocytopenia suggesting the causative effect following tenofovir exposure. Though drug specific autoantibodies and antiplatelet antibodies were not done, improvement with steroids, intravenous immunoglobulin and tenofovir withdrawal suggests our patient indeed have a drug mediated adverse effect. We did not consider reintroducing tenofovir for fear of a hypersensitive reaction. Instead we reintroduced entecavir and patient is doing well with no further set back.

The present case report highlights an unlikely side effect of tenofovir therapy that should be kept in mind by prescribing physicians.

COMMENTS

Case characteristics

Post liver transplant patient presented with bleeding diathesis and thrombocytopenia within 4 wk of starting tenofovir therapy for hepatitis B.

Clinical diagnosis

Bleeding diathesis probably related to low platelets.

Differential diagnosis

Possibilities of immunosuppression induced blood dyscrasias, immune throm-

bocytopenia and drug induced thrombocytopenia were considered.

Laboratory diagnosis
Confirmed thrombocytopenia in the absence of anti-nuclear antibodies, elevated d-Dimer levels and autoantibodies.

Pathological diagnosis
Normocellular marrow with megakaryocytes.

Treatment
Intravenous immunoglobulin, cessation of tenofovir.

Experiences and lessons
Knowledge of monitoring of platlets in patients of tenofovir therapy may help to prevent drug related severe thrombocytopenia.

Peer-review
This report highlights a rare case of thrombocytopenia after switching therapy to tenofovir DF.

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