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Case Report

Cyclophosphamide and varicella zoster virus induced disseminated intravascular coagulopathy with fatal outcome

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ABSTRACT

Varicella is usually a mild self-limiting disease, commonly occurring in paediatric population. However, in adults and in specific groups of patients, such as those who are immunosuppressed, varicella virus infections can be fulminant and life threatening. We are hereby reporting two cases of Pemphigus vulgaris on cyclophosphamide therapy, who succumbed due to disseminated intravascular coagulopathy (DIC) after varicella zoster virus infection.

Keywords: Pemphigus vulgaris, Varicella zoster virus, Disseminated intravascular coagulopathy, Cyclophosphamide

INTRODUCTION

Varicella zoster virus infection is considered to be mild and ubiquitous, predominantly affecting the paediatric population, but also affects adults frequently.[1] Infection caused by this virus has two distinct clinical presentations; varicella (chickenpox) and herpes zoster. Varicella in adults may be associated with systemic involvement and complications. Pemphigus vulgaris is an autoimmune skin disorder, with antibodies directed against desmoglein antigens. High dose immunosuppressants are the mainstay of treatment and may be associated with various adverse effects.

CASE REPORT

Case 1: A 28 years HIV sero-negative male with pemphigus vulgaris since 4 years, presented to dermatology out-patient department with recurrent oral ulcers and few flaccid bullae on chest and back (Figure 1 and 2) which were recalcitrant despite low dose oral and topical corticosteroids. After admission and baseline investigations (hemogram, liver function tests, renal function tests, ultrasound and XR chest) he was started on daily oral prednisolone 40 mg with oral cyclophosphamide 100 mg as steroid sparing agent. A week later, patient had fever followed by appearance of multiple vesicles over trunk and extremities suggestive of varicella which became umbilicated and hemorrhagic over the next few hours. All the above drugs were withheld and he was started on intravenous acyclovir 10 mg/kg/dose eight hourly. Within 3- 4 hours of vesicular eruption, patient started bleeding profusely from oral lesions and gums (Figure 3) along with massive hematuria. He was immediately shifted to medical intensive care unit. Respiratory and cardiovascular system examination was unremarkable. Liver function and renal function tests were normal. Coagulation profile was deranged with elevated bleeding, clotting and prothrombin time. Platelet counts had drastically dropped to 30,000/cmm with raised levels of D-dimer (87.6 µg/ml) and low fibrinogen levels (0.7 g/L). Thus,

diagnosis of DIC was confirmed (score 6) according to algorithm of International Society of Thrombosis and Hemostasis.[2] Meanwhile patient was administered tranexamic acid and vitamin k injections along with fresh frozen plasma and MESNA (2-mercaptoethane sulfonate sodium) and saline bladder wash. Unfortunately patient succumbed within 12 hours of onset of bleeding.

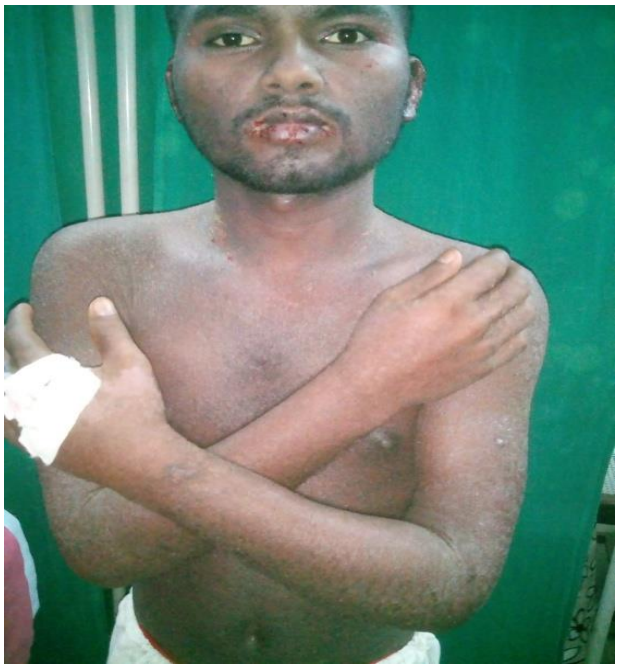

Figure 1: pemphigus lesions on chest.

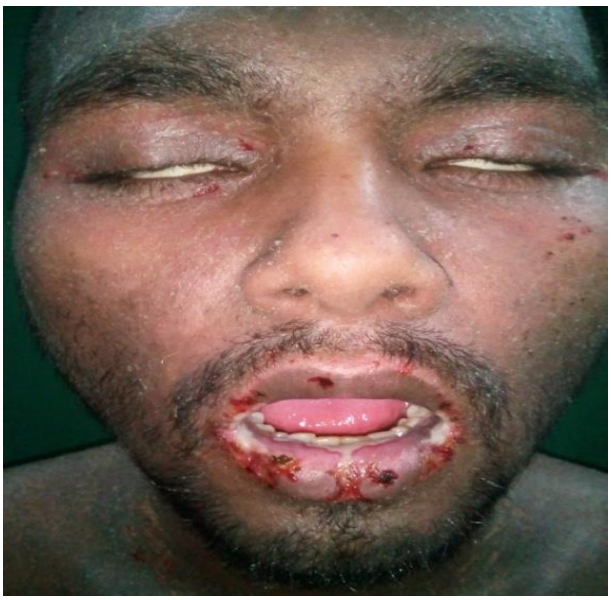

Figure 2: oral erosions in pemphigus patient.

Case 2: A 55 years HIV sero-negative male on treatment for pemphigus vulgaris, presented with painful grouped fluid filled lesions in dermatomal distribution since 1 day, on left side on chest below the nipple, associated with extreme pain and burning. He had been initiated Dexamethasone and Cyclophosphamide (DCP) pulse therapy with daily oral cyclophosphamide 100 mg, since two months with previous pulse given 1 month ago. Diagnosis of herpes zoster (T4 dermatome) was made clinically. Above medications were withheld and intravenous acyclovir (10 mg/kg/dose) was started. Within an hour he suffered a bout of hematemesis with persistent per oral and nasal bleeding followed by progressive deterioration of general condition and vital parameters. The patient could not be salvaged despite all resuscitative measures.

Figure 3: Bleeding from oral lesions and epistaxis.

DISCUSSION

DIC (consumption coagulopathy or defibrination syndrome), is an acute condition wherein process of coagulation and fibrinolysis become abnormally activated, leading to on-going thrombosis and thrombolysis. Though potentially life threatening, aggressive management with fresh frozen plasma and other supportive measures is associated with a favourable outcome. Cyclophosphamide, an alkylating agent can cause myelosuppression, which is primarily leukopenic with relative sparing effect on platelets. There are reports of DIC in malignancy patients on chemotherapeutic regimens containing cyclophosphamide. Only 2.9% of patients on cyclophosphamide treatment are reported with DIC, according to an FDA report.[3] Natarajan et al reported a case of 26-year-old female who developed the syndrome of inappropriate antidiuretic hormone (SIADH) secretion and subsequently features of disseminated intravascular coagulation (DIC) and secondary septicemia following dexamethasone and cyclophosphamide pulse (DCP).[4]

Varicella zoster virus is a DNA virus causing two distinct clinical diseases; varicella/chickenpox and herpes zoster/shingles. Chickenpox, which develops after initial

exposure to the virus, is a trivial illness of childhood and is rarely fatal, although it is generally more severe in adult males than in adult females.[5] Characterised by pleomorphic rash appearing on the trunk and face initially, with malaise, sore throat, fever. After the primary episode the virus remains latent in sensory root ganglion and can reactivate later and manifest as grouped vesicles on erythematous base namely herpes zoster. Fulminant serious conditions like pneumonia, encephalitis, hepatitis are reported in adult or immunosuppressed patients.[6,7] In A study from Saudi Arabia found the complication and overall fatality rate in varicella infection to be 1.5% and 0.05% respectively.[7] Hemorrhagic manifestations are a rare complication with not a single case mentioned in 2 large series of varicella related complications.[7,8] Bajaj et al documented varicella induced ARDS, DIC, myocarditis and hepatitis successfully managed with acyclovir and mechanical ventilation.[8]

Both our patients who were already on cyclophosphamide therapy developed varicella zoster virus infection. In patients with impaired cell mediated immunity, disseminated Herpes zoster with widespread cutaneous and visceral involvement may develop one of 4 forms: local (classic) zoster, atypical generalized zoster with or without visceral involvement, and visceral zoster without skin lesions. However, though our patient (case 2) had classical localised form, the rapid deterioration was a striking feature. It remains debatable whether the DIC was a rare adverse effect of either cyclophosphamide or varicella zoster virus infection. However the synergistic effect of drug and infection was perhaps responsible for the fulminant course leading to fatal outcome even in the second patient with a unidermatomal Herpes zoster.

To conclude, our experience emphasises the need for extreme vigilance in patients on cyclophosphamide therapy acquiring a seemingly innocuous viral infection. CDC recommends vaccination of all individuals with weakened immune systems without immunity against varicella zoster virus. Additionally, timely provision of Varicella Zoster Immunoglobulin (if available) to susceptible patients on immunosuppressive therapy would avert such poor outcomes.

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