Stevens-Johnson Syndrome-Like Exanthema Secondary to Methotrexate

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ABSTRACT

Methotrexate is an antineoplastic drug used commonly in leukemia treatment. Because of becoming resistant to standard doses after 1970s, it is used intermediate or high doses. The complications of high doses are mucositis, vomiting, dermatitis exfoliativa, B-cell dysfunction, hepatotoxicity, nephrotoxicity and bone marrow depression. There were only two studies in literature about Stevens-Johnson syndrome occuring in two patients with acute lymphocytic leukemia and non-Hodgkin lymphoma after receiving high doses methotrexate and leukoverin. We have reported a two-year-old boy patient suffering from acute lymphocytic leukemia (ALL) developed a severe skin reaction two days after administration of high dose methotrexate. The skin lesions simulated Stevens-Johnson syndrome with ulceration of the oral mucosa and erythema multiforme-like target lesions.

Key Words: Methotrexate, Stevens-Johnson syndrome, Acute lymphocytic leukemia (ALL).

Turk J Haematol 2002;19(3): 427-430

Received: *23.10.2001* ***Accepted:*** *01.01.2002*

INTRODUCTION

The Stevens-Johnson syndrome (SJS) is characterized by severe erythema multiforme associated with orogenital mucosal ulceration and may be complicated by severe systemic upset and hepatic, renal and neurological disturbances[1]. Methotrexate has increasingly been used in combination with chemotherapeutic regimens for the treatment of acute lymphocytic leukemia (ALL). Its principal toxic effects are bone marrow suppression, gastrointestinal mucositis, hepatitis, renal impairment, and erythematous rashes[2]. In this study, we have reported a case of Stevens-Johnson syndrome-like exanthema following high dose methotrexate (HDMTX) treatment in a patient receiving chemotherapy for treatment of ALL.

CASE REPORT

A two-year-old boy was referred to our clinic because of paleness and lack of appetite. On physical examination, he had hepatosplenomegaly and lympha denopathies. Laboratory findings

were thrombocytopenia and anemia. Bone marrow aspiration revealed ALL-L_1 type. The result of the flowcytometry was CALLA (+) B-ALL. Hence, we began ALL-TXIII remission induction treatment with prednisone, vincristine, asparaginase, vepeside, arabinoside. In addition to the intrathecal therapy with methotrexate, hydrocortisone and arabinoside were administered. On the 44th and 51st days, consolidation treatment was continued with HDMTX (2 g/m^2), leucoverin (10 mg/m^2) and 6-mercaptopurine. The control bone marrow was in remission. While he was receiving second dose of remission treatment two days after, the administration of HDMTX, a fever of 39.2°C, headache, malaise, and soreness of the throat and mouth were appeared. Soon after, the constitutional symptoms including weak pulse, rapid respiration, prostration and joint pain became severe. Stomatitis began with vesicles on the lip, tongue and buccal mucosa, and later became more severe with pseudomembranous exudation, salivation, and ulceration, so that eating and drinking became difficult. Bilateral conjunctivitis, rhinitis with epistaxis, erosive balanitis, and crusting of the nares developed. Involvement was observed in his anal mucosa (Figures 1). In our case, skin lesions such as vesicubullous or erythematous eruption involved especially the face, hands, feet and trunk (Figures 2,3). After he had Stevens-Johnson syndrome-like exanthema secondary to methotrexate, he had the evidence of infection manifested by septicemia three days after the skin lesions. A dermatologist from our hospital clinically confirmed the diagnosis of SJS in our clinic. A week later our patient in neutropenia died because of sepsis.

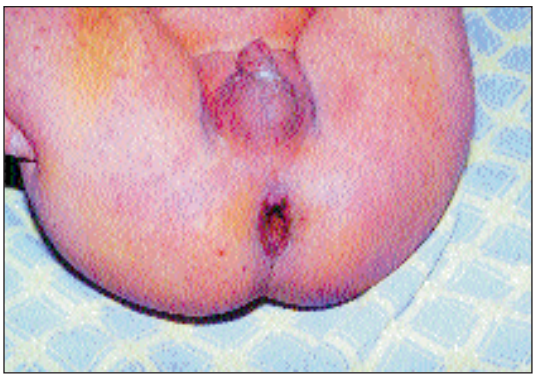

Figure 1. Erythematous and confluent macules, oral and anal mucosal lesions and multiple erosions on skin of patient.

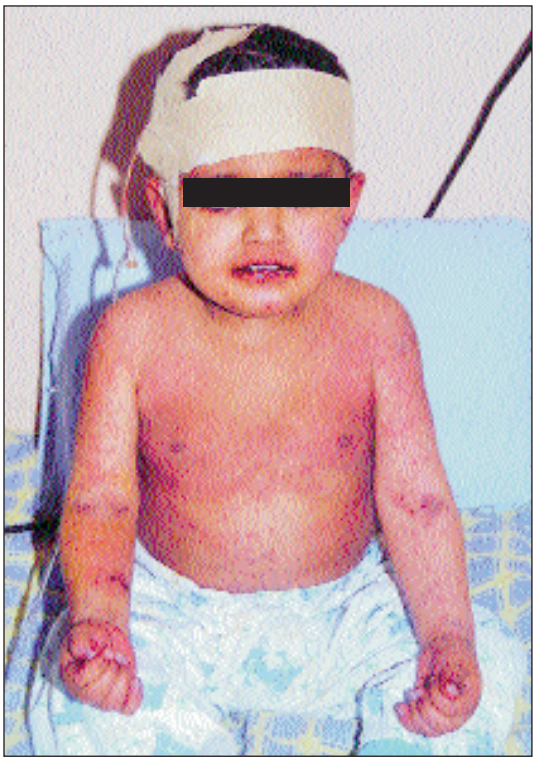

Figure 2. Allergic toxic skin reactions and conjunctivitis including Stevens-Johnson syndrome-like exanthema in the patient with acute lymphocytic leukemia.

DISCUSSION

SJS is a serious systemic disorder in which at least two mucous membranes and the skin are involved. Purulent conjunctivitis and stomatitis usually develop and cutaneous lesions tend to rupture leaving denuded skin that may result in significant fluid loss, anemia and a high risk for bacterial super infection and sepsis. The pathogenesis of erythema multiforme is unknown but is generally regarded as a hypersensitivity reaction triggered by drugs, infections, and exposure to toxic substances. Approximately 20% of cases, however, have no identified cause of the problem[3].

SJS has been reported previously in two children, one receiving HDMTX with leucoverin for tre-

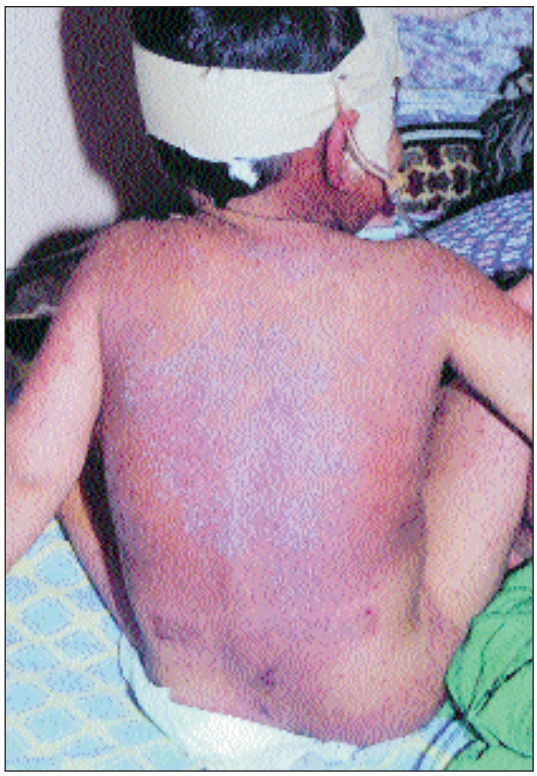

Figure 3. Denuded skin lesions that result in significant fluid loss, anemia and a high risk for bacterial super infection.

atment of ALL and the other receiving HDMTX regimen used for the treatment of non-Hodgkin's lymphomas[4,5]. Because of development of resistance to standard doses, high dose and intermediate dose methotrexate have been used after 1970. Mucositis, nausea, dermatitis exfoliativa and disturbances of B-lymphocytes have been reported after HDMTX, and the clearest toxic symptoms have been on bone marrow, liver and kidney. A clinical trial with methotrexate as consolidation therapy in ALL was started in June 1975[6]. Moe et al observed that stomatitis was a frequent complication of HDMTX and skin reactions which seemed to be dose related occurred in six of their patients[5]. Allergic toxic skin reactions including SJS-like exanthema occurred in our patient with ALL. The SJS caused by medication with MTX was clinically diagnosed, and the methotrexate was discontinued in our patient due to adverse reaction.

Although dermatological complications of methotrexate therapy appear to be relatively rare, they may be serious when they occur[7]. Our case demonstrates that the SJS can occur following 2 g/m^2 dose methotrexate in ALL. The syndrome was not present before the initiation of chemotherapy suggesting that it was not part of the presently features of his illness. He had the evidence of infection manifested by septicemia, but this occurred after the onset of the mucocutaneous reaction, and therefore, it appeared more likely a complication than the cause. These arguments provide a strong support for a causal relationship between the SJS and methotrexate administration in our case. Thus in the treatment of ALL with HDMTX, methotrexate toxicity should be carefully considered due to the increased toxicity and the risk of severe skin reactions.

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