

BRIEF REPORT

Systemic Near-Fatal Anaphylactic Reaction After Intrathecal Methotrexate Administration

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Hypersensitivity reactions after administration of antimicrobial agents is a well-known phenomenon. However, hypersensitivity reactions to anticancer chemotherapeutic agents have not received much attention [1]. Methotrexate (MTX) is a folic acid antagonist used in the treatment of various malignant and other diseases. It has been extensively used for more than 45 years, but there are few reports of immediate systemic hypersensitivity reactions attributed to MTX. The few recorded were usually produced by high doses of the agent [2,3].

Since the mid-1960s intrathecal MTX has been widely used for prevention or therapy of CNS leukemia, and a number of neurotoxicities have been identified [4–6]. These effects can be divided into acute, subacute, and delayed adversities. Systemic anaphylactic reactions being rare, we record our experience with this problem in a 9-year-old boy and review the relevant literature to familiarize clinicians with this urgent situation.

Our patient was admitted to hospital in March, 1998, for acute lymphoblastic leukemia (ALL). He had a 2-week history of sore throat, fever, and abdominal pain. Laboratory investigations revealed the following: hemoglobin 8.7 g/dl, white blood cell count (WBC) 156,000/mm³, platelets 66,000/mm³. The bone marrow aspiration was typical of ALL-L2. Immunophenotype revealed T-cell, CALLA(-) ALL. Molecular genetic studies identified no abnormality. Treatment was initiated using the BFM 86 protocol, and he achieved a complete remission after phase I.

During phase II, at the fifth intrathecal 12 mg MTX administration, paraparesis and hypoesthesia below the umbilicus occurred suddenly. One hour later the patient developed generalized pruritus and urticaria. Epinephrine, diphenhydramine, and oxygen were administered. One half hour later hypotension, respiratory wheezing and dyspnea, and tachycardia were noted. Antishock therapy was initiated immediately. Blood gases revealed severe acidosis and hypoxia so the patient was transferred to the intensive care unit where mechanical ven-

tilation was needed for five days. The patient's paraparesis recovered 10 hr later, but he developed right hemiparesis and right central facial paresis as a sequel. Magnetic resonance imaging of the brain revealed an increase in echogenicity of left basal ganglia and capsula interna, which was interpreted as an infarct. The patient is now well, and CNS prophylaxis has been switched to intrathecal cytarabine, and maintenance chemotherapy has also changed in order not to use oral MTX. His right hemiparesis has almost resolved with physical therapy.

DISCUSSION

Lumbar MTX administration is of proved value both for prophylaxis and for treatment of meningeal leukemia [7]. The most common reaction is an acute chemical arachnoiditis and meningismus developing within hours of administration, with symptoms such as back pain, nuchal rigidity, and fever [6–10]. The second type is a subacute neurotoxic reaction. There is more serious and lasting damage to the spinal cord and/or nerves with the development of paresis or paralysis [5–7,11,12]. It is generally associated with multiple intrathecal MTX injections and apparently results from prolonged elevation of MTX levels in the CSF [5]. The third type of neurotoxicity is a necrotizing encephalopathy. It occurs many months to several years after treatment and has been recognized with the longer survival of children who have been successfully treated for leukemia [6–8]. The inci-

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dence of leukoencephalopathy is dose-related, with respect to both MTX and cranial irradiation [13].

Our patient's problem was different. He exhibited an acute hypersensitivity reaction to MTX given intrathecally rather than neurotoxicity. Hypersensitivity reactions have been reported in nearly 20 cases and include anaphylaxis, urticaria, angioedema, acute pneumonitis, cutaneous vasculitis, severe epidermal toxicity, hemolytic anemia, and hepatitis [2,14,15]. MTX given for psoriasis by either the oral or the parenteral route has resulted in isolated instances of urticarial reactions; none was severe [16,17]. In recent years MTX has been used at extremely high doses especially in osteogenic sarcoma. Severe anaphylactic reactions to high-dose MTX have been reported in nine patients [1–3,14,18]. The mechanism of the anaphylaxis from high-dose MTX is not known. Da Costa and colleagues [19] studied seven patients on high-dose MTX and found that MTX coupled noncovalently to IgG in the plasma. In three of these patients, severe anaphylaxis developed after repeated MTX therapy. These authors suggested that, if the molar ratio of MTX to protein is high enough, as it is when large doses are used, protein–drug complexes can form and can be immunogenic.

Our patient is unique in the onset of acute systemic anaphylaxis after intrathecal MTX administration. MTX was responsible for the reaction because the preparation was preservative-free. Analysis of the drug was made by the Istanbul University Forensic Medicine Institute for purity of the same lot. They reported that there was no contamination by any toxic substance. The only similar case in the literature about hypersensitivity after intrathecal MTX administration was reported by Back [20] in an 11-year-old girl who developed urticarial rashes on her legs. Loss of sensation below the nipples supervened with no muscle power in the legs; after one half hour the patient died from cardiac arrest. Necropsy showed no anatomical cause of death. The remaining MTX was analyzed and no abnormality was found in the specimen [20].

In conclusion, intrathecal MTX administration is unquestionably an important part of the therapeutic armamentarium against leukemia and lymphoma. Clinicians must be aware not only of the neurotoxicity of the drug but also of the possibility of a systemic, near-fatal anaphylactic reaction, however rare this might be.

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