Rhabdomyolysis: an unusual complication of cytotoxic chemotherapy

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Acute rhabdomyolysis has rarely been reported after cytotoxic chemotherapy, including cytarabine and 5-azacytidine. We observed a case of acute rhabdomyolysis and renal failure after treatment with mitoxantrone and cyclophosphamide. No other cause of muscle injury could be identified, although biochemical analysis of a muscle biopsy specimen revealed a deficiency of muscle phosphorylase activity. Retreatment with doxorubicin and paclitaxel was not associated with recurrent rhabdomyolysis.

Keywords: cyclophosphamide; mitoxantrone; chemotherapy; acute rhabdomyolysis; phosphorylase deficiency.

INTRODUCTION

Rhabdomyolysis can be attributable to toxic injury to skeletal muscle that results in necrosis and release of the muscle cell contents. Myalgia associated with an increased creatinine phosphokinase (CPK) and myoglobinuria confirms the diagnosis [1]. The most common causes of rhabdomyolysis include trauma, vigorous exercise, heat exposure, high-voltage electrical shock, seizures, polymyositis, viral infections (e.g. influenza, cytomegalovirus, and human immunodeficiency virus), parasitic infections (e.g. toxoplasmosis and malaria), overwhelming bacterial infections, toxins (e.g. spider venom, hemlock, and carbon monoxide), alcohol abuse, and illicit drugs (e.g. heroin) [1,2]. Rhabdomyolysis has also been reported after the use of some prescription drugs, including some anaesthetic agents, iohexol contrast, antihistamines, and specific antihyperlipidemic agents (e.g. lovastatin) [2]. Antineoplastic agents have been rarely implicated as a cause of rhabdomyolysis [3-5]. We now report an unusual case of rhabdomyolysis after administration of mitoxantrone and cyclophosphamide, which has not been previously reported for these drugs.

CASE REPORT

A 46-year old African American woman with inflammatory breast cancer received mitoxantrone 28 mg m$^{-2}$ (57 mg), cyclophosphamide, 1200 mg m$^{-2}$ (2424 mg) and ondansetron 32 mg intravenously. Subcutaneous daily injections of granulocyte-colony stimulating factor (G - CSF) 5 $\mu$g kg$^{-1}$ (550 $\mu$g) began the next day. Six days later the patient noted myalgias, generalized muscle weakness, and fatigue; she discontinued G - CSF. Ten days after chemotherapy, the physical examination was remarkable in that there was only mild thigh tenderness. The creatinine phosphokinase (CPK) was 71 600 u/l (normal 10-100 u/l), aspartate aminotransferase 1079 u/l (normal 5-40 u/l), lactate dehydrogenase 3509 u/l (normal 50-250 u/l), blood urea nitrogen (BUN) 66 mg dl$^{-1}$ (normal 10-26 mg dl$^{-1}$), and the serum creatinine was 7.0 mg dl$^{-1}$. Urinalysis showed large occult blood and 1-2 red blood cells per high power field. There was no history of seizure, alcohol use or illicit drug use.
CHEMOTHERAPY INDUCED RHABDOMYOLYSIS

Fig. 1. Photomicrograph of muscle biopsy specimen showing necrotic skeletal muscle fibre (arrowheads) characterized by loss of fibrillar quality, absent cross-striations and surrounded by mononuclear cell inflammatory infiltrate.

There was no prior history of rhabdomyolysis or a family history of muscle disorder. The CPK and other muscle enzymes returned to normal level within 22 days, and haemodialysis was necessary for approximately 1 month. The serum creatinine returned to normal levels after approximately 5 months.

Diagnostic testing included: (1) a renal ultrasound—mild bilateral nephromegaly; (2) urine toxicology screen-negative for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and phencyclidine; (3) serum anti-nuclear and anti-Jo-1 antibody-negative; (4) thyroid stimulating hormone 6.03 μU/ml (0.5-5.0 μU/ml) and thyroxine 5.0 μg/dl (4.2-13.0 μg/dl); (5) herpes simplex and toxoplasma IgG titres - 1:8 and 1:256, respectively; (6) electromyography (EMG)—spontaneous activity consistent with myopathic changes of the muscle; and (7) muscle biopsy—rare basophilic degeneration of muscle fibres and rare lymphocytic infiltration surrounding a necrotic focus (Fig. 1). In addition, biochemical analysis of muscle biopsy revealed a reduced total phosphorylase level of 8.689 μmol min⁻¹ g⁻¹ (normal 24 ± 7.4 μmol min⁻¹ g⁻¹), but other enzymes including phosphoglycerate kinase, phosphoglcerate mutase, phosphofructokinase, and lactate dehydrogenase were normal.

The patient subsequently received doxorubicin 60 mg m⁻² (116 mg) every 3 weeks for five cycles and paclitaxel 175 mg m⁻² (350 mg) for four cycles. She underwent general anaesthesia with nitrous oxide, isoflurane, fentanyl, atracurium, vecuronium, and thiopental for a modified radical mastectomy without recurrent rhabdomyolysis. She was never rechallenged with mitoxantrone, cyclophosphamide, ondansetron, or G-CSF. She received radiotherapy to the right chest wall without incident. The patient remains without evidence of disease 18 months after her diagnosis.

DISCUSSION

A 46-year old woman with inflammatory breast cancer developed acute rhabdomyolysis complicated by acute renal failure within one week of receiving cyclophosphamide, mitoxantrone, ondansetron, and G-CSF. There was no obvious cause for rhabdomyolysis including trauma, alcohol use, heatstroke, or seizures. Other potential causes of myopathy such as illicit drugs, hypothyroidism, infection, and polymyositis were either excluded or not evident. Therefore, it appears that the rhabdomyolysis in the patient occurred as a consequence of the chemotherapeutic agents employed, ondansetron, or G-CSF.

Acute rhabdomyolysis is a rare complication of