

Thalidomide in Combination With Dexamethasone-Induced Rhabdomyolysis in a Patient With Refractory Myeloma

Thalidomide (Thalomid), an oral immunomodulatory and antiangiogenic agent, has been reported to restore and enhance the antimyeloma activity of dexamethasone.¹ In patients with untreated multiple myeloma (MM), the addition of dexamethasone to thalidomide is associated with a 63% response rate, but it also increases the incidence of venous thrombosis.^{1,2} We present here a patient with rhabdomyolysis in whom thalidomide was prescribed in combination with dexamethasone for refractory MM.

A 55-year-old man was diagnosed as immunoglobulin-A-lambda multiple myeloma (stage IIIA). Treatment with vincristine, doxorubicin, and dexamethasone was started at the time of diagnosis; however, the patient was refractory to therapy. This regimen was discontinued, and treatment was initiated with oral thalidomide (200 mg/d) in combination with dexamethasone (40 mg/d) for 12 days per month.

Several hours after the thalidomide/dexamethasone administration, the patient developed acute and intense generalized muscle pain. Laboratory testing showed increased levels of creatinine kinase (221 IU/L), lactic dehydrogenase (2,553 IU/L), aspartate aminotransferase (127 IU/L), and creatinine (2.2 mg/dL) in the patient's serum. Myoglobinuria was demonstrated by the urine sample, which was taken on the fourth day of initiation of his muscle pain (due to technical limitation) by using immunoturbidimetric assay. Myoglobinuria measured as 480.0 ng/mL (normal, 0.0–200 ng/mL) in the absence of red blood cells in the urinary sediment. Electromyography of the extremities revealed myopathic changes. The patient rejected muscle biopsy.

Analysis of metabolic detoxification enzymes cytochrome P450 (CYP),

glutathione S-transferase (GST), and N-acetyltransferase 2 (NAT2) polymorphisms were done using real-time polymerase chain reaction analysis (Roche Diagnostics, GmbH, Mannheim, Germany). For CYP, the findings were CYP2C9 (*2 and *3) heterozygous, and CYP2C19 (*2 and *3) wild. For GST, the findings were GSTP1 AB (heterozygous) and GSTT1 and GSTM1 positive. For NAT2, the findings were NAT2*5A heterozygous and NAT2 (*6A, *7A/B, and *14A) wild.

Therapy was promptly discontinued; within several days, the laboratory values returned to pretreatment levels, and his symptoms disappeared. Monotherapy with thalidomide (100 mg/d) was started 2 weeks after cessation of the patient's symptoms. The patient's hematologic condition deteriorated after about 1 month, and dexamethasone was added again. However, the patient once again developed the same adverse effects, and therapy was discontinued. Treatment with bortezomib (Velcade) was then successfully initiated.

Glucocorticoids and Muscle Injury

Glucocorticoids (mainly fluorinated steroid dexamethasone) have been reported to possess a myotoxic effect, and the incidence of steroid-induced myopathy has varied from 7% to 60%.³ The pathogenetic mechanisms of glucocorticoid-induced muscle injury remain unclear, though there is evidence that mitochondrial dysfunction and oxidative stress are involved in this process.⁴ The risk of rhabdomyolysis with glucocorticoid use can be exacerbated by a compromised specific drug-metabolizing enzyme profile.⁴ Unlike glucocorticoids, thalidomide is not reported to cause rhabdomyolysis. Our patient had evi-

dence of inherited absence or deficiency of xenobiotic enzymes. Monotherapy with thalidomide or dexamethasone in combination with vincristine and doxorubicin did not exhibit a myotoxic effect. However, the patient had an immediate myotoxic effect from thalidomide in combination with dexamethasone in the first administration, and this adverse effect recurred in the second administration. Therefore, we present this case to increase clinicians' awareness for the potential of combination therapy with thalidomide and dexamethasone to adversely affect muscles in susceptible patient populations. To our knowledge, this is the first known case of rhabdomyolysis associated with this therapy.

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