Hyperpyrexia, Allergic-Type Response and Death occurring with Low-Dose Bleomycin Administration

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Key Words

Hyperpyrexia
Bleomycin
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Abstract

This is a case report of hyperpyrexia, shock and death following initial injection of low-dose bleomycin (7.5 units) for a poorly differentiated metastatic carcinoma. Premedication with high-dose dexamethasone and acetaminophen did not abort the reaction. A review of the literature uncovered one nearly fatal reaction to a test dose of 1 unit of bleomycin. All previously reported fatal cases were in patients with lymphoma who had received an initial dose of at least 25 units/m². Since the 'safe' test dose of bleomycin is not known, test doses of 1 unit or lower should be routinely used; the effect of premedication is also unclear.

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Introduction

Bleomycin was approved in the United States in 1975 for use against squamous cell cancers, malignant lymphomas and testicular cancers with proven efficacy against all these malignancies. Its toxicities are many and a peculiar allergic-type of reaction has been observed almost exclusively in lymphoma patients receiving at least 25 units/m². We report a dramatic case of this toxic reaction in a patient receiving low-dose bleomycin and suggest the continued usage of 1 unit or less test dose administration to hopefully select out those patients susceptible to this life-threatening response.

Case Report

A 67-year-old white male was admitted to the medical service in July 1977 for evaluation of a persistent fever. Physical examination disclosed a rapidly growing, painful 8x6 cm, deeply indurated red skin plaque located superior to the left medial malleolus. Deep incisional biopsy revealed a poorly differentiated tumor which could not be further characterized microscopically or by electron microscopy.

Because of its aggressive nature with infiltration to the periosteum and poor differentiation, it was treated as a poorly differentiated sarcoma with an above the knee amputation.

Fever and general malaise disappeared. Multiple laboratory studies and lymph node biopsy failed to show tumor spread. 5 weeks later he rapidly developed multiple indurated raised red skin plaques and three subcutaneous nodules. Biopsy showed features of tumor stage mycosis fungoides.

Multiple lung nodules were now seen on chest X-ray. A brain scan, performed after sudden onset of grand mal seizures, showed a left frontal parietal mass. Tumor cells were found in the cerebrospinal fluid. Seizures were controlled with dilantin, phenobarbital, and de-cadron. His rapidly metastasizing tumor was treated with a single dose of methotrexate 450 mg with citrovorum rescue according to the National Mycoses Fungoides Chemotherapy Protocol. The response was dramatic with marked shrinkage of tumor nodules.

Adriamycin, 60 mg i.v., and bleomycin, 7.5 units i.m. were injected on the 15th day. 3 h after the bleomycin injection, he spiked a temperature to 107 °F and blood pressure dropped to 80/30. A wheal and flare reaction developed at the injection site. Shock was vigorously treated with hydration, subcutaneous and intravenous epinephrine, intravenous diphenhydramine, alcohol baths, and cooling blanket. Over the next 2 h his temperature decreased to 102 °F and his blood pressure stabilized to 130/60. However, 4 h later, he again became hypotensive, blood pressure dropping to 50/20 and urine output to 10cm³/h. His pressure normalized and an epinephrine drip was discontinued. For the next 2 days he remained febrile

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(103 °F) and oliguric (5–10 cm³/h), despite vigorous therapeutic measures.

Before expiring he developed intractable hyperkalemia without evidence of hemolysis or rhabdomyolysis. Multiple antemortem and postmortem urine, blood and sputum cultures showed no growth. Autopsy revealed disseminated, poorly differentiated tumor infiltrates: acute tubular necrosis.

Discussion

Bleomycin's prominent toxicities include skin rashes, pyrexia and pulmonary complications. Pyrexia is quite common, occurring in 20–50% of patients receiving the drug. Fever greater than 103 °F. is not unusual. The mechanism of fever production in man is unknown. Dinarello [x] showed that supernatant fluid of human and rabbit leukocytes, incubated overnight with bleomycin, produced a rapid-acting pyrogen. Endotoxin was carefully searched for, but not found. The effects of bleomycin on the hypothalamic thermoregulator could not be measured. In addition to the frequent pyretic complication, a rare, acute fulminant reaction to bleomycin has been described. Blum et al. [1] report four lethal reactions (all in lymphoma patients) characterized by profound hyperpyrexia and cardiopulmonary collapse after their first course of high-dose bleomycin (25–40 units/m²).

In addition to the four noted above, Blum et al. [1] report 5 additional lymphoma patients with milder, but severe hyperpyretic reactions to initial high-dose bleomycin. Of a total of 149 lymphoma patients studied, 9 (6%) developed this unusual response. Durkin [2] reported a nearly fatal reaction in a patient with histiocytic lymphoma who received a test dose of 1 unit (1 mg) bleomycin.

We describe our patient as the first reported case of a death directly related to low-dose bleomycin. Our patient was receiving acetaminophen 650 mg every 4 h, dexamethasone 16 mg daily beginning 1 week before the reaction and was acutely treated with epinephrine and antihistamines. All these measures neither prevented nor substantially altered his course. There is previous anecdotal evidence that premedication with antihistamines and antipyretics may prevent or mitigate the response [3]. The appearance of a wheal and flare reaction at the site of injection directly implicates bleomycin and points to the possible use of intradermal skin testing for

uncovering hypersensitivity reaction, although skin testing in humans with bleomycin has never been studied.

Severe reaction to bleomycin can occur with small or large doses of the drug and many centers no longer 'pretest' with the empirical 1 unit dose of bleomycin. However, we recommend that the unit test dose be administered, since ours is the only reported death we could find in the literature which was directly related to the initiation of low-dose bleomycin (7.5 units).

References

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