Pulmonary Granulomas in a Patient on MER Therapy

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Received March 30, 1977

A patient with metastatic melanoma developed symmetric miliary infiltrates of the lungs while receiving injections of MER into tumor containing lymph nodes of the groin. Open lung biopsy identified the pulmonary lesions as caseating epithelioid granulomas. After cessation of MER therapy, the pulmonary lesions regressed spontaneously. The possible etiology of this so-far-unreported complication of MER therapy was briefly discussed.

INTRODUCTION

The complications of Bacillus Calmette-Guerin (BCG) immunotherapy have been recently reviewed in detail [1]. The most serious include fatal anaphylactic reactions, disseminated BCG infection and hepatic dysfunction. Although the majority of those complications have been noted with intratumoral BCG, complications of this nature have also been reported using scarification techniques [2]. A recent report implicated oral BCG as a cause of granulomatous pneumonitis [3].

The use of the methanol extraction residue of BCG (MER) as a non-specific immunopotentiator is attractive because it avoids administration of live organisms to immunosuppressed patients. The extract is also more readily quantified, considered stable, and of low toxicity [4].

A previously unreported complication of intratumoral MER is presented.

Case Report

A 51 year old white female with surgically resected Stage II melanoma (positive nodes) of the left lower extremity was seen at the University of Connecticut Health Center for consideration of adjuvant immunotherapy.

Immunologic evaluation at this time showed her to be reactive to two of four recall antigens in vivo (mumps and streptokinase/streptodornase). Lymphocyte proliferative response to the non-specific T cell mitogens, phytohemagglutinin and concanavalin A, was normal. Stimulation indices in vitro to specific antigens (candida, mumps, streptokinase/streptodornase) were all greater than 12. However, response to purified protein derivative of tuberculin both in vivo and in vitro was negative. Immunoglobulin levels were normal. Clinical evaluation revealed no evidence of distant metastases.

The patient was given a total of 0.5 mg of MER BCG (Phipps Strain) intradermally into 5 sites according to the protocol of Dr. Mitchell.1

1 Melanoma protocol originating from the Yale Comprehensive Cancer Center, Malcolm S. Mitchell, Principal Investigator

Four weeks after

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admission into the protocol, the patient developed multiple amelanotic nodules around the lymphadenectomy incision site in the groin and a subcutaneous mass appeared just below the incision.

The patient was then given intralesional MER. A test dose of 50 ugm (25 ug each in each of two skin nodules) was injected and the patient responded vigorously within 24 hours with local erythema and induration. There was an associated systemic reaction with chills and temperature reaching 39.5C.

Four days later, 20 additional nodules were injected, using a total dose of 40 ug. A single dose of hydrocortisone, 100 mg intramuscular, was administered one hour after MER injection and no fever or chills developed. One week later, the remaining skin nodules were injected with another 40 ug dose of MER.

Shortly following the last injection, the patient complained of fatigue and a dry cough. Chest radiograph at this time, in striking contrast to a previous normal study three weeks earlier, revealed a fine nodular miliary pattern involving both lungs symmetrically suggesting an interstitial pattern (Figs. 1 and 2). The differential diagnosis included granulomatous disease, pneumoconiosis, hypersensitivity, sarcoïd or highly vascular metastatic neoplasms [5,6]. Arterial blood gases and respiratory screening function tests were within normal limits.

A transient minimal elevation of the alkaline phosphatase was the only laboratory abnormality noted. Liver scan at this time was normal.

Repeat immune testing at this time showed reactivity to PPD both in vivo and in vitro. Peripheral blood T cells (by E rosette) and B cells (by EAC rosette) were normal in number.

In order to clarify the nature of the pulmonary changes, an open lung biopsy was performed.

Light microscopic examination of the lung biopsy revealed numerous histiocytic granulomas measuring up to 1 mm in diameter. Admixed with the histiocytes, there were scattered lymphocytes and occasional multi-nucleated giant cells (Fig. 3a, b). The central portion of the larger granulomas had undergone caseation necrosis. No acid-fast bacilli or particles were identified in slides stained according to the Ziehl-Neelsen method.

Within a month after cessation of MER therapy, the chest infiltrate had cleared completely.

DISCUSSION

Miliary granuloma of the liver and lung have been reported as complications of BCG therapy by various routes of administration [1,2,3]. Only rarely are organisms recovered from these lesions [2]. MER is purportedly a cell free extract of BCG, and it is not surprising that no mycobacteria were found in the lung of this patient.

The appearance of caseating granulomas in the lungs was interpreted as a sign of local hypersensitivity reaction, although we have not identified the causative antigen nor fully elucidated the exact pathogenesis. The formation of granulomas in the lungs was temporarily related to MER treatment, and the discontinuation of MER therapy led to spontaneous regression of pulmonary lesions. One could thus postulate that the formation of granulomas occurred due to the presence of an incitive antigen in the MER or that MER treatment only potentiated and made possible a localized granulomatous response to an inhalation antigen. The latter explanation seems more plausible. An analogy could be made between our observation and an experiment reported by Petersen et al. [7]. In those experiments, animals were exposed to an inhalation antigen, known to produce pigeon breeders' disease, and concomitantly
injected with killed BCG. Animals developed a granulomatous cell-mediated hypersensitivity reaction localized exclusively to the lungs.

The main purpose of this report was to indicate that MER may produce pulmonary granulomas. Unanticipated as it was in our patient, this complication may be confused with dissemination of the tumor, miliary tuberculosis or some other granulomatous or fulminant infectious disease. In future cases that develop pulmonary infiltrates while on MER therapy for cancer, tissue diagnosis of the lesion may be required, but a more conservative approach could be also chosen, since it appears that the granulomas could spontaneously regress upon cessation of therapy, as illustrated in the present case.
FIG. 3. Pulmonary granuloma a. low power view of the lesion. H & E x 120. b. high power view of the granuloma. Note caseation necrosis and multi-nucleated giant cells. H & E x 210.

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