Reversible Bone Marrow Granulomata and Fever Induced by Phenytoin Administration

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Bone marrow biopsy in the evaluation of idiopathic febrile illness can yield very useful information. The incidence of bone marrow granuloma formation in core needle biopsies is 1.2%.[1] Although the vast majority of bone marrow granulomata are due to infectious and neoplastic causes, a number of reported cases have been related to pharmacologic agents.[2–4] In a large published series, 12% of cases of granulomata found in bone marrow were attributable to drug administration.[5] This report describes a patient whose bone marrow granulomata and fever rapidly resolved after the cessation of phenytoin.

CASE REPORT

R.T., a 47-year-old male patient followed at the Riverside Family Practice Center, was admitted to the hospital on January 4, 1989, after a generalized seizure. He had noted fever, chills, and malaise for approximately 2 days prior to admission. The patient had a history of a generalized seizure disorder after a head injury in 1959 and had been taking phenytoin, 100 mg three times daily, since that time. His other medical problems included chronic alcoholism, ataxic gait, diarrhea, and episodic depression. Six months before admission, phenobarbital had been prescribed after the patient had a generalized seizure despite a therapeutic serum phenytoin level. The only other regularly prescribed medication was fluoxetine for depressive symptoms. The patient had been abstinent from alcohol for a period of 6 months and had been attending an outpatient detoxification program. At admission, R.T. was alert, oriented, and appeared somewhat emaciated. His oral temperature was 39.5 °C (103.1 °F), blood pressure 124/68 mm Hg, pulse 102 beats per minute, and respirations 24/min and unlabored. The skin was warm and clammy, but no cutaneous lesions were seen. Examination of the head, neck, chest, and abdomen were unrevealing. No adenopathy was noted in the axillae or inguinal regions. A neurologic examination revealed marked cerebellar ataxia and bilateral positive Babinski signs, which had been documented on previous examinations. No focal neurologic signs were found, and there was no evidence of meningeal irritation.

Laboratory studies demonstrated a normocytic anemia with a hemoglobin of 125 g/L (12.5 g/dL) and a white blood cell count of 13.8×10^9/L ($13.8 \times 10^3/\mu$L) with 0.88 segmented neutrophils, 0.07 monocytes, and 0.05 lymphocytes. A serum chemistry profile was significant only for an alkaline phosphatase of 3.2 μkat/L (190 μ/L) and cholesterol of 5.80 mmol/L (225 mg/dL). A Westergren sedimentation rate was 30 mm/h. The serum phenytoin level was 85 μmol (21.5 mg/L) and the phenobarbital level 68 μmol/L (15.8 mg/L). A lumbar puncture yielded clear fluid that contained only 1 white blood cell per cubic millimeter, revealed no organisms on Gram stain, and had normal glucose and protein values. Computed tomography of the head demonstrated marked cerebellar degeneration but no acute features. Samples of blood, cerebrospinal fluid, urine, sputum, and stool were sent to the laboratory for culture.

In the hospital, fevers were noted daily for 2 weeks, ranging from 38.3 to 40.2 °C (101.0 to 104.4 °F) orally. Phenobarbital was discontinued because of excessive sedation and an apparent lack of efficacy in preventing recurrent seizures. An extensive workup was performed because of the fever of unknown origin. Cultures of all body fluids were repeatedly negative. A chest x-ray examination was unremarkable. Paranasal sinus x-ray examinations were negative, but the patient was treated with oral ampicillin for 10 days because of complaints of maxillary congestion and pressure. There was no response to antibiotic administration. First and second strength PPD skin tests were negative, and there was a positive response to *Candida* and mumps controls. Serum fungal titers were negative. Sero-

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logic tests for Lyme disease, syphilis, streptococcal infection, mononucleosis, rheumatoid factor, antinuclear antibodies, cold agglutinins, and specific febrile agglutinins were negative. Tests for HIV antibody and antigen were negative, and T cell studies were normal. Computed tomography of the abdomen revealed a lesion in the liver that was determined to be a hemangioma by ultrasonography and hepatic radionuclide scanning. An echocardiogram showed evidence of mitral valve prolapse, but no valvular vegetations. The patient experienced some watery stools, which were negative for ova and parasites. Colonoscopy was performed, and no active inflammation was exhibited. A repeat sedimentation rate rose to 55 mm/h.

An infectious disease consultant suggested the discontinuation of phenytoin therapy when no source for this febrile illness could be found despite a lengthy evaluation. It was decided to substitute carbamazepine for control of seizures. When a serum carbamazepine level was in the therapeutic range on the 14th hospital day, phenytoin was discontinued. The patient promptly defervesced over the next 48 hours and remained afebrile for the remainder of the hospitalization. A bone marrow biopsy performed on the 15th hospital day contained numerous noncaseating granulomata. Stains for acid-fast bacilli were negative.

Because of the patient's marked clinical improvement, he was sent home and continued on carbamazepine and fluoxetine. His weight increased by 10 pounds, his hemoglobin rose to 130 g/L (13 g/dL), and the sedimentation rate fell to 8 mm/h as an outpatient over the ensuing 6 weeks. Cultures of aspirated bone marrow were negative for mycobacteria after 6 weeks. A repeat bone marrow core biopsy performed 7 weeks after the initial biopsy was normal, with no evidence of granulomata.

DISCUSSION

The majority of cases of bone marrow granuloma formation in the medical literature arise from infectious and malignant causes.[1,5,6] A syndrome of idiopathic granulomatosis and fever of unknown origin has also been recently reported.[7] This report is the third to link bone marrow granuloma formation with phenytoin.[2,5] Unique to this case, however, is the association of reversible fever and bone marrow granulomatosis with the drug as well as the long duration of therapy prior to the emergence of symptoms. Bodem et al[5] described administration of medications up to 2 years before the onset of symptoms that ultimately led to the performance of a diagnostic core needle biopsy. The idiosyncratic nature of the relationship between the time of onset of drug administration and bone marrow granulomatosis is suggestive of a hypersensitivity reaction. It is possible, however, that such a reaction to a previously well-tolerated drug requires another unknown co-factor for clinical expression.

This report should raise awareness in clinicians to a potential hazard of a commonly prescribed agent. This case also demonstrates the utility of bone marrow core biopsy in the evaluation of fever of unknown origin, especially in a patient with a contraindication to liver biopsy (ie, liver hemangioma). Although the pathologic findings in the bone marrow were unspecific, they provided objective laboratory markers that implicated a medication as the source of iatrogenic illness. Phenytoin administration should be considered as a potential cause of fever of unknown origin, even in patients in whom the drug has been administered for long periods of time without any obvious difficulty.

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