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Rickets associated with gastrointestinal disease in a patient with chronic granulomatous disease

Mary Beth HoganMD^a [[MEDLINE LOOKUP](#)]

Eric MillmanMD^b [[MEDLINE LOOKUP](#)]

Evan JonesMD^a [[MEDLINE LOOKUP](#)]

Nevin W. WilsonMD^a [[MEDLINE LOOKUP](#)]

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ALT Alanine aminotransferase

CGD Chronic granulomatous disease

NBT Nitroblue tetrazolium

Chronic granulomatous disease (CGD) is a primary immunodeficiency characterized by the defective production of superoxide by neutrophils, resulting in recurrent infections from organisms

such as *Staphylococcus aureus*, *Serratia* species, and *Aspergillus* species.¹ Other complications include colitis and hepatic granuloma formation, resulting in elevated liver enzymes, malabsorption, or obstruction.² Rickets has not previously been reported in children with CGD despite the fact that children with other gastrointestinal diseases³ may develop rickets. We describe a child with chronic granulomatous disease with gastrointestinal disease associated with rickets.

Case report

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The patient is a 3-month-old black male who initially presented with adenopathy and fever. His family history was negative for immunodeficiencies or familial rickets. Immunoglobulins were elevated except for his IgE level, which was 6 U/ml (normal range, 12 to 56 IU/ml). An HIV test result was negative. It was noted that his stool tests were hemocult positive, and his alanine aminotransferase (ALT) level was 250 U/L (normal range, 7 to 46 U/L).

Four months later, the child had fever, hepatomegaly, and left hand swelling. His ALT level was 403 U/L. X-ray films revealed osteomyelitis of the left hand, arm, and frontal bone. Pneumonia was noted on chest x-ray films. Pus aspirated from the left ulna grew *Serratia marcescens*.

The child was sent to another hospital for evaluation of his gastrointestinal problems. A colon biopsy revealed colitis. T- and B-cell subsets were normal, and a nitroblue tetrazolium (NBT) result of 95% (normal range, 95% to 100% reduction) was obtained. He was noted to have developed rickets. The child was started on oral 1,25-OH vitamin D replacement therapy and referred to our institution.

When first seen at our hospital, he was very irritable when moved or touched. Positive findings on examination included hepatomegaly and tenderness on palpation of all long bones. He refused to sit, stand, or hold his bottle. The child also had marked failure to thrive. Laboratory evaluations included a blood urea nitrogen level of 7 mg/dl (normal range, 5 to 17 mg/dl) and a creatinine level of 0.3 mg/dl (normal range, 0.3 to 0.6 mg/dl). His ALT level was 403 U/L, and his alkaline phosphatase level was 1058 U/L (normal range, 115 to 460 U/L). Vitamin D levels were normal. The parathormone level was elevated at 97 pg/ml (normal range, 10 to 55 pg/ml). Malabsorption studies were normal except for a serum CO₂ level of 14 mmol/L (normal range, 18 to 27 mmol/L). Rachitic changes were noted on chest x-ray and long bone films (Fig. 1, *left*).

Fig. 1. Left, Anterior posterior view of right knee before treatment of CGD demonstrating frayed distal femoral metaphysis, mild bowing of the femur, and fraying of proximal tibia and fibula. **Right,** AP view of right knee following treatment of CGD with complete resolution of rachitic bone changes.



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An abdominal ultrasound showed a thickened bowel wall, and a liver biopsy revealed small granuloma formation.

The patient was identified as having chronic granulomatous disease when his dihydrorhodamine test was identified as abnormal. Trimethoprim-sulfamethoxazole and interferon- γ therapy were initiated. Four days later, the patient's ALT level was 394 U/L, and his alkaline phosphatase level had fallen to 702 U/L. By day 6, the ALT level was close to the normal range (114 U/L), and the alkaline phosphatase level had significantly declined to 554 U/L. Long-term follow-up of the patient has shown resolution of his metabolic and radiographic bone disease (Fig. 1, *right*) and his failure to thrive.

Discussion

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Rickets is a metabolic bone disease of childhood. Clinically, rickets is noted by growth failure, bowed extremities, and pain. Radiographic and clinical evaluations were used to determine the etiology of this child's rickets. Key radiographic points in this patient elucidating gastrointestinal rickets include the presence of frayed metaphyses of long bones, the equal involvement of both upper and lower extremities, and the bowing of the lower extremities.⁴ Clinically, this patient demonstrated gastrointestinal symptoms of colitis (hemocult-positive stools) and signs of hepatitis (elevated liver enzymes) from an early age. An abdominal ultrasound revealed thickening of the bowel wall. Biopsy of the patient's liver and colon showed granuloma formation and colitis, respectively. These factors support a gastrointestinal disease process as the origin of the rickets.

Radiographic and clinical information also helped to exclude other known causes of rickets. Osteomalacia is a major radiographic finding of renal rickets, which was not found in our patient, and metabolic renal studies were normal. Inherited forms of vitamin D-resistant rickets are characterized by short squat bones, and the lower extremities are more affected than the upper extremities.⁵ These radiographic findings were not present in this child.

Biochemical improvement in rickets usually will be apparent within a few days to 1 week after 1,25-OH vitamin D supplementation.⁵ However, this child deteriorated clinically over the time period of vitamin D supplementation. Only after treatment for CGD was initiated did a decline in the alkaline phosphatase occur, suggesting slowing of the metabolic turnover of bone. We speculate that this

improvement occurred because the underlying cause for the rickets was no longer active.

It is important to note that the referring hospital considered CGD in the differential diagnosis and obtained a normal NBT test. However, the clinical presentation of this child's illness still made CGD the most likely cause. The dihydrorhodamine test was subsequently performed, and it confirmed that the immunodeficiency was indeed CGD. False-normal NBT tests have been noted previously.² We agree with Liese et al.² that the NBT test may no longer be an appropriate test for CGD because our patient may eventually have had a fatal outcome because of the inappropriate exclusion of CGD based on an erroneous NBT test.

This child had CGD with hepatic and gastrointestinal granulomatous involvement. He had rickets during the period that his CGD was undiagnosed and untreated. There was no evidence of other causes of rickets. There was no improvement in his rickets, despite vitamin D therapy, until treatment for his CGD was initiated. We conclude that CGD may be complicated by rickets. This rickets is likely a result of chronic inflammation and granulomatous involvement of the gastrointestinal tract.

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- *From the Departments of ^aPediatrics and ^bRadiology, West Virginia University School of Medicine, Morgantown.*
- *Reprint requests: Mary Beth Hogan, MD, West Virginia University School of Medicine, Department of Pediatrics, Morgantown, WV 26506-9214.*
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