Chronic Recurrent Multifocal Osteomyelitis and Thalidomide in Chronic Granulomatous Disease

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abstract

Chronic granulomatous disease (CGD) is a primary immunodeficiency that leads to severe recurrent infection and inflammatory complications that are usually difficult to diagnose and treat. Several hyperinflammation mechanisms, such as decreased neutrophil apoptosis, toll-like receptor activation imbalance, Th17 cell induction, Nrf2 activity deficiency, and inflammasome activation, have been described in CGD patients However, there have been no reports of chronic recurrent multifocal osteomyelitis as an inflammatory complication in CGD, and the differential diagnosis of this condition with infectious osteomyelitis is challenging. Thalidomide has been used to treat several inflammatory manifestations in CGD patients with good clinical results. Here, we report the case of a previously asymptomatic 11-year-old boy who consulted for difficulty walking and pain at the back of the right thigh, with increased inflammatory markers. Multifocal bone involvement was seen on bone scintigraphy, and acute-phase reactants were elevated. On the basis of a suspected diagnosis of infectious osteomyelitis, broad-spectrum antibiotic therapy was started, with no clinical response. Bone biopsy and microbiological tests yielded negative results; at that point, chronic recurrent multifocal osteomyelitis was suspected. The patient was unresponsive to nonsteroidal antiinflammatory drugs and corticosteroids. Thalidomide was started, and within 6 months, clinical and radiologic resolution of the condition was achieved with no adverse effects. More than 1 year after stopping thalidomide, the patient remained free of symptoms and inflammatory parameters are within normal levels. Thalidomide has a favorable safety profile compared with other alternatives and could be considered a feasible therapeutic option for this type of condition in selected patients.

Chronic granulomatous disease (CGD) is an uncommon primary immune deficiency caused by abnormal phagocytic activity. The disease results from defects of dinucleotide phosphate oxidase (NADPH oxidase), an essential enzyme involved in mediating the destruction of certain microorganisms, including *Staphylococcus aureus*, *Aspergillus* spp, *Burkholderia cepacia*, and other Gram-negative bacteria.[1,2] Inflammatory manifestations in the gastrointestinal tract, urogenital tract, and lungs are a great concern in CGD patients.[3,4]

Chronic recurrent multifocal osteomyelitis (CRMO) is an uncommon chronic inflammatory illness of unknown origin that courses with chronic pain and aseptic inflammatory bone lesions

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Dr Martín-Nalda drafted the initial manuscript; Drs Roca, Fontecha, Fernández-Polo, Barber, Martinez-Gallo, and Soler-Palacin critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2015-4017

Accepted for publication May 13, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Martín-Nalda A, Roca I, Fontecha CG, et al. Chronic Recurrent Multifocal Osteomyelitis and Thalidomide in Chronic Granulomatous Disease. *Pediatrics.* 2016;138(2):e20154017

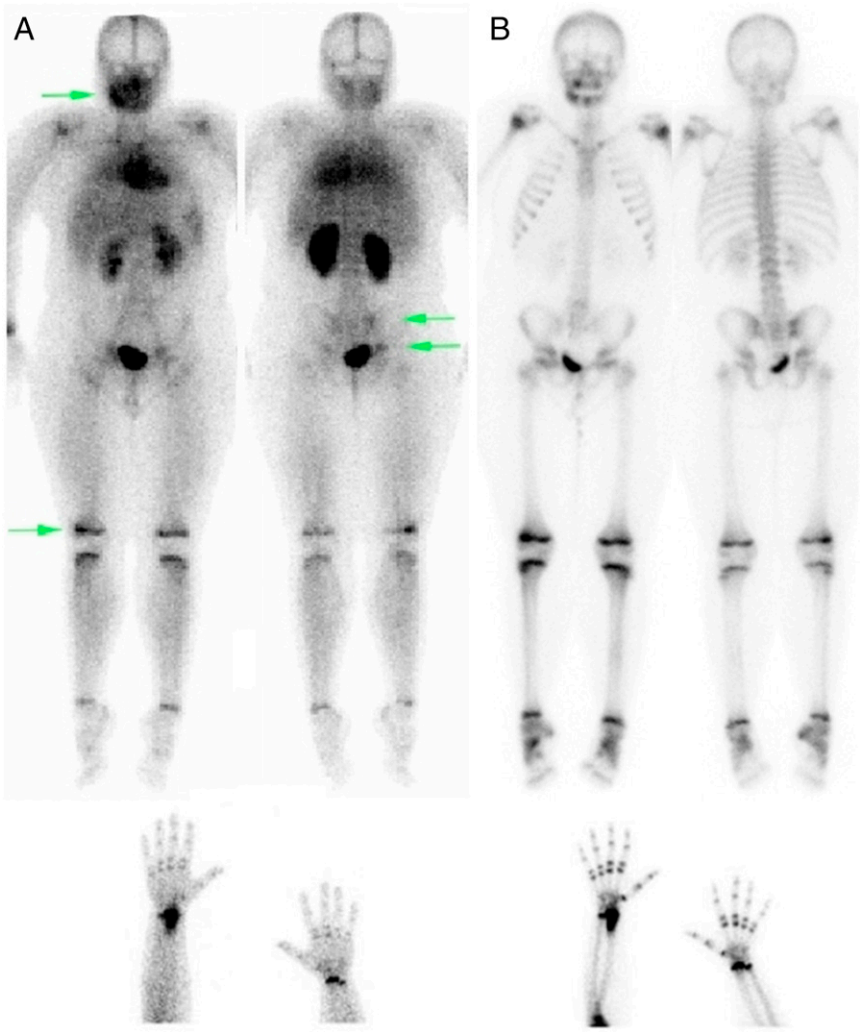

FIGURE 1
Bone scintigraphy at diagnosis. A, The blood pool whole-body image shows several hyperaemia located on the right mandibula, distal right radius, right iliac bone and right acetabulum, and distal submetaphyseal area of the right femur. B, On the whole-body bone images, all these lesions show an increased bone uptake.

unresponsive to antibiotics. Neutrophils, which have critical effector functions, are essential in this autoinflammatory bone disease, as are other factors, such as caspase-1, caspase-8, and interleukin-1β.[5] The differential diagnosis includes chronic infectious osteomyelitis, Ewing sarcoma, and Langerhans histiocytosis among other conditions.[6]

Radiography of the symptomatic regions may show osteolytic lesions affecting long bone metaphyses, but this finding is neither sensitive nor specific for CRMO. Whole-body bone scintigraphy is useful for identifying other affected sites and is more sensitive than radiography for detecting inflammatory bone lesions, whereas MRI provides better anatomic definition of the affected bone and soft tissue. Bone biopsy with compatible histologic findings and negative microbiological culture are usually needed to establish a definite diagnosis.[7]

Thalidomide has properties similar to those of tumor necrosis factor-α (TNF-α) antagonists (ie, immunomodulatory, antiinflammatory, and potentially antineoplastic activities) but with a lower associated risk of developing infections. Data from in vitro studies and clinical trials suggest that these properties are related to suppression of excessive TNF-α production, down-modulation of selected cell surface adhesion molecules involved in leukocyte migration, and antiangiogenic activity. Thalidomide has been proposed as appropriate therapy for several inflammatory manifestations in CGD patients (eg, colitis, interstitial lung disease, neutrophilic dermatosis) with good clinical results.[8,9] Because of its known teratogenicity, thalidomide use should be accompanied by strict precautions in women of childbearing age and postpubertal men.[10]

We present the case of a child with CGD who developed CRMO and was successfully treated with oral thalidomide. Written informed consent and institutional review board approval were obtained.

CASE PRESENTATION

An 11-year-old boy consulted for difficulty walking and pain in the back of the right thigh. He had been diagnosed with X-linked CGD at age 1 month on the basis of a family history of the condition. Molecular study of the *CYBB* gene identified the 387G>A mutation in exon 5, which generates a premature stop codon in Trp125×, resulting in the defect.[11] He had been receiving an appropriate prophylaxis regimen (trimethoprim-sulfamethoxazole and itraconazole) for his condition, together with subcutaneous interferon-γ, and had experienced no complications up to the time of the visit.

Blood tests showed elevated inflammatory parameters (total white cell count 11 200/mm^3, C-reactive protein 7.25 mg/dL, and erythrocyte sedimentation rate 101 mm/h). ^{99m}Tc-DPD bone scintigraphies were performed at diagnosis and after treatment and included whole

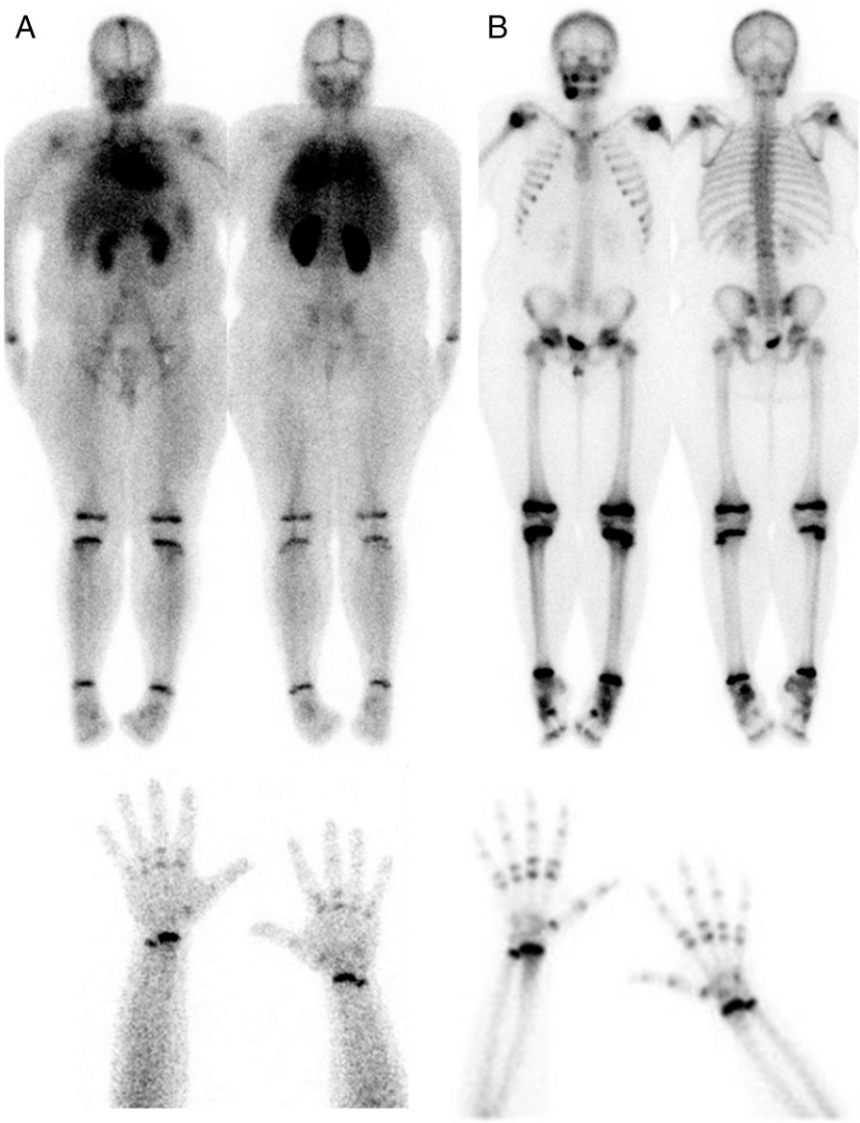

FIGURE 2
Bone scintigraphy after treatment. A, The blood pool whole-body images do not detect hyperaemic lesions. B, On the whole-body bone images, the bone uptake continues to be increased on the right mandibula and slightly on the distal radius but is normalized on all the other bone lesions.

body blood pool images (obtained just after the tracer injection) and 2-hour whole-body bone images. At diagnosis, the images detected multiple hyperemic blood-pool positive lesions with increased bone uptake located on the right mandibula, distal right radius, right iliac bone and right acetabulum, and distal submetaphyseal area of the right femur (Fig 1). MRI of the pelvis and proximal femur showed hyperintensities on T2 and hypointensities on T1 in these locations, suggesting bone edema. On the basis of a suspected diagnosis of infectious osteomyelitis, broad-spectrum antibiotic therapy was initiated. Biopsy of the iliac bone was carried out. Microbiologic studies, including broad-range 16S ribosomal DNA and panfungal polymerase chain reaction, were negative. Histopathological evaluation showed polymorphonuclear cells, a mild infiltrate of plasma cells, and small devitalized bone fragments with signs of bone resorption, findings consistent with acute osteomyelitis. Repeated blood cultures yielded negative results.

Empirical antibiotic therapy with meropenem was maintained for 2 months, but the patient remained symptomatic, and acute-phase reactants were persistently elevated in blood tests (C-reactive protein 2 mg/dL and erythrocyte sedimentation rate 75 mm/h). A new bone scintigraphy demonstrated an increasing number of bone lesions, including the right jaw, both proximal humeral metaphyses, both distal femoral metaphyses, and the distal metaphysis of the right radius. The patient showed no signs of pustulosis or acne suggesting SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis) syndrome; hence, CRMO was suspected. Nonsteroidal antiinflammatory drugs (ibuprofen 600 mg every 8 h) and corticosteroids (1.5 mg/kg per day) were started. After 3 weeks of treatment, the symptoms persisted, and there was only a mild clinical response. At that point, oral thalidomide was initiated (100 mg daily) with an excellent response: the pain disappeared, and acute-phase reactant levels returned to normal after 6 weeks. Six months later, the patient remained asymptomatic, and scintigraphy showed almost complete resolution of the bone lesions except for persistently increased uptake in the angle and descending branch of the right jaw (Fig 2). Thalidomide treatment was then stopped, and there had been no adverse effects over its duration. More than 1 year after completion of treatment, the patient was symptom-free, and inflammatory parameters were within normal range. No further imaging studies have been performed.

DISCUSSION

Because there are no pathognomonic findings for the diagnosis of CRMO, establishing a definitive diagnosis is challenging, particularly in immunocompromised patients

such as those with CGD, in whom infectious osteomyelitis is relatively common. This is especially true in patients unresponsive to nonsteroidal antiinflammatory drugs in whom corticosteroids and anti-TNF agents may be needed, with the risk of potential complications if infectious osteomyelitis is overlooked.[12] To our knowledge, no cases of CRMO have been reported in CGD patients to date. In our patient, infectious osteomyelitis was initially suspected, but the persistent symptoms, lack of response to antibiotics, and increasing number of bone lesions led to the diagnosis of CRMO. Theoretically, CRMO is a possible diagnosis in CGD patients, in whom other disorders associated with neutrophil dysregulation, such as palmoplantar pustulosis, Sweet syndrome, Crohn disease, and ulcerative colitis have been described.[13] Several mechanisms of hyperinflammation, such as decreased neutrophil apoptosis, toll-like receptor activation imbalance, induction of Th17 cells, Nrf2 activity deficiency, and inflammasome activation, have been described in CGD patients related to their higher risk of inflammatory complications.[13]

Although there is a genetic susceptibility to develop CRMO (located on chromosome 18),[14] there is no evidence of genetic predisposition between CGD and CRMO. Some studies have suggested that *Propionibacterium acnes* infection could trigger inflammation through activation of the innate immune pathway that requires TLR9, but its pathogenic role in CGD remains doubtful.[15,16] In our patient, there was no evidence of infection, investigated by classic culture and molecular techniques.

Thalidomide was started as an immunomodulatory and antiinflammatory drug because of its favorable safety profile compared with other therapeutic options such as methotrexate or anti-TNF agents, the long-term consequences of which in immunocompromised patients are unknown.[17] Our patient showed clinical improvement and no adverse events during thalidomide therapy. This experience indicates that thalidomide could be considered in the treatment of inflammatory disorders such as CRMO in patients with CGD. However, additional data are needed to better define the specific indications for its use and the optimal dose and duration of treatment.

ACKNOWLEDGMENTS

The authors thank the patient and his family and Celine Cavallo for English language assistance.

ABBREVIATIONS

CGD: chronic granulomatous disease
CRMO: chronic recurrent multifocal osteomyelitis
TNF: tumor necrosis factor

REFERENCES

1. Winkelstein JA, Marino MC, Johnston RB Jr, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)*. 2000;79(3):155–169
2. van den Berg JM, van Koppen E, Ahlin A, et al. Chronic granulomatous disease: the European experience. *PLoS One*. 2009;4(4):e5234
3. Roxo-Junior P, Simão HM. Chronic granulomatous disease: why an inflammatory disease? *Braz J Med Biol Res*. 2014;47(11):924–928
4. Magnani A, Brosselin P, Beauté J, et al. Inflammatory manifestations in a single-center cohort of patients with chronic granulomatous disease. *J Allergy Clin Immunol*. 2014;134(3):655–662.e8
5. Ferguson PJ, Laxer RM. New discoveries in CRMO: IL-1β, the neutrophil, and the microbiome implicated in disease pathogenesis in Pstpip2-deficient mice. *Semin Immunopathol*. 2015;37(4):407–412
6. Alshammari A, Usmani S, Elgazzar AH, Ashkanani RA. Chronic recurrent multifocal osteomyelitis in children: a multidisciplinary approach is needed to establish a diagnosis. *World J Nucl Med*. 2013;12(3):120–123
7. Girschick HJ, Huppertz HI, Harmsen D, Krauspe R, Müller-Hermelink HK, Papadopoulos T. Chronic recurrent multifocal osteomyelitis in children: diagnostic value of histopathology and microbial testing. *Hum Pathol*. 1999;30(1):59–65
8. Noel N, Mahlaoui N, Blanche S, et al. Efficacy and safety of thalidomide in patients with inflammatory manifestations of chronic granulomatous disease: a retrospective case series. *J Allergy Clin Immunol*. 2013;132(4):997–1000.e1, 4
9. Sokol H, Suarez F, Meatchi T, et al. Thalidomide as a treatment for refractory CGD colitis. *Am J Gastroenterol*. 2009;104(4):1069
10. European public assessment report (EPAR) product information: Thalidomide Celgene: EPAR—Conditions imposed on member states for safe and effective use—Annex IV. London, United Kingdom: European Medicines Agency; February 25, 2009. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000823/human_med_001090.jsp&mid=WC0b01ac058001d124. Accessed August 3, 2015
11. Stasia MJ, Bordigoni P, Floret D, et al. Characterization of six novel mutations in the CYBB gene leading to different sub-types of X-linked chronic granulomatous disease. *Hum Genet*. 2005;116(1–2):72–82
12. Walsh P, Manners PJ, Vercoe J, Burgner D, Murray KJ. Chronic recurrent multifocal osteomyelitis in children: nine years' experience at a statewide tertiary paediatric rheumatology referral centre. *Rheumatology (Oxford)*. 2015;54(9):1688–1691
13. Rieber N, Hector A, Kuijpers T, Roos D, Hartl D. Current concepts of hyperinflammation in chronic

granulomatous disease. *Clin Dev Immunol*. 2012;2012(138):252460

14. Golla A, Jansson A, Ramser J, et al. Chronic recurrent multifocal osteomyelitis (CRMO): evidence for a susceptibility gene located on chromosome 18q21.3–18q22. *Eur J Hum Genet*. 2002;10(3):217–221
15. Tchaptchet S, Gumenscheimer M, Kalis C, et al. TLR9-dependent and independent pathways drive activation of the immune system by *Propionibacterium acnes*. *PLoS One*. 2012;7(6):e39155
16. Bourdeaut F, Quartier P, Alkaer G, Fischer A, Casanova JL, Blanche S. *Propionibacterium acnes* chest infections in patients with chronic granulomatous disease: case reports. *Clin Infect Dis*. 2002;34(6):853–854
17. de Luca A, Smeekens SP, Casagrande A, et al. IL-1 receptor blockade restores autophagy and reduces inflammation in chronic granulomatous disease in mice and in humans. *Proc Natl Acad Sci USA*. 2014;111(9):3526–3531

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Pediatrics 2016;138;
DOI: 10.1542/peds.2015-4017 originally published online July 19, 2016;

PEDIATRICS®
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