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Editorial

Whole-body MRI Imaging Is an Essential Tool in Diagnosing and Monitoring Patients With Sterile Osteomyelitis

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From the first description in 1972 as "subacute and chronic recurrent osteomyelitis" to the currently recognized chronic recurrent multifocal osteomyelitis (CRMO) or chronic nonbacterial osteitis (CNO), diagnosis and monitoring of patients with this disease has been and continues to be a challenge[1,2]. While the most common presenting symptom is focal bone pain, its waxing and waning nature tends to contribute to the diagnostic odyssey that many patients must endure. Objective changes on examination such as swelling and tenderness over a lesion may not be present or may mimic inflammatory arthritis. Laboratory findings are equally nonspecific, with some patients having a mildly elevated C-reactive protein and/or erythrocyte sedimentation rate, while most other laboratory findings remain normal[3]. In about one-quarter of patients, a comorbid inflammatory condition such as psoriasis or inflammatory bowel disease, when present, often provides the vital clue to establishing a diagnosis[4]. However, in those with osseous involvement only, the lack of specific findings makes the diagnosis of CNO challenging, with patients averaging 2 years between initially presenting with symptoms and receiving a diagnosis of CNO[5]. Given the lack of pathognomonic features in most patients, a high index of suspicion and close collaboration between clinicians and radiologists are important to making a timely diagnosis.

While imaging is essential in establishing a diagnosis of CNO, imaging features of CNO can also be relatively nonspecific. Plain films lack sensitivity, especially early in the disease course and may be completely normal despite significant disease activity. When positive, plain films demonstrate mixed lytic and sclerotic lesions, most common in the metaphyses of long bones in the lower extremities and mimicking radiologic features of infectious osteomyelitis. Magnetic resonance imaging (MRI) of the painful area is more sensitive for the early findings of CNO, but even with MRI, the findings of marrow edema on T2 or short-tau inversion recovery (STIR) sequences are not specific to this disease process[6].

When a patient presents with CRMO, although they often present with just a single site of pain, multifocal disease is present. Whole-body imaging can identify additional asymptomatic or minimally symptomatic lesions, aiding in making a diagnosis of CRMO[7]. While bone scans can provide whole-body imaging, compared to whole-body MRI (WB-MRI), they require radiation and have decreased sensitivity, spatial resolution, and limited ability to evaluate physeal disease, making WB-MRI superior to bone scan in delineating the extent of disease.

Given that symptomatology is often discordant with radiologic findings, it is important to understand whole-body disease burden not only at diagnosis but also when making treatment decisions[2]. Further, patients with CNO often need long-term surveillance imaging, and WB-MRI provide an excellent radiation-free tool for monitoring disease.

When performing WB-MRI, it is important to have a tailored examination for the patient population and disease process you are evaluating. In the case of children with CNO, it is important to have a relatively short scan time to eliminate or at least minimize the necessity for sedation. A full-sequence WB-MRI may take 4–6 hours, which is not realistically feasible in this patient population[8]. STIR sequences are relatively fast sequences that are sensitive to the marrow edema seen in CNO[9]. Many CNO WB-MRI imaging protocols include STIR sequences only, whereas others also include diffusion and/or T1-weighted imaging[10,11,12]. Protocol designs for WB-MRI need to take into account typical disease distribution. For example, in

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patients with CNO, it is helpful to cover the whole body in a coronal plane, but additional planes such as sagittal spine, axial pelvis, and sagittal ankle/feet are needed for better lesion visualization in these regions[11]. At our institution, we have created a STIR-based CNO screening/monitoring WB-MRI protocol that can be performed in a single 40-minute MRI time slot, with approximately 25 minutes of MRI scan time. No single acquisition takes longer than 3 minutes, and sedation is rarely necessary (Table 1).

When reviewing a WB-MRI protocol, it is important to understand the potential shortcomings as well. CNO screening/monitoring WB-MRI protocols based only on STIR sacrifice additional sequences for speed of the exam. Because of this, if there are unexpected or atypical findings, the patients may have to return for a more focused full-sequence regional MRI for complete characterization. At our institution, this rarely must be performed; however, it is important for both the clinician and the radiologists to have an understanding of the strengths and limitations of this type of WB-MRI examination. Despite these limitations, WB-MRI has become the standard for diagnosing and monitoring patients with CNO, with a significantly increased sensitivity and lack of radiation compared to other whole-body imaging (bone scans and skeletal surveys).

The best treatment for CNO remains obscure. Zhao, *et al* surveyed pediatric rheumatologists who participate in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and found wide variation in how children with CNO are treated[13]. One reason is because of the low-quality evidence available to guide treatment decisions. Most data are retrospective from case series with a just a few prospective studies and no randomized trials. And while WB-MRI has become a vital tool in the clinical care of patients with CNO, standardization in WB-MRI acquisition and interpretation is needed to be able to use imaging as an outcome measure in research, such as in gauging response to therapy in a drug trial.

In this issue of *The Journal of Rheumatology*, Panwar, *et al* present a WB-MRI scoring tool for CNO that was then used to determine treatment response to pamidronate in a retrospective study of pediatric patients with CNO[14]. They identified 32 patients that met the Bristol Criteria and/or had a bone biopsy consistent with CNO in which serial WB-MRI were performed at defined intervals pre- and posttreatment with pamidronate (average period of 5 months after each pamidronate cycle and a total of 88 WB-MRI studied). These patients had failed nonsteroidal antiinflammatory drug therapy and were treated with intravenous pamidronate at a dose of 1 mg/kg/day (max 60 mg) once per month for 3 months (defined as 1 pamidronate cycle). Two blinded radiologists reviewed the 88 scans using their WB-MRI scoring tool, with excellent interreader reliability of k ranging from 0.93 to 1.00. Using this tool, they found that 34% of CNO lesions resolved after a single cycle of pamidronate, while in a subset of 11 patients that required 2 cycles, 76% of lesions resolved.

Using this tool, the authors demonstrate how standardized scoring can be used to demonstrate responses to therapy. Here they used MRI as a readout to gauge response to pamidronate in 32 patients with CNO who had been treated with pamidronate. While the study was retrospective and the treatment approach was not fixed, it provides additional data supporting the effectiveness of pamidronate in the treatment of CNO. Although this study demonstrated good interreader reliability for the WB-MRI scoring tool, having only 2 readers and both from the same institution limits the generalizability of the study and further validation at other centers will be needed. Despite this, Panwar, *et al*[14] have done an excellent job in laying the foundation for further investigation, and as CRMO monitoring practices become more standardized, further investigation and evaluation of treatment efficacies can be performed to develop stronger, data-driven treatment regimens.

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Table 1. A suggested whole-body MRI protocol for screening and monitoring CRMO.

Plane	TR/TE, ms	Slick Thickness/Space, mm	FOV, cm[a]	Matrix	Acquisition time[1], min	Stations/Scans	Total time[b], min
Coronal whole-body 3D STIR	4000/287	4/0	45	512 ′ 307	1:37–2:08	4–5	6:28–10:40
Sagittal upper spine 3D STIR	4000/290	3/0	40	384 ′ 230	1:46	1	1:46
Sagittal lower spine 3D STIR	4000/289	3/0	40	384 ′ 230	1:46	1	1:46
Axial pelvis 3D STIR	4000/291	4/0	40	384 ′ 230	2:56	1	2:56
Axial knees 3D STIR	000/292	4/0	40	384 ′ 230	2:30	1	2:30
Sagittal ankle 3D STIR	4,000/294	3/0	30	320 ′ 192	1:46	2	3:32
Total time							18:58–23:10

[a] Varies based on size. [b] Time reflects usage on 1.5-Tesla (T) Aera, 1.5-T Avanto Fit, and 3-T Vida scanners (Siemens Healthcare) with total imaging matrix whole-body suite. CRMO: chronic recurrent multifocal osteomyelitis; FOV: field of view; MRI: magnetic resonance imaging; STIR: short-tau inversion recovery; TE: echo time; TR: repetition time.

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