



Brief communication

Cutibacterium acnes and autoinflammatory bone disease: Case series of three patients

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1. Introduction

Autoinflammatory bone disease - i.e. chronic recurrent multifocal osteomyelitis (CRMO) or chronic non-bacterial osteomyelitis (CNO) and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteomyelitis) - is rare and typically affects young patients. Bone pain is the main clinical symptom. The diagnosis is based on clinical and radiological findings and exclusion of alternative causes such as neoplasms or infection. The etiology and pathogenesis are largely unknown as is the optimal treatment strategy. Although CRMO is considered to be sterile, the pathogenic role of *Cutibacterium acnes* (*C. acnes*, formerly known as *Propionibacterium acnes*) is increasingly recognized [1]. In this report, we describe three cases of presumed autoinflammatory bone disease with concomitant positive tissue cultures with *C. acnes*, and discuss the possible relation between this microorganism and autoinflammatory bone disease and its implications for clinical management.

2. Case descriptions

2.1. Case 1

A 20-year old female with a history of previous diagnosis of CRMO

of the tibia, was referred to our center with an atypical progressive thoracic scoliosis (Cobb 43°, Fig. 1), and severe unilateral thoracic pain unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs). Single Photon Emission Computed Tomography/computerized tomography (SPECT/CT) showed hyperostosis and osteomyelitis in the dorsolateral second and third right costae, shown in Fig. 2. C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) were mildly elevated (24 mg/L and 35 mm/h, respectively). Leukocytes were $12.9 \times 10^9/L$ and neutrophils were $9.39 \times 10^9/L$. Other laboratory findings were normal. Differential diagnosis included infectious osteomyelitis and CRMO. An open biopsy of the right costovertebral joint T2 and rib showed chronic, active osteomyelitis and two cultures yielded a single colony of *C. acnes* each (one culture also grew a single colony of viridans streptococci), which we considered to be contamination. However, since a low-grade infection could not be excluded, clindamycin 600 mg three times daily was administered for two months. Treatment with oral bisphosphonates (risedronic acid 35 mg weekly) was added to the NSAIDs, according to the suggested algorithm for CRMO [2,3]. Additional pain management included pregabalin, amitriptyline and oxycodone, which did not effectively reduce pain. Intercostal nerve blocks initially reduced pain, but were only effective for a few days. After four months, SPECT/CT showed diminished activity of the costa but increased activity of the right facet joint T7-T9, after which anti-

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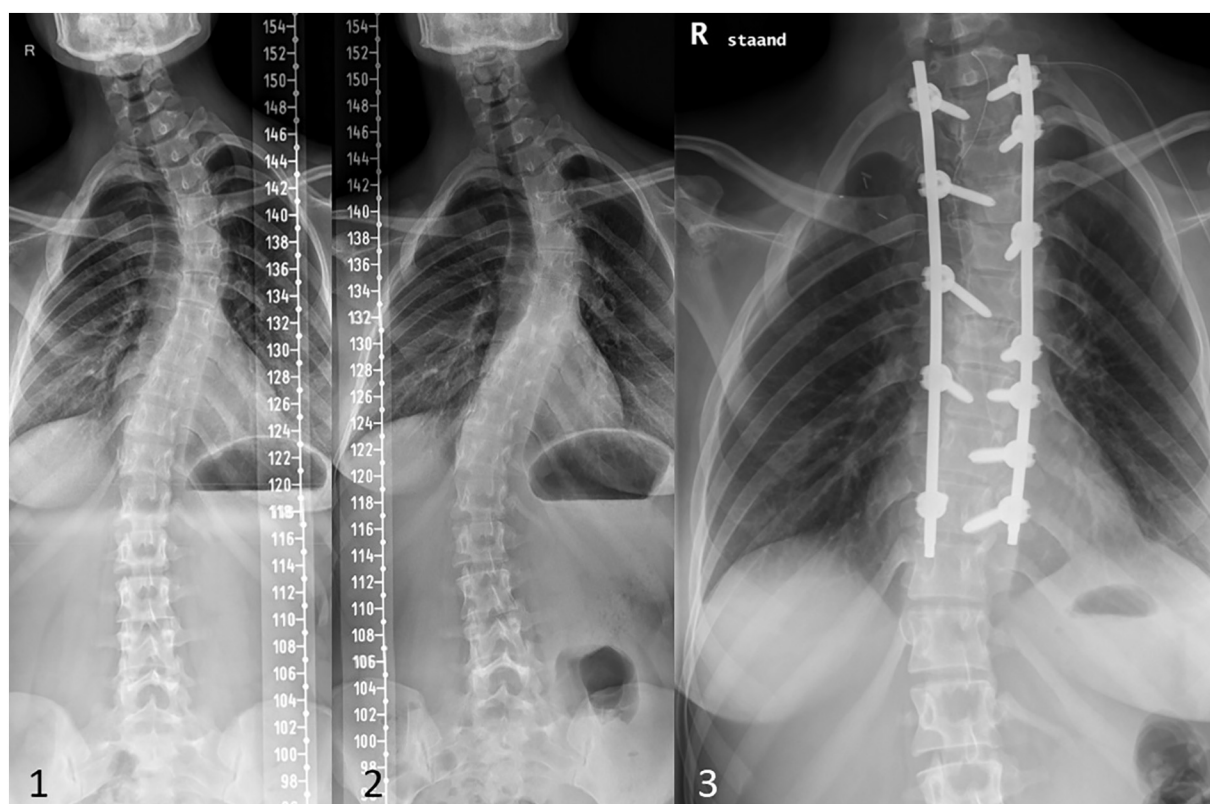


Fig. 1. A-typical scoliosis of case 1. 1: A-typical high thoracic left convex scoliosis, likely secondary to pain; 2: Scoliosis progressed to 50 degrees Cobb angle over two years; 3: Post operative image showing instrumentation and the partial resections of the right 2nd and 3rd costae.

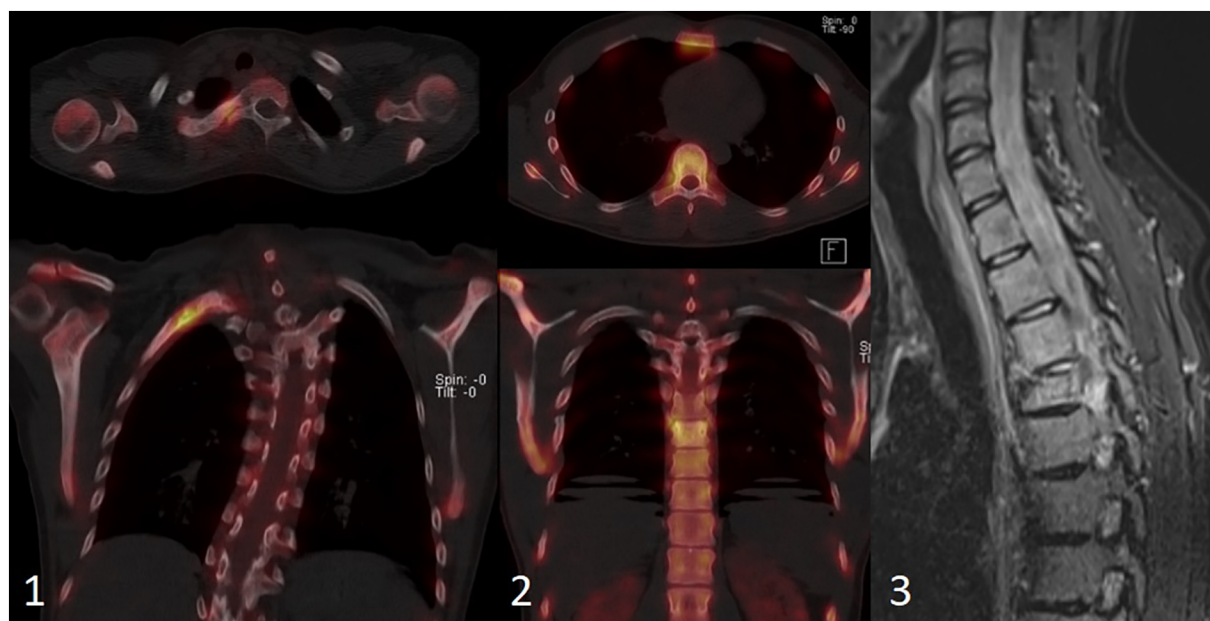


Fig. 2. Imaging of all three cases. 1: SPECT images of case 1 showing increased bone metabolism in the right dorsal costae T2 and 3 and costovertebral joint; 2: SPECT images of case 2 showing moderately increased bone metabolism in the sclerotic vertebral body T8 continuing into the right pedicle; 3: T2 weighted MRI of case 3 shows edema around T4.

tumour necrosis factor (aTNF) treatment (adalimumab 40 mg two-weekly), was started. Still, symptoms remained, even after an additional nerve root block of T2/3, transcutaneous electrical nerve stimulation (TENS) and cognitive therapy. Eight months after initiation of adalimumab, SPECT/CT showed disease activity in the second right rib again. By that time the scoliosis had increased to 50 degrees, shown in

Fig. 1. After shared decision making, it was decided to opt for correction of the scoliosis and fusion of the spine together with resection of the affected parts of the second and third costae. A non-quantitative liquid culture of a bone fragment was positive for *C. acnes*. The recurrent presence of *C. acnes* was considered to indicate either a chronic or recurrent low-grade infection or a factor maintaining the

inflammatory process. She was therefore treated with oral clindamycin 600 mg three times daily for three months, also because of the presence of hardware. Eventually, scoliosis was corrected (Fig. 1) and pain medication could be discontinued.

2.2. Case 2

A 26-year old male, with no medical history, presented with night sweats, weight loss and decreased appetite for six months, followed by pain in the lower rib and flanks since three months. He recalled to have had a self-limiting episode with similar complaints three years earlier. Physical examination showed no abnormalities and pain was not excitable. Laboratory findings indicated elevated BSE (39 mm/h) and CRP (31 mg/L), and normal complete blood count, liver and kidney function. A positron emission tomography/CT (PET/CT) scan showed increased uptake and sclerosis of T8, shown in Fig. 2. Differential diagnosis included malignancy, infection and sarcoidosis. A CT-guided biopsy of vertebrae T8 showed inflammatory cells and fibrosis, without any sign of granulomas or malignant cells. Culture yielded growth of *C. acnes*. Serology for *Mycobacterium tuberculosis* and *Brucella* were negative. Two additional percutaneous biopsies of T8 were taken two weeks later, to confirm the culture results, but both cultures remained negative. Therefore, the first culture with *C. acnes* was considered to be contamination. In the meantime, a SPECT/CT was done due to progressive back pain, showing increased activity in T8 and L4. At this point, CRMO was suspected because of the multifocal distribution and exclusion of malignancy or infection. After NSAIDs failed to improve symptoms, intravenous bisphosphonates (pamidronate 90 mg monthly) were initiated. Symptoms only partly resolved although scintigraphy showed normalisation of the prior signals in T8 and L4. Due to side-effects of pamidronate, this treatment was discontinued after 3 months. Based on the patient's preference, no other treatment was initiated. Three years after presentation at our hospital, the patient presented with recurrent symptoms and activity of L4 on SPECT/CT. Considering the prior positive culture with *C. acnes* and reluctance of the patients towards reintroduction of bisphosphonates, combination therapy with NSAIDs and clindamycin 600 mg three times daily for three months was started. After two months symptoms decreased gradually.

2.3. Case 3

A 29-year old female was referred to our center with pain located between scapulae and at the sternum for three months and occasionally pustular abnormalities on both hand palms. Her family history was positive for rheumatoid arthritis, vitiligo, systemic lupus erythematosus and Hashimoto's disease. CRP was normal (< 0.1 mg/L) and ESR was mildly increased (52 mm/h). MRI and CT revealed sclerotic anomalies at T3 and T4 and the left 10th costovertebral joint, shown in Fig. 2. Percutaneous biopsies yielded no microorganisms; however, the cultures had only been incubated for 10 days. Differential diagnosis included discitis, spondylitis and autoinflammatory condition (i.e. spondylarthropathy). A subsequent open biopsy showed no abnormalities at T3 and T4, yet the sample from T10 did disclose osteomyelitis. *C. acnes* was cultured from all three biopsies: of T4, of discus T3–T4 and of T10. Therefore, the bacterium was considered to have a possible pathogenic role in her disease and treatment was initiated with clindamycin 600 mg three times daily for a duration of six weeks. Due to the co-occurrence of pustular abnormalities on the hand palms and osteomyelitis, the diagnosis SAPHO was made and according to the recommended algorithm a NSAID was started [2]. At three months follow-up, her pain had significantly improved.

3. Discussion

We describe three patients with recalcitrant autoinflammatory bone disease that we initially considered sterile (CNO /CRMO) despite

sporadic sporadic cultures of *C. acnes*. However, based on repeated positive cultures and the response to antibiotic treatment we believe *C. acnes* did play a pathogenic role. *C. acnes* is a commensal microorganism generally associated with relatively mild chronic skin conditions like acne. However, deep infections especially in combination with orthopaedic implants are notorious [4,5]. The presented cases highlight the difficulties in establishing the role of *C. acnes* in presumed autoinflammatory bone disease, both in general and in the individual patient. In our patients, finding an effective treatment was difficult. We started with NSAIDs and if necessary, added bisphosphonates. In case 1, even the combination of bisphosphonates and biologic DMARDs failed to reduce symptoms, and surgical resection of the inflamed bone segments was required. Antibiotics were not initiated initially, because the cultures with *C. acnes* were interpreted as contamination. Eventually, these patients were treated with antibiotics due to repeatedly positive cultures (case 1) or multiple positive cultures from one open biopsy (case 3). In case 2 we started empiric treatment with antibiotics because of refractory disease, despite the repeat cultures remaining negative. Still, there is room for speculation about the exact role of *C. acnes* in our cases. Contamination or non-pathogenic colonisation can be considered. Also, pre-existing CRMO sites might be susceptible for secondary infections with i.e. *C. acnes*. A third explanation could be, that *C. acnes* triggered and/or perpetuated the an autoinflammatory process.

Distinguishing between infection and contamination with *C. acnes* is difficult, in particular with cultures of samples from the spine. The skin on the human back is a sebaceous environment, where *C. acnes* species make up more than half of the microbiota [6]. *C. acnes*, which is in general the most common and abundant bacterial species on the skin, predominantly colonizes deep in within the follicles and pores and is prone to contaminate tissue cultures. On the other hand, *C. acnes* is an anaerobic bacterium with selective growth that requires up to ten days incubation under anaerobic conditions [7].

The diagnosis of autoinflammatory bone disease can be complex since it is made by exclusion and a broad differential diagnosis, including neoplasms and osteomyelitis, needs to be ruled out. It typically presents with bone pain, but also skin manifestations (particularly in SAPHO syndrome), subfebrile temperature and mildly elevated inflammatory parameters are frequent [5]. Autoinflammatory bone disease can develop in all bones, but it most frequently affects the vertebral column, thoracic cage, shoulder girdle and pelvis. Whole-body imaging techniques, such as MRI, SPECT/CT and technetium bone scans, may be used to detect lesions and screen for multifocality [8]. Such techniques may also detect silent lesions, particularly in the spine [2].

Proinflammatory cytokines and chemokines play a central role in autoinflammatory bone disease but the exact pathogenesis is incompletely understood [2]. Results from murine and human in-vitro studies suggest that dysregulation of the Interleukin-1 (IL-1) pathway is associated with autoinflammatory bone disease [9–11]. IL-1 blockade led to rapid and sustained improvement of bone inflammation and systemic inflammatory markers in chronic sterile osteomyelitis in human, murine and canine models [12–19]. Similarly, in a study of patients with chronic non-bacterial osteitis refractory to NSAIDs and bisphosphonates, 6 out of 9 patients showed a decrease in disease activity and number of bone lesions within six months of treatment with the IL-1 receptor antagonist anakinra in [20], suggesting IL-1 blockade as a potential therapeutic option in refractory CRMO and SAPHO.

Interestingly, the relation between IL-1 and *C. acnes* seems to be reciprocal: increased IL-1 β due to a genetic predisposition may cause impaired clearance of *C. acnes* [1], whereas *C. acnes* was found to enhance the inflammasome activation and increase the IL-1 β release in some patients [21].

Furthermore, several cohort studies identified an association between *C. acnes* and inflammatory bone disease. In a study with 21 SAPHO patients, 66% of open bone biopsy cultures yielded *C. acnes* [22] and a review of CRMO and SAPHO case reports found that 49%

had positive bone biopsies for *C. acnes* [1]. A study with asymptomatic patients (e.g. undergoing a routine cervical spine surgery for degenerative disc disease) found 27% of bone biopsy culture to yield *C. acnes* [23]. Though this may support the hypothesized relation between the two, it should be recognized that (publication) bias can overestimate the percentage in the first two studies. Also, the long incubation time required for *C. acnes* (reported to be up to 10 days, but also over 13 days), could have led to false-negative cultures [7]. The first two studies both had an incubation time of 14 days while the last study only incubated cultures for 7 days. However, in all these studies the majority of biopsies were obtained by an open procedure instead of percutaneously, reducing risk of contamination. Given these circumstances, it is plausible that at least part of the cases diagnosed as autoinflammatory bone disease, are actually low-grade osteomyelitis with a pathogenetic role for *C. acnes* in the inflammatory process.

Treatment of autoinflammatory bone disease includes NSAIDs as first-line therapy, followed by bisphosphonates, synthetic disease-modifying antirheumatic drugs (DMARDs), such as sulfasalazine or methotrexate, and biologic DMARDs, such as anti TNF therapy, in case of sustained disease activity or relapse [2]. Interestingly, there is no consensus on the need for assessment and optimal treatment of *C. acnes* in this condition. Although difficult to reach, *C. acnes* seems susceptible to a broad range of antibiotics. A minimum treatment duration of 6 weeks is proposed with some reports recommending treatment duration of 10 to 12 weeks [24]. After antibiotic discontinuation, however, disease relapse was observed, indicating that some treatments may need to be prolonged [22].

Based on current literature and our experience, we believe biopsies should be considered at an early stage, with specific attention to the presence of *C. acnes*. To assure sensitivity and specificity, we suggest taking multiple biopsies, preferably without toughing the skin and culture for a of minimum of ten days [7]. To establish the difference between CRMO and infectious osteomyelitis in case of positive cultures with *C. acnes*, however, remains a challenge in clinical practice and should be based on both cultures and disease course. If *C. acnes* is present, patients may be treated with antibiotics during at least three months. However, more research is needed to confirm the effect and optimal treatment regime. In the absence of *C. acnes*, or failure of first line pharmaceuticals, second-line therapy, including IL-1 receptor antagonists, may have a place considering the growing evidence of IL-1 dysregulation in autoinflammatory bone disease. Also empiric antibiotic therapy can be considered since *C. acnes* can easily be missed. In case non-invasive therapies fail, resection or curettage of the affected bone may be considered.

4. Conclusion

We describe three cases of autoinflammatory bone disease with *C. acnes* identified in tissue biopsies of the affected sides. Initially these positive cultures were considered to be contamination, but eventually these patient were treated with antibiotics. The potential pathogenetic role of *C. acnes* should be recognized early in autoinflammatory bone disease, although more research is necessary to confirm this role and the effect and optimal duration of (empiric) antibiotic therapy.

Ethical considerations

Written consent to share patient's data was obtained from all patients.

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