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ORIGINAL ARTICLE

The role of *Cutibacterium acnes* in auto-inflammatory bone disorders

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Abstract

Chronic nonbacterial osteomyelitis (CNO) and SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome are auto-inflammatory disorders manifesting as chronic inflammation of bones and joints, which in SAPHO is often accompanying by skin changes. The aetiology of these diseases is unknown, but includes genetic, infectious and immunological components. It has been proposed that *Cutibacterium* (formerly *Propionibacterium) acnes* plays a role in the pathogenesis. In this review, we summarise reported cases of CNO or SAPHO syndrome in which *C. acnes* has been isolated from bones. To identify cases, a search was done in May 2018 using the MEDLINE Ovid interface (1946 to present). We found 14 publications reporting 98 patients with auto-inflammatory bone disorders, of whom 48 (49%) had positive bone biopsies for *C. acnes.* This bacterium was more frequently isolated from open biopsies than percutaneous ones (43/69 (62%) vs 1/7 (14%); $p = 0.04$) and biopsies were more frequently positive in patients who presented with simultaneous skin manifestations (19/36 (53%) vs 4/12 (33%); $p = 0.03$).

Conclusion: In patients with CNO or SAPHO, *C. acnes* can be isolated from open biopsies suggesting that in these patients, *C. acnes* might be a pathogen rather than a contaminant. The fact that biopsies are more frequently positive in patients who present with simultaneous skin manifestations suggests that these individuals might have a genetic predisposition for impaired clearance of *C. acnes*.

What is known

- *Chronic nonbacterial osteomyelitis (CNO) and SAPHO (synovitis, acne, pustulosis, hyperostosis and osteitis) syndrome are auto-inflammatory disorders manifesting as inflammation of bones. Both diseases are an important differential diagnosis in children who present with symptoms of (multifocal) osteomyelitis.*
- *The pathogenesis of CNO and SAPHO is multifactorial emcompassing genetic, infectious and immunological components, including interleukin (IL)-1 dysregulation. There is a controversy as to whether Cutibacterium (formerly Propionibacterium) acnes plays a role in the aetiology of CNO and SAPHO. It has been postulated that the presence of C. acnes might trigger auto-inflammatory chronic inflammation in genetically predisposed individuals.*

What is new

- *In patients with CNO or SAPHO, C. acnes can be isolated more frequently from open biopsies, than from percutaneous ones, suggesting that C. acnes might be a pathogen rather than a contaminant.*
- *Biopsies are more frequently positive in patients who present with simultaneous skin manifestations suggesting that these individuals might have a genetic predisposition for impaired clearance of C. acnes. Impaired C. acnes clearance likely leads to increased IL-1 beta (β) production by skin cells, bone cells and phagocytes, which is one of the main cytokines underlying chronic inflammatory bone disorders.*

Keywords SAPHO · Spondyloarthopathies · Chronic recurrent multifocal osteomyelitis · CRMO · DSOM · Osteitis · Hyperostosis · Synovitis · Pustulosis · Osteomyelitis

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Abbreviations

C. acnes	*Cutibacterium acnes*
CNO	Chronic nonbacterial osteomyelitis
CRMO	Chronic recurrent multifocal osteomyelitis
DSOM	Diffuse sclerosing osteomyelitis of the mandible
IL	Interleukin
PPP	Palmoplantar pustulosis
SAPHO	Synovitis, acne, pustulosis, hyperostosis and osteitis
TNF	Tumour necrosis factor

Introduction

SAPHO is an acronym for synovitis, acne, pustulosis, hyperostosis and osteitis [42]. Patients with SAPHO present with chronic inflammation of bones and joints, most commonly affecting the anterior chest wall (mainly the sternum, clavicles and sternocostoclavicular joints), the vertebrae and the sacroiliac joints and less commonly peripheral or flat bones. Clinical presentations range from mild unifocal to chronic active or recurrent multifocal osteomyelitis. The bone changes may be accompanied by skin manifestations, which are often severe forms of acne or palmoplantar pustulosis (PPP). The acronym SAPHO was introduced by Chamot in 1987 [7]. Before this, the term chronic recurrent multifocal osteomyelitis (CRMO) was used to describe an auto-inflammatory disorder of bones. Until recently, it was thought that CRMO was the paediatric presentation of SAPHO. Currently, it is assumed that both diseases are part of a clinical spectrum. This is supported by the fact that skin manifestations have previously been underreported in children [3] and that adults can also solely present with osteoarticular manifestations [9, 29]. Recognising the more chronic than recurrent course of CRMO, chronic multifocal osteomyelitis without skin symptoms is now more frequently called chronic nonbacterial osteomyelitis (CNO) [21]. However, CNO is not always chronic and patients sometimes present with episodic symptoms or even a single episode.

Patients with diffuse sclerosing osteomyelitis of the mandible (DSOM) might also present with PPP, and DSOM is now recognised as a form of CNO or SAPHO. Other related auto-inflammatory diseases are Majeed syndrome, (which, in addition to the inflammatory osteoarticular symptoms and skin changes, presents also with congenital dyserythropoietic anaemia (CDA)) and DIRA (deficiency in interleukin-1 receptor antagonist) syndrome (a disease affecting young children, presenting with multifocal osteomyelitis and diffuse pustular rash).

The diagnosis of CNO and SAPHO is based on clinical and radiological findings, in addition to exclusion of alternative diagnoses, such as malignancy or bone infection with typical and atypical bacteria. The aetiology and pathogenesis of CNO and SAPHO remain uncertain, but include genetic, infectious and immunological components. *Cutibacterium acnes* (previously called *Propionibacterium acnes*) is a Gram positive, non-spore-forming bacillus that can produce biofilm [6] and prefers anaerobic conditions. *C. acnes* is involved in the pathogenesis of acne and has been isolated from joint fluid and bone biopsies from patients with CNO and SAPHO. However, since *C. acnes* is part of the normal flora, including the oral cavity, large intestine, conjunctiva and the skin (in particular the sebaceous follicles), it is often difficult to differentiate whether it is a pathogen or contaminant. However, *C. acnes* has been associated with serious invasive disease, mostly neurosurgical and orthopaedic infections [40], as well as chronic inflammation leading to prostate cancer, sarcoidosis and sciatica [2, 31], confirming its role as a pathogen. In this review, we summarise cases of CNO and SAPHO (including DSOM) in which *C. acnes* has been isolated from bones.

Systematic review methods

To identify reported cases of CNO or SAPHO in whom *C. acnes* was isolated, a search was done in May 2018 using the MEDLINE Ovid interface (1946 to present) with the following search terms: (SAPHO OR 'chronic recurrent multifocal osteomyelitis' OR 'chronic nonbacterial osteomyelitis' OR osteomyelitis OR hyperostosis OR osteitis OR 'diffuse sclerosing osteomyelitis of the mandible' OR palmoplantar pustulosis) AND (*Propionibacterium* OR *Cutibacterium*). References were hand-searched for additional articles. We found 16 publications reporting 50 patients with CNO, SAPHO or DSOM in whom *C. acnes* was isolated from bone or synovial biopsies (Table 1) [1, 8, 10, 12–14, 16, 18, 20, 24, 25, 27, 33, 35, 38]. One publication/patient was excluded from our review because sufficient clinical data was not provided [18] and one publication (with one patient) was excluded because *C. acnes* was found only in synovial fluid and not bone [37].

Systematic review results

We found 14 publications reporting 98 patients with auto-inflammatory bone disorders which included clinical details of the patients, of whom 48 (49%) had positive bone biopsies for *C. acnes* (Table 1) [1, 8, 10, 12–14, 16, 20, 24, 25, 27, 33, 35, 38]. In two of the publications, including nine patients, *C. acnes* was cultured from the mandible in patients suffering from DSOM [14, 20]. In the remaining cases, *C. acnes* was isolated from the sternoclavicular region [10, 13, 25], sternum [7, 8, 27], clavicle (3) [24, 35] vertebrae [9] [12, 16, 25, 38], tibia [33, 42] and femur [10, 42]. One publication, including 14 patients with positive cultures for *C. acnes*, did not specify

Table 1 Clinical details and biopsy results of 98 patients with auto-inflammatory bone disorders of whom 48 had positive bone biopsies for *C. acnes*

Proportion of patients with positive biopsy and locations	Median age (range, mean) in years	Skin manifestations in patients with		Median duration (range, mean) in years of osteo-articular symptoms before biopsy in patients with		No. of patients with prior antibiotics in patients with		Biopsy method	Culture methods	Antibiotic treatment in patient with positive biopsies (duration)	Outcome of patient with positive biopsies (duration of follow-up)	Reference
		Positive biopsies[2]	Negative biopsies[2]	Positive biopsies	Negative biopsies	Positive biopsies	Negative biopsies					
Chronic nonbacterial osteomyelitis (CNO) and SAPHO syndrome												
14/21 (67%) NS	51 (20–72, 52)[1]	PPP 21[1] Psoriasis vulgaris 1[1] Acne conglobata1[1] Acne papulopustulosa 2[1] None 5[1]	None 7	11 (1–27, 9)[1]		0	0	Skin incision then CT-guided needle biopsy	Schaedler's agar and chocolate agar for ≥ 14 days at 35 ± 2 °C	Azithromycin 11 (4 m) Doxycycline 2 (4 m, one patients discontinued) Clindamycin 1 (4 m)	Pain relief, radiological improvement and improvement in skin manifestations (4 m), no individual data available	Assman [1] 2009
1/6 (17%) Sternum 1	39 (28–52, 40)	PPP 1	Acne conglobata 1 PPP 2 None 2	0.3	0.7 (0.3–1.1, 0.6)	0	NS	CT-guided needle biopsy through skin	Blood agar, Sabourad s agar and tryptoneyest--glucose with furalizadone for 7 days at 37 °C	Doxycycline 1 (> 2 m)	Pain relief, no improvement of skin manifestations 1 (24 m)	Colina [8] 2007
8/14 (57%) Sternoclavicular 7 Vertebra 2	47 (24–63, 46)	PPP 7 Acne vulgaris 1	PPP 4 Acne vulgaris 2	3 (1–9, 4.1)	4 (1–10, 4.5)	0	0	Skin incision then CT-guided needle biopsy	Schaedler's broth or Schaedler's agar and chocolate agar for 14 days at 35 ± 2 °C	Azithromycin 6 (5 m) Doxycycline 1 (5 m) Discontinued antibiotics 1	NS	Kirchhoff [25] 2003
1/1 (100) Vertebra 1	15 (−)	Severe facial acne 1	–	0.1		0	–	Open biopsy	NS	None	Remodelling of bone (10 m)	Do [12] 2003
2/8 (72%) Clavicle 2	45 (5–63, 35)	None 2	Pustular psoriasis 1 PPP plus acne 1 None 4	1.7 (1.5–1.8, 1.7)	1.5 (0.01–7, 2.3)	0	0	NS	Aerobic and anaerobic bacterial cultures	None 2 (NS)	Pain relief 1 (6 m) Some pain relief 1 (1 m)	Reith [35] 1996
1/1 (100%) Sternum 1	50 (−)	PPP 1	–	0.4	–	1	–	Surgically removed bone	Broth immersion cultures	Clindamycin 1 (6 m)	No pain relief, improvement of skin manifestations 1 (6 m)	Kotilainen [27] 1996
1/1 (100%) Tibia 1	39 (−)	Non-PPP 1	–	0.5	–	0	–	Open biopsy	NS	Tetracycline 1 (2 m)	NS	Pillon [33] 1991
1/1 (100%) Vertebra 1	45 (−)	PPP plus psoriasis 1	–	1	–	0	–	Skin incision followed by bunch biopsy	Columbia blood agar and Schaedler's broth	Amoxicillin/clavulanate 1 (NS)	NS	Gerster [16] 1990
7/15 (47%) Stemoclavicular 7	44 (15–63, 44)	PPP 5 None 2	PPP 6 None 2	4 (0.5–14, 5.4)	6.5 (0.25–10, 6.2)	NS	NS	Open biopsy	Aerobic and anaerobic bacterial cultures	Doxycycline 3 (NS) Flucloxacillin 1 (NS) Penicillin, doxycycline, plus clindamycin 1 (NS) None 2 (NS)	No pain relief 2, some pain relief 1 (NS) Pain relief 1 (NS) No pain relief 1 (NS) NS 2	Edlund [13] 1988

Table 1 (continued)

Proportion of patients with positive biopsy and locations	Median age (range, mean) in years	Skin manifestations in patients with		Median duration (range, mean) in years of osteo-articular symptoms before biopsy in patients with		No. of patients with prior antibiotics in patients with		Biopsy method	Culture methods	Antibiotic treatment in patient with positive biopsies (duration)	Outcome of patient with positive biopsies (duration of follow-up)	Reference
		Positive biopsies[2]	Negative biopsies[2]	Positive biopsies	Negative biopsies	Positive biopsies	Negative biopsies					
1/7 (14%) Clavicle 1	11 (8–13, 11)	Psoriasis vulgaris 2 None 5		0.04–2		NS	NS	Biopsy (technique NS) 6 Aspirate 1	Aerobic and anaerobic bacterial cultures (HCMGA-SuIa/II)	NS	NS	King [24] 1987
1/1 (100%) Vertebra 1	27 (–)	Acne vulgaris 1	–	2	–	0	–	Open biopsy	NS	Penicillin 1 (1.3 m)	Pain relief and radiological improvement 1 (1.3 m)	Serushan [38] 1982
1/8 (13%) Femur 1	15 (6–20, 16)	NS	NS	6	0.6 (0.08–2)	NS	–	NS	Aerobic cultures 8 Anaerobic cultures 1	NS	NS	Collert [10] 1980
Diffuse sclerosing osteomyelitis of the mandible (DSOM)												
2/5 (40%)	42 (12–61, 38)	NS	NS	NS	NS	0	0	Skin incision, dissection to bone, by cylinder biopsy	Anaerobic culture on brain-heart medium	NS	NS	Frid [14] 2009
7/9 (78%)	NS	NS	NS	NS	NS	NS	NS	Skin incision followed by bunch biopsy	Anaerobic and aerobic cultures	NS	NS	Jacobsson [20] 1982

PPP palmoplantar pustulosis

[1] Includes 16 patients who did not have a biopsy

[2] Skin findings in 8 patients were not reported

the biopsy location [1]. In three publication (including the two publications with patients suffering from DSOM) [14, 20], the presence or absence of skin manifestations was not specified [10], while in all other reports, skin manifestations were present, which means that the majority of patients suffered from SAPHO rather than CNO.

C. acnes was more frequently isolated from open biopsies than percutaneous ones (43/69 (62%) vs 1/7 (14%); $p = 0.04$) (the biopsy technique was not specified in 22 patients of whom four had positive biopsies). Only one patient received antibiotics prior to having a biopsy and the biopsy was positive for *C. acnes*. A wide variety of culture methods were used.

Biopsies were more frequently positive in patients who presented with simultaneous skin manifestations than those without (19/36 (53%) vs 4/12 (33%); $p = 0.03$) (skin findings were not available or clearly assignable to biopsy results in 50 patients).

The choice of antibiotic and duration of treatment in patients with CNO/SAPHO where *C. acnes* isolated from bone or joint biopsies was variable (azithromycin 17, doxycycline 7, clindamycin 2, amoxicillin/clavulanate 1, flucloxacillin 1, penicillin 1, tetracycline 1, penicillin, doxycycline plus clindamycin 1, roxithromycin plus rifampicin 1, no antibiotics 5, not specified 3). The median treatment duration in the 24 patients for whom this information was available was 4 (range 1.3–6, mean 4) months. In the majority of cases, it was not specified whether treatment was given intravenous or orally. In the patients suffering from DSOM, no information about treatment was available. The clinical response to antibiotic treatment was available for 11 patients: total pain relief in 5, some pain relief in 2 and no pain relief in 4 patients.

Discussion

Although an aetiological role for *C. acnes* in CNO or SAPHO has not been proven, this review suggests that it might be involved in the pathogenesis of auto-inflammatory bone disorders. Additionally, studies in animals show that when *C. acnes* is injected directly into the joints of rats, it induces erosive arthritis [41]. In our study, the finding that *C. acnes* was more frequently isolated from open biopsies than percutaneous ones suggests that *C. acnes* might be a pathogen rather than a contaminant. Further evidence that *C. acnes* is a pathogen comes from one of the studies of patients suffering from DSOM, in which skin samples from all patients were also cultured and compared to the bone samples. While cultures from the skin samples showed only sparse growth of *C. acnes*, growth from bone samples was moderate to heavy, suggesting contamination was less likely [20]. In one of the cases, six surgically obtained bone cultures from one individual grew *C. acnes* as the only pathogen [27]. Biopsies were more frequently positive in patients who presented with skin manifestations (in patients that presented with SAPHO rather than CNO). However, as previously mentioned, these diseases are part of a clinical spectrum of the same disorder and it is questionable whether differentiation is useful.

C. acnes is a fastidious bacterium and factors such as duration of the disease before biopsy, previous antibiotics, sample technique and culture media and duration of culture all may influence the ability to isolate the bacterium. This might lead to an underestimation of the role of *C. acnes* in CNO or SAPHO. To detect *C. acnes*, it is recommended that biopsies from bones and joints are incubated for 10 days. Thioglycolate broth has the highest sensitivity (66%) and anaerobic agar plates have the highest positive predictive values (97%) for detecting *C. acnes* [5]. Future studies using molecular techniques will help clarify the role of *C. acnes* in SAPHO.

One theory for the pathogenesis of CNO and SAPHO is that *C. acnes* triggers an auto-inflammatory chronic inflammation in genetically predisposed individuals. In acne, *C. acnes* activates the NLRP-3-inflammasome and leads to increased secretion of interleukin (IL)-1β from skin cells and phagocytes [26, 28, 34]. NLRP-3-deficient mice have an impaired inflammatory response to *C. acnes* [28]. The inflammasome and IL-1β have been proposed as possible therapeutic targets in the treatment of acne [26].

IL-1 dysregulation is also important in the pathogenesis of auto-inflammatory bone disorders. When blood from healthy individuals is stimulated with *C. acnes*, increased capase-1 activity in neutrophils is associated with enhanced production of IL-1β and IL-18 [36]. Additionally to stimulating IL-1 and IL-18 production, in vitro studies also show that *C. acnes* leads to increased IL-8 and tumour necrosis factor alpha (TNF-α) production by monocytes, keratinocytes and dendritic cells [17], and produces a number of chemo-attractants activating the innate immune system through Toll-like-receptor-9 signalling [22]. SAPHO is associated with increased plasma levels of IL-8 and IL-18 [19]. Additionally, after stimulation, IL-8 and TNF- TNF-α production is higher in phagocytes from patients with SAPHO than from healthy controls. However, induction of IL-8 and TNF-α production by *C. acnes* is impaired in SAPHO patients [19]. A recent publication suggests that a relative deficiency of the metabolic transcription factor forkhead box 01 (Fox01), which is found in the nucleus of sebaceous cells in acne and psoriasis skin lesions, might help *C. acnes* escape innate immunity to persist in a latent state in bone cells [4]. This supports the theory that SAPHO is triggered by persistence of *C. acnes* in phagocytes, skin and bone cells in genetically predisposed individuals (e.g. deficiency of Fox01). This contributes to a strong humoral and cellular inflammatory response leading to chronic inflammation and consequent osteitis and hyperostosis [17]. The fact that in our review, biopsies were more frequently positive in patients who presented with simultaneous skin manifestations supports the theory of a genetic predisposition to impaired

clearance of *C. acnes*, which in turn leads to increased IL-1β production by skin cells, bone cells and phagocytes. Blocking the IL-1 pathway has been proposed as therapeutic option in auto-inflammatory bone disorders [39].

Most reports addressing the management of *C. acnes* infections are retrospective, case series. The optimal treatment for bone infections has not yet been determined. *C. acnes* is susceptible to a broad range of antibiotics, including penicillins and cephalosporins (lowest minimal inhibitory concentrations), vancomycin and rifampicin. It is intrinsically resistant to metronidazole, and there is increasing resistance to moxifloxacin (82%), clindamycin (7–9%) and penicillin (4%) [11, 23, 32]. Combination therapy has been proposed to prevent resistance, to increase biofilm penetration and to treat polymicrobial infections. In vitro studies show additive effects with the combination of penicillin and rifampicin. In *C. acnes* biofilm infections, a combination of rifampicin and daptomycin has a higher eradication rate than rifampicin and vancomycin [15, 23]. One study reported that antibiotic treatment combined with surgical intervention did not show any benefit over antibiotic treatment only [32]. In *C. acnes* prosthetic joint infections, recommended treatment durations are 4 to 6 weeks with intravenous penicillin or ceftriaxone [30]. There are no recommendations for the choice of antibiotics or duration in SAPHO syndrome with proven *C. acnes* infection.

In summary, the fact that *C. acnes* is more frequently isolated from open bone biopsies suggests that it might be involved in the pathogenesis of auto-inflammatory bone disorders. Individuals with auto-inflammatory bone disorders might have a genetic predisposition for impaired clearance of this bacterium, leading to chronic inflammation mediated by increased IL-1beta (β) production by skin cells, bone cells and phagocytes.

Authors' contributions PZ drafted the initial manuscript and approved the final manuscript as submitted. NC critically reviewed and revised the manuscript and approved the final manuscript as submitted.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Research involving human participants and/or animals N/A

Informed consent N/A

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