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CASE REPORT

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Intracellular infection of *Cutibacterium acnes* in macrophages of extensive peri-implantitis lesions: A clinical case series

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Abstract

Cutibacterium acnes is a facultative anaerobic, gram-positive rod, and a commensal bacterium of the body surface including oral cavity. A causal relationship between *C. acnes* and chronic granulomatous diseases, such as sarcoidosis and orthopedic implant-associated infections, has been previously reported. Typically, *C. acnes* has been observed inside macrophages, allowing evasion of host immunity, and triggering a persistent inflammatory response. However, such findings have not been reported in peri-implantitis lesions. In this case series, we collected inflamed tissues from extensive peri-implantitis lesions of eight patients. Out of the eight samples, seven tested positive for the 16 s rRNA gene of *C. acnes* by polymerase chain reaction, and six were positive by immunohistochemistry. Immunohistochemical staining revealed the presence of *C. acnes* in the cytoplasm of macrophages, suggesting a role in lesion formation. This finding may enhance our understanding of the pathophysiology of persistent peri-implantitis lesions and provide implications for future therapy.

KEYWORDS
case report, *Cutibacterium acnes*, immunohistochemistry, peri-implantitis, polymerase chain reaction

Summary box

What is known

Cutibacterium acnes has been identified as a significant opportunistic pathogen, instigating a persistent inflammatory response in conditions like sarcoidosis and implant-associated infections. Although *C. acnes* has seldom been linked with peri-implantitis, this scarcity of association may stem from previous sampling methodologies.

What this study adds

Cutibacterium acnes was found in the cytoplasm of macrophages. The survival of *C. acnes* within the body's natural immune cells may complicate treatment of resultant lesions. Consequently, peri-implantitis lesions may exhibit persistent chronic inflammatory features akin to other infectious conditions such as sarcoidosis.

Jin-Young Park and Dawool Han contributed equally to this study and share first authorship.

1 | INTRODUCTION

Cutibacterium acnes—well known for causing acnes vulgaris of the skin—is a slow-growing, facultative anaerobic, gram-positive rod.[1] In health, *C. acnes* is a commensal bacterium comprising the normal flora of the oral cavity; however, it can exhibit pathogenicity by attaching to target cells, synthesizing polysaccharide-based biofilms, producing virulence factors mediating inflammation, and enzymatically degrading host tissues.[2] Moreover, *C. acnes* has been shown to survive intracellularly in macrophages, enabling evasion of the host immune response.[3] Pathogenic activity of *C. acnes* has yet to be reported in the oral cavity; however, *C. acnes* has been suggested as an important opportunistic pathogen in numerous inflammatory diseases and implant-associated infections, including sarcoidosis,[4] orthopaedic implants,[5] cardiac devices,[6] breast implants,[7] and intraocular lens.[8]

Peri-implantitis is a highly prevalent disorder affecting the osseointegrated implants, characterized by inflammation of the peri-implant soft tissues and the progressive loss of supporting bone.[9,10] Accumulation of biofilm has been demonstrated to evoke an inflammatory response at the peri-implant mucosa.[11–16] Biofilm retention along with sustained inflammation can initiate the progression of tissue destruction.[17,18] The subsequent peri-implantitis lesions tend to exhibit more rapid and pronounced bone loss when compared with that of periodontitis.[19,20] A clinical comparison of periodontitis and peri-implantitis lesions revealed that the peri-implantitis lesions were more than twice as large and contained larger numbers and densities of immune cells.[21] Such aggressive progression of peri-implantitis has been attributed to the lack of protective anatomical structures such as root cementum, periodontal ligament and supra-crestal attachment fibers at implants, thereby continuously exposing the crestal bone and the inflamed connective tissues to the microorganisms and their pro-inflammatory products.[22]

Despite these assumptions, the current understanding of the role of bacterial community during peri-implantitis progression is very limited, and further validation of etiological pathogens is warranted. Early studies on the microbial composition of submucosal biofilms have utilized targeted identification of pathogens such as DNA–DNA checkerboard hybridization to demonstrate that periimplantitis lesions often shared the common periodontopathogens from the "red complex" such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*.[23] However, recent studies employing the next-generation sequencing methods have detected bacterial taxa that were distinct to the peri-implant niche.[24,25] One study showed that sulcus around dental implants harbor high levels of both gram-positive and -negative anaerobic rods including *C. acnes*[26]; however, the presence of *C. acnes* has never been reported in active peri-implantitis lesions, until now.

In this case series, inflamed tissues were collected from extensively progressed peri-implantitis lesions from eight clinical cases and processed for immunohistochemistry (IHC) and polymerase chain reaction (PCR). The objective of this case series was to report the findings of *C. acnes* from the samples taken from eight clinical cases.

2 | METHODS

2.1 | Study design and subjects

This was a single-centered, retrospective case series. The study was conducted under the Declaration of Helsinki, and its protocol was approved by the Institutional Review Board of Yonsei University Dental Hospital (approval no. 2-2022-0036), which abides by the Good Clinical Practice guidelines and the regulatory requirements. Informed consent was waivered due to the retrospective design of this report.

The study was performed on the data collected from eight subjects who attended the periodontology department of Yonsei University Dental Hospital for the treatment of advanced peri-implantitis. The included subjects had enucleation biopsies of inflamed tissues from surgical sites and records of intraoral and radiographical investigation showing extensively progressed peri-implantitis lesions requiring removal of the implant.

2.2 | Implant removal and sample biopsy

The procedures were performed under infiltration anesthesia of lidocaine 2% and adrenaline 1:100 000. Preoperatively, the surgical site was cleaned using saline irrigation and wet gauze. Sulcular incisions were made around the implants and the adjacent teeth. Full-thicknessed mucoperiosteal flaps were raised using periosteal elevators. The ailing implants were removed using elevators and forceps. The whole granulation tissue surrounding the implants were carefully collected from the surgical site using surgical curette to avoid contamination and immediately fixated in 10% neutral-buffered formalin. The flaps were repositioned and closed using monofilament sutures (monosyn; B Braun, South Korea).

2.3 | Diagnostic assessment

2.3.1 | Histopathologic evaluation and immunohistochemistry (IHC) stain

Harvested samples were sent to the Department of Oral Pathology at Yonsei University Dental Hospital and processed according to standard operating procedure of the department. After histopathologic evaluation of hematoxylin and eosin (H&E) stained slides, samples unsuitable for molecular pathologic examination, such as decalcified sample or those predominantly consisting of fibrous tissue, were excluded. Immunohistochemical analysis was performed to investigate the presence of intracellular infection of *C. acnes* in peri-implantitis tissue. 6 μm thickness tissue sections were deparaffinized and rehydrated followed by antigen retrieval in 10 mM sodium citrate buffer (pH 6.0) at 94°C for 30 min. Endogenous peroxidase activity was blocked with 3% H_2O_2 solution, followed by blocking and permeabilization in PBS containing 2.5% normal goat serum and 0.3% Triton X-100. Sections were then incubated overnight at 4°C with primary

antibody (PAB antibody 1:10 000, MBL Life Science) specific for *C. acnes* as described by Negi et al.[27] After washing, sections were incubated for 1 h with HRP-conjugated antimouse/rabbit IgG and developed with diaminobenzidine (DAB) (Agilent, K500711-2). Counterstaining was performed with Mayer's hematoxylin.

2.3.2 | Polymerase chain reaction (PCR) test

DNA extraction from formalin-fixed paraffin-embedded (FFPE) tissues was performed using the QIAamp DNA FFPE Tissue Kit (Qiagen). Briefly, 10 sections of 10 µm thick paraffin blocks were washed with xylene and 100% ethanol, followed by digestion with proteinase K and lysis buffer. After digestion, DNA was extracted using mini elute column and washing buffers supplied by the Kit. DNA was eluted in 50 µL AE buffer, and concentration of DNA was measured by spectrophotometer (NanoDrop 2000, Thermofisher). PCR amplification was performed using 100 ng of sample DNA for 40 cycles. The target genes included the 16 s rRNA gene of *Cutibacterium acnes* (CA), *Cutibacterium (Propionibacterium) granulosum* (PG), *Mycobacterium tuberculosis* (MT), and human beta-globin gene (BG), as previously described by Eishi et al.[28] (Table 1). The annealing temperature was 57°C for 30 seconds with extension at 72°C for 1 minute. PCR products were analyzed by 1.5% agarose gel electrophoresis alongside a 100 bp DNA ladder.

3 | RESULTS

3.1 | Subjects

There were 5 male and 3 female subjects with a mean age 60 ± 11.1 years (Table 2). One subject was on medication due to a cerebrovascular condition, one was on medication due to hypertension, and one was on medication for hyperlipidemia and prostate disorder that included aspirin.

Eleven implants were removed from the eight participants: nine from the maxilla and two from the mandible. The mean age of the implants at removal was 8 years and 10 months (min: 5 months, max: 20 years). When multiple implants were removed from a patient, the inflamed tissue from one representative site with the largest lesion size was taken for biopsy apart from sample no. 8, in which a lesion was shared by two implants that were closely positioned (Table 2).

3.2 | Clinical findings

All sites healed uneventfully after removal of the implants and the surrounding inflamed tissues.

3.2.1 | Implant type

All implants had internal connections with tapered shapes, however, had heterogenous manufacturers (some unknown) and thread designs. All implants had modified surfaces. Four implants had micro thread designs at the shoulder region (Figure 1A–H).

3.2.2 | Peri-implantitis lesions

All samples had severe bone loss progressed to the apical third or entire length of the implants so that they could be removed with ease using extraction forceps. One sample from the upper right first molar region exhibited progression of bone loss to the sinus floor and subsequent oroantral communication. Most of the lesions exhibited extensive bone loss resulting in the loss of the entire circumferential bone tissues of the alveolar ridge (Figure 2).

3.3 | Polymerase chain reaction

PCR analysis revealed amplification of the 16s rRNA gene of *C. acnes* in seven out of the nine samples (Figure 3A). A sarcoid lymph node was utilized as a positive control of *C. acnes* infected FFPE sample (Figure 4A). Notably, genes associated with other microbes, such as *C. granulosum* and *M. tuberculosis*, were not amplified in any of the samples (Figure 3A).

3.4 | Immunohistochemistry

Immunohistochemical staining using the PAB antibody, which reacts with lipoteichoic acid of *C. acnes* cell membrane, revealed positive staining in six out of eight samples (Figure 3B,C). Small round bodies positive for PAB were observed within the cytoplasm of macrophages in the inflamed tissue of peri-implantitis (Figure 3C), as well as in extracellular bacterial colonies (data not shown). Positive control

TABLE 1 Primer sequence of PCR test.

Primer name	Target gene	Forward sequence (5′ → 3′)	Reverse Sequence (5′ → 3′)	Amplicon size (bp)
CA	16s rRNA of *C. acnes*	GCGTGAGTGACGGTAATGGGTA	TTCCGACGCGATCAACCA	131
PG	16s rRNA of *C. granulosum*	ACATGGATCCGGGAGCTTC	ACCCAAC ATCTCACGACACG	102
MT	Insertion sequence 6110 of *M. tuberculosis*	TCCTATGACAATGCACTAGCCG	GCCAACTCGACATCCTCGAT	101
BG	Beta-globin	TGCCTATCAGAAAGTGGTGGCT	GCTCAAGGCCCTTCATAATATCC	150

TABLE 2 Patient demographics, results of the immunohistochemistry (IHC), polymerase chain reaction (PCR), and implant age at the time of surgery (removal).

Subject no.	Age	Sex	Tooth site	IHC	PCR	Implant age (years)
(+) control	Lung sarcoidosis sample			+	+	
1	70	M	18	+	+	3
2	65	M	25	+	+	10
3	51	F	41	+	+	5 months
4	57	F	15	+	+	14
5	81	M	13	+	+	11
6	50	F	36	+	+	20
7	55	M	16	–	–	8
8	51	M	25, 26	+	–	5
Mean ± SD	60 ± 11.1					8 years and 10 months

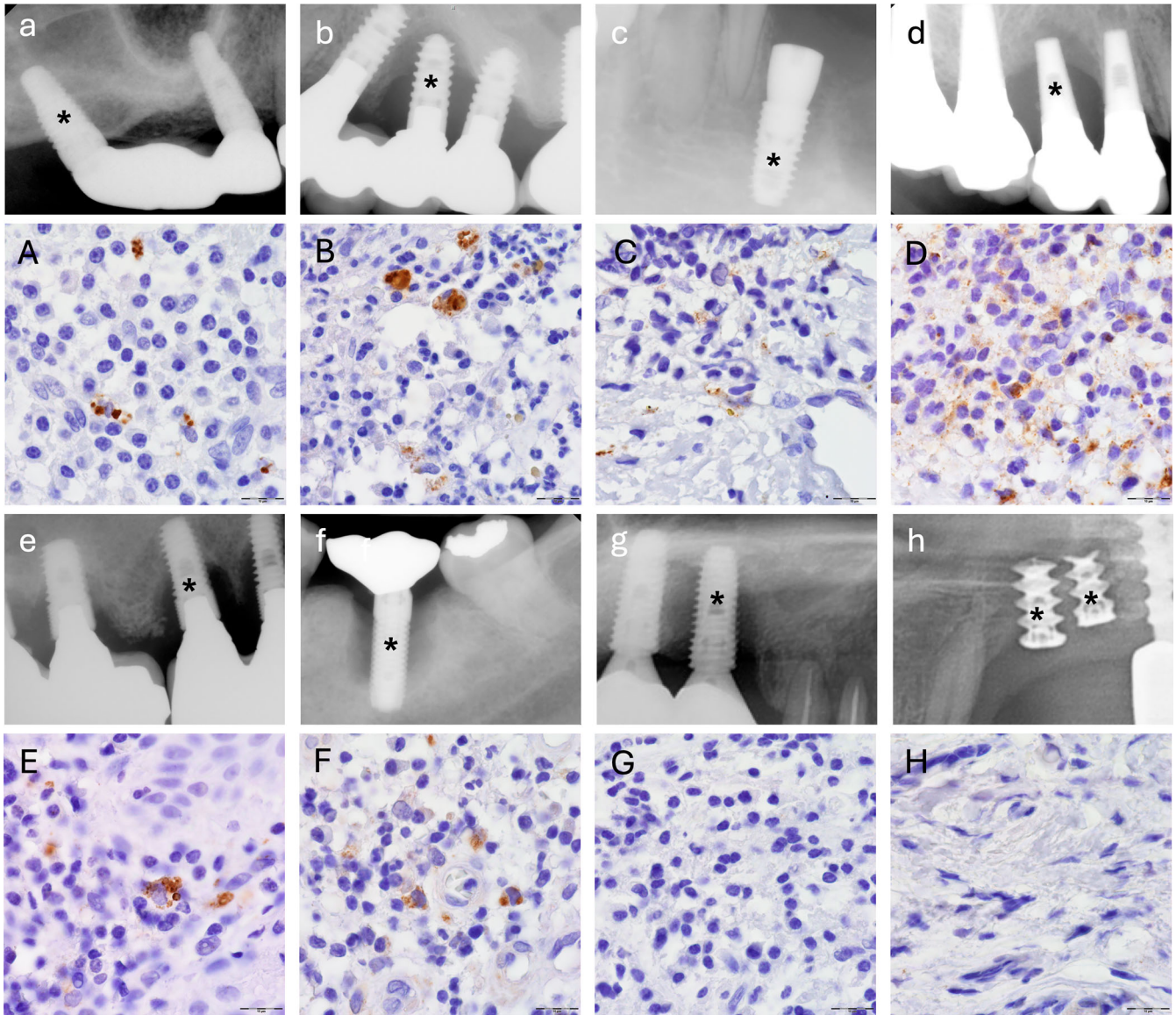

FIGURE 1 Periapical radiographs showing the eight sites in this case series with peri-implantitis lesions from which samples were collected for immunohistochemistry and polymerase chain reaction (a–h). IHC staining of peri-implantitis samples from all eight sites of the study (A–H) (original magnification: X1000, scale bar: 10 μm). All samples were positively stained for *C. acnes* except for samples 7 and 8 (G, H). Analyzed implant sites were marked with *.

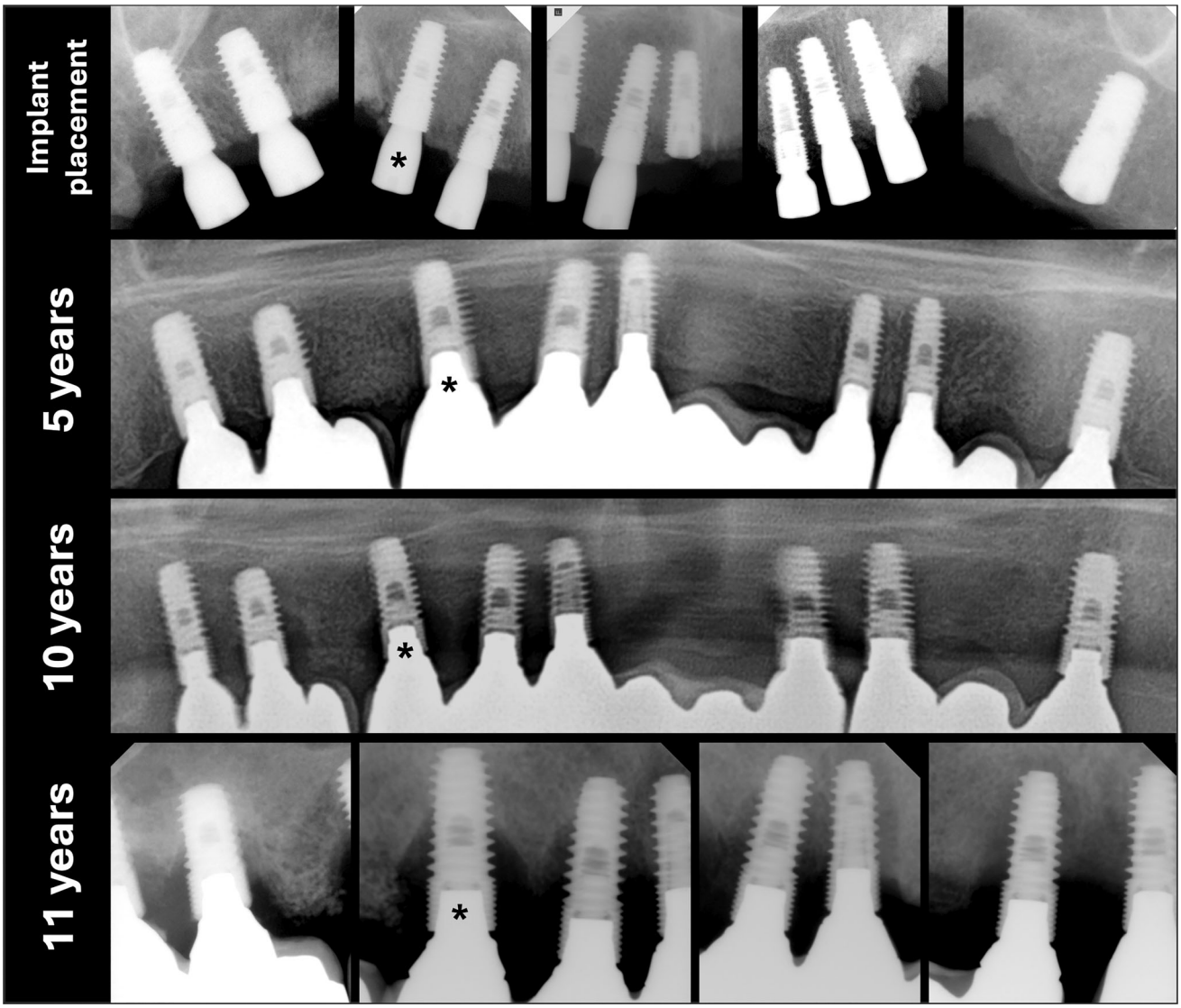

FIGURE 2 Serial intraoral and panoramic radiographs from Case 5 represents a persistent and progressive peri-implant bone loss. At 5 years after placement, peri-implant inflammation was accompanied by marginal bone loss, therefore, implants were treated non-surgically using submucosal instrumentation and locally delivered minocycline gel. Despite the continuous therapy, persistent progression of lesions led to the removal of the implants 11 years after placement. The granulation tissues around the implant in the upper right canine area (marked with *) was collected for immunohistochemical analysis.

samples, including para-cortical macrophages and aggregated macrophages in the sarcoid lymph node, exhibited PAB-positive round bodies in the cytoplasm (Figure 4B,C). Notably, the single sample that tested negative in the PCR analysis also lacked PAB-positive round bodies within the macrophages in IHC staining.

4 | DISCUSSION

C. acnes is a commensal bacterium typically found on the body surface, yet it can emerge as an opportunistic pathogen in implant-associated infections. Despite its wide array of pathogenic characteristics and numerous reports of invasive infections associated with implant devices across various anatomical sites, its association with dental implant infections has not been previously reported. This case series represents the inaugural documentation of clinical findings, revealing the presence of *C. acnes* within inflamed tissues of advanced peri-implantitis lesions in eight clinical cases, as demonstrated by IHC and PCR.

In this case series, IHC and PCR were employed for the detection of *C. acnes*. Previous studies have demonstrated the utility of commercially available *C. acnes*-specific antibodies in detecting the bacterium in the granuloma of sarcoidosis lesions. In our case series, IHC staining revealed the presence of round bodies in six out of eight samples, suggesting an association between *C. acnes* and the formation of inflamed tissues. Intriguingly, these round bodies were observed within the cytoplasm of macrophage, akin to positive control samples from sarcoidosis lesions. Pathogens are typically phagocytosed by

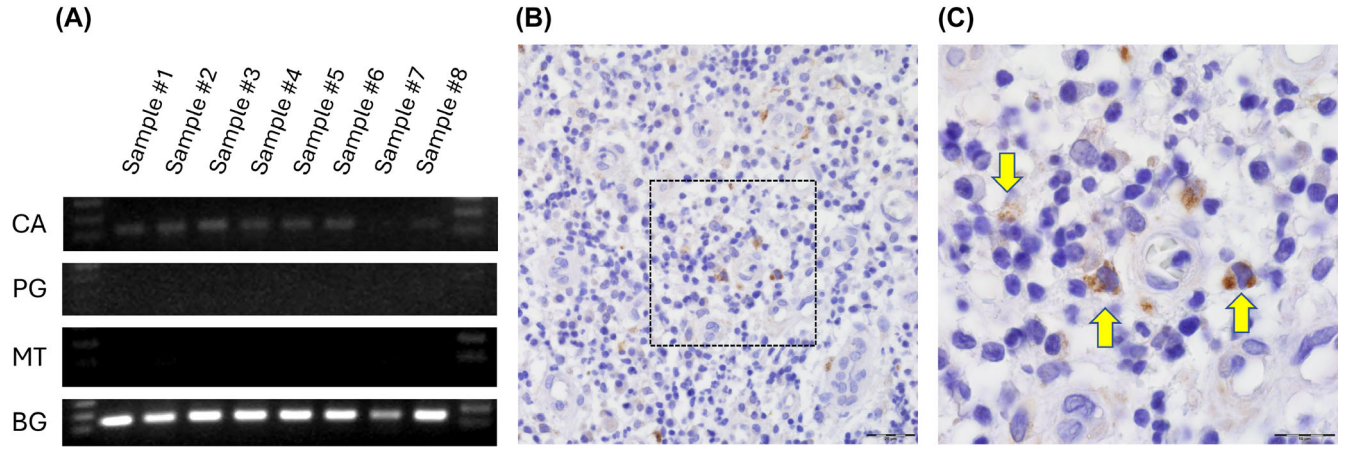

FIGURE 3 The PCR analysis and IHC staining of a peri-implantitis sample. (A) The PCR analysis revealed amplification of the gene of *C. acnes* (CA) in the seven out of eight peri-implantitis samples. Gene associated other bacteria (PG and MT) were not amplified in any of the samples. The human beta-globin gene was utilized as a control gene for PCR analysis. (B) Admixed inflammatory cells were observed in the inflamed tissue of peri-implantitis samples. PAB-positive round bodies were detected in the cytoplasm of macrophages in the six out of eight samples (original magnification: X400, scale bar: 20 μm). (C) High-power view of the region delineated by the dashed line in the (B). PAB positive round bodies in the cytoplasm of macrophages in the inflamed tissue (yellow arrow) (original magnification: X1000, scale bar: 10 μm).

macrophages, which serve to ingest and sterilize infectious agents. However, certain pathogens, such as *Salmonella typhimurium*, *Legionella pneumophila*, *and Mycobacterium tuberculosis*, have evolved mechanisms to survive and proliferate within macrophages. Similarly, *C. acnes* has been demonstrated to persist within macrophages, thereby maintaining its virulence factors in diseases like sarcoidosis and prostate cancer, allowing it to evade immune responses and induce persistent inflammatory response.[3]

Furthermore, *C. acnes* has frequently been identified in orthopedic implants within the shoulder region, where the presence of deep-seated sebaceous glands increases the risk of contamination during surgical procedures. Once introduced to the implant site, the bacterium adheres to the implant surface using surface antigens, facilitating polysaccharide biofilm formation and the expression of proteolytic enzymes that contribute to tissue destruction. Notably, *C. acnes* has demonstrated the ability to adhere to metal implant surfaces, including titanium and steel alloys, potentially enhancing the persistence of biofilm accumulation and infection.[1] The current findings of *C. acnes* in peri-implantitis lesions suggest the possible expression of its virulence factors in peri-implantitis.

Peri-implantitis lesions from the eight subjects in this case series were from extensively progressed sites resulting in removal of the implant, and disease progression occurred over a mean period of approximately 9 years. Apart from the early implant failure after 5 months in case 3, all other cases were late failures of osseointegrated implants induced by the presence of biofilm. It has been shown that the complexity of microbiota composition at the peri-implant mucosa increases with disease progression; therefore, the sites from this study can be assumed to comprise of mature and complex colonies of microorganisms.[24] A recent study employing the 16s rRNA sequencing revealed differently abundant bacterial taxa in health and peri-implantitis.[25] *Bacteroidetes*, *Spirochetes*, and *Synergistetes* were dominant in peri-implantitis, whereas *Actinobacteria*—the phylum-containing *C. acnes*—prevailed in peri-implant health. Similarly, another study using 16s rDNA gene-based PCR showed that *C. acnes* was dominant in healthy peri-implant sites; however, peri-implantitis lesions seemed to be abundant in other anaerobic gram-positive rods including species of *Eubacterium*.[29] *C. acnes* was mentioned to be more prevalent in peri-implantitis compared to health in only one study using DNA–DNA hybridization with 79 bacterial species.[30]

The reason for the rare discovery of *C. acnes* in the peri-implantitis lesions in this case series might be due to the method of sample collection in this study, which included the entire inflamed tissue from the surgical site. On the other hand, sampling methods described in the literature were mainly by collection of the submucosal plaque or peri-implant crevicular fluid using paper points, which would only be a partial representation of the disease site. In addition, *C. acnes* has been detected only in small proportion in the normal flora of the oral cavity, and very slow growth (5–7 days) in aerobic conditions reduces the reliability of detection by culture. There have been few reports of *C. acnes* in the literature in relation with periodontal diseases. *C. acnes* was detected in subgingival plaque samples of aggressive periodontitis lesions using checkerboard DNA–DNA hybridization especially in those with suppuration.[31,32] In a prospective clinical trial, *C. acnes* was found in higher proportions in subgingival plaque samples of Down syndrome patients compared to the non-Down syndrome patients, owed to the possible thumb-sucking habit of this cohort.[33] In the oral cavity, *C. acnes* has been found most frequently in persistent apical periodontitis in the periapical tissues collected during apicoectomy.[34] Their virulence factor in the root apex has been linked with the ability to suppress the host immune response and synthesize biofilm that cause persistent lesions resulting in endodontic failure.[35]

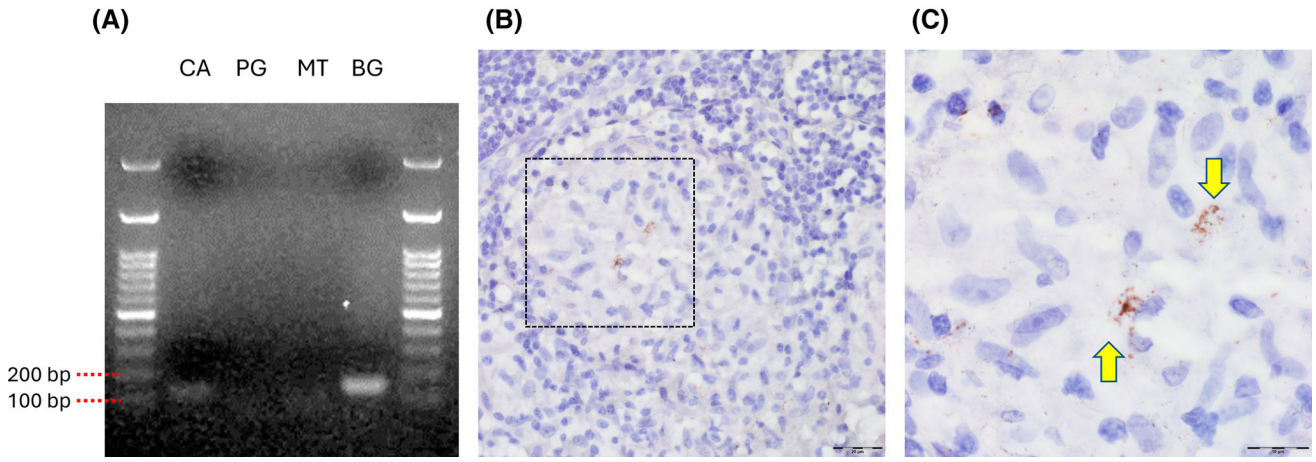

FIGURE 4 The PCR analysis and IHC staining of a sarcoid lymph node sample (positive control). (A) The PCR analysis demonstrated amplification of the gene of *C. acnes* exclusively in the sarcoid sample among the three granuloma-associated bacteria. The human beta-globin gene served as a control gene for PCR analysis. (B) Non-caseating granuloma within the sarcoid lymph node exhibited aggregated macrophages surrounded by lymphocytes. PAB-positive small round bodies were frequently observed within the cytoplasm of macrophages in the granuloma and paracortical area (original magnification: X400, scale bar: 20 μm). (C) High-power view of the region delineated by the dashed line in the (B). PAB-positive round bodies were evident within the macrophages in the granuloma (yellow arrow) (original magnification: X1000, scale bar: 10 μm).

Although several observational studies have revealed the presence of *C. acnes* in disease sites, a direct causal relationship and mechanism of action are yet to be verified. These studies were only able to demonstrate that *C. acnes* was present in the periimplant or periodontal lesions among a community of numerous bacterial species. To further elucidate whether *C. acnes* plays a key role in periimplant or periodontal disease progression, a well-designed animal experiment is required. In an appropriate animal model, *C. acnes* from a site of pathology must be cultured, and then introduced to a healthy site in a controlled environment to gain a deeper understanding of its pathogenic characteristics.

This case series reported histological findings of *C. acnes* within macrophages of periimplant inflammatory tissue samples. Since it would be possible to semi-quantify the number of *C. acnes* visible on immunohistochemical images, in future clinical trials, inflammatory tissue samples could be obtained at different stages of periimplantitis progression to investigate the relationship between the abundance of *C. acnes* and disease progression.

The treatment of infections caused by *C. acnes* presents a challenge for clinicians. Despite its low virulence, *C. acnes* has the capability to interact with the immune system, eliciting persistent chronic inflammation. Moreover, its ability to survive within macrophages, form biofilms, and adhere to implant surfaces confers antimicrobial resistance primarily through tolerance rather than mutation-related mechanisms or inactivating enzymes. Rifampin, a small molecule capable of penetrating biofilms, has demonstrated efficacy against *C. acnes* within biofilms.[1] In this case series, all sites healed uneventfully after implant removal suggesting etiological agents were fully removed by curettage of inflamed tissue and implant removal. Additional larger-scale clinical studies are warranted to confirm the presence of *C. acnes* in peri-implantitis lesions. Furthermore, animal studies could be valuable to assess the virulence of *C. acnes* under controlled conditions within the peri-implant mucosa. Such research endeavors would provide deeper insights into the role of *C. acnes* in peri-implantitis and inform the development of more targeted treatment strategies.

5 | CONCLUSION

In this present case series, *C. acnes* was identified within macrophages in extensively progressed peri-implantitis lesions associated with failing implants. The clinical manifestation of persistent peri-implantitis lesions may be elucidated by *C. acnes*' opportunistic virulence factors and its capability to circumvent host immunity.

AUTHOR CONTRIBUTIONS

J.-S.L. and J.I.Y. conceived the ideas. Y.P. managed clinical data. E.S.C. and D.H. analyzed and interpreted histologic/molecular results. J.-Y.P. led the writing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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