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*Cutibacterium ances*에 의해 유발된 안면 육아종과 치성감염의 임상 경과 : 증례 보고

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〈Abstract〉

Cutibacterium acnes-induced Facial Granulomas Associated with the Clinical Course of Distinct Dental Infections: A Case Report

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Acneiform eruptions are skin diseases that mimic acne vulgaris but lacking typical follicular blockage features. Acne vulgaris and some granulomatous variants of acneiform eruptions can involve *Cutibacterium acnes*, an anaerobic opportunistic bacterium; however, some cases remain resistant to standard antibiotics treatments. We report a 56-year-old male with facial acneiform granulomas unresponsive to long-term antibiotic and steroid treatments. The patient had no history of additional medications or other diseases, except symptomatic apical periodontitis in a molar toot. Both facial skin and dental lesions shared a key finding, intracellular infection of *C. acnes* within macrophages, despite differing histopathological features. The facial acneiform eruptions did not respond to initial minocycline treatment.

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However, following extraction of the infected tooth, the facial granuloma responded to the antibiotics and resolved without complications. PCR analysis confirmed *C. acnes* DNA in both the dental and skin biopsies. This case indicates the *C. acnes*-associated oral-skin-microbiome axis although a direct causal link between the distinct lesions could not be fully established. Odontogenic infection may act as reservoirs, impairing efficacy of antibiotic treatment. We recommend dental evaluation for case of facial acneiform granulomas that do not respond to antibiotics alone.

Key words: Apical periodontitis, *Cutibacterium acnes*, Granuloma, Oral-skin axis, Dental infections

Ⅰ. INTRODUCTION

Acneiform eruptions are a group of skin conditions that clinically resemble acne vulgaris but lack typical comedonal (hair follicle-blocked) features and may occur beyond the usual age range for acnes vulgaris[1]. Various skin diseases can present as acneiform eruptions with granulomatous components including granulomatous rosacea, perioral granulomatous dermatitis, cutaneous sarcoidosis, granuloma annulare, idiopathic facial aseptic granulomas and demodicosis[2-6]. While some granulomatous components arise as secondary responses to hair follicle destruction, systemic and genetic chronic granulomatous disorders can also mimic acneiform lesions, indicating that the granulomatous variants of acneiform eruptions are distinct pathologic entities[2,7-9].

Granulomatous variants share some clinical features with other types of acneiform diseases but have the distinct histopathological features, the presence of granulomas within the lesion. These variants commonly involve hair follicle units with histopathologic features of follicular rupture and destruction[3]. This is not surprising, as the hair follicle niche nourishes commensal microorganisms' potential for infectious or immune granuloma initiation. A well-known example is *Cutibacterium acnes* (formerly termed *Propionibacterium acnes*), which has been implicated in granulomatous disorders such as sarcoidosis and lupus miliaris disseminatus faciei[10-12].

However, hair follicle involvement is not always necessary for granulomatous acneiform inflammations. Systemic granulomatous infections or chemical agents can induce cutaneous lesions independently of the follicular unit. In the case of localized acneiform eruptions, subdermal or interstitial foreign materials close to the clinical manifestations may be causal factors rather than follicular microorganisms[13].

Here, we present a case of *C. acnes*-induced facial acne-like (acneiform) granulomas that were refractory to routine long-term antibiotics. Interestingly, the dermal granulomas were adjacent to but did not include the local hair follicles or skin appendages, suggesting an alternate anatomical source for the infection. We identified intracellular *C. acnes* within distant dental lesions, supporting the hypothesis that odontogenic infection may play a role in triggering facial granulomatous acneiform eruptions. This case highlights the need for dental evaluation in patients with acneiform granulomas that do not respond to conventional antibiotic treatment.

Ⅱ. CASE REPORT

A 56-year-old male presented with multiple papules and skin rashes on his lower lip and chin, which had persisted for over 18 months. Previous medical institute had diagnosed the lesions as cutaneous granulomas through skin biopsy, and the patient was treated with unspecific antibiotics and steroids for more than a year, without significant

improvement. He had no known medical conditions or history of medication use.

At his initial visit to our hospital, the patient exhibited localized erythema and mild swelling on the skin of the lower lip, vermillion border, and mid-chin, along with multiple indurated papules resembling acne with rosacea (Fig. 1A). Given that our institute is a dental hospital, we conducted a comprehensive oral examination. No mucosal or structural abnormalities were found in the oral cavity, except for the lower left first molar, which showed gingival swelling, redness, and pus discharge. The problematic tooth had a history of endodontic root canal filling and exhibited a well-defined osteolytic apical lesion recognizable on panoramic x-ray, suggesting localized apical periodontitis.

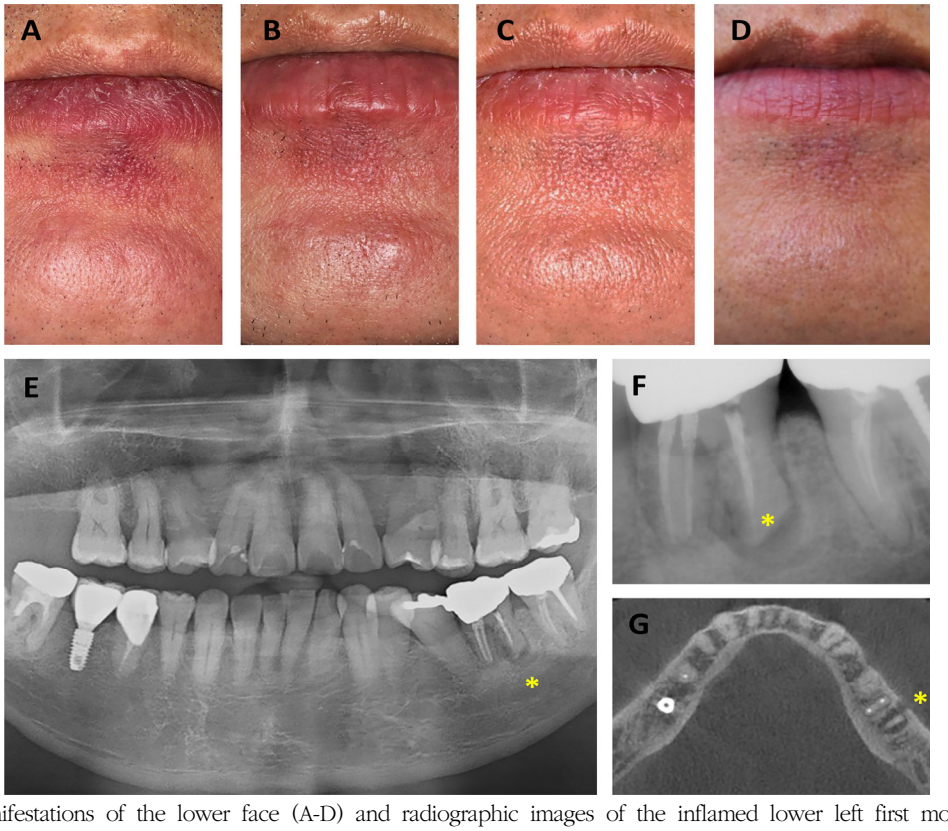

Fig. 1. Clinical manifestations of the lower face (A-D) and radiographic images of the inflamed lower left first molar, #36 (E-G, yellow asterisks).

A. 1st visit at our hospital, after over a year of antibiotic and steroid treatment for the facial lesions. Diffuse redness, swelling on the lower lip, vermillion border, and chin with multiple firm papules resembling acne vulgaris (acneiform eruptions).

B. 14 months after first visit to our hospital. Minocycline had been used throughout this period, but the lesions persisted with repeated wax-and-wane events.

C. Two months after extraction of the inflamed tooth (#36). The inflammatory symptoms and acneiform eruptions reduced rapidly after tooth and apical inflammation removal with the maintained aid of minocycline.

D. Ten months after extraction of the inflamed tooth (#36). The facial papules have completely resolved, leaving only a few streaks of cutaneous erythema on the chin.

E. Panoramic radiograph of the patient before dental treatment. The lower left first molar showed a history of endodontic treatment (root canal filling) and an osteolytic apical lesion.

F. Periapical radiograph of the inflamed tooth before dental treatment. An apico-periodontal lesion is seen with alveolar bone loss and external root resorption.

G. Axial view of cone beam computed tomography on the lower jaw. The apical bone destruction of #36 has penetrated the buccal cortical bone (arrow), implying open communication between the apical lesion and adjacent gingival tissue.

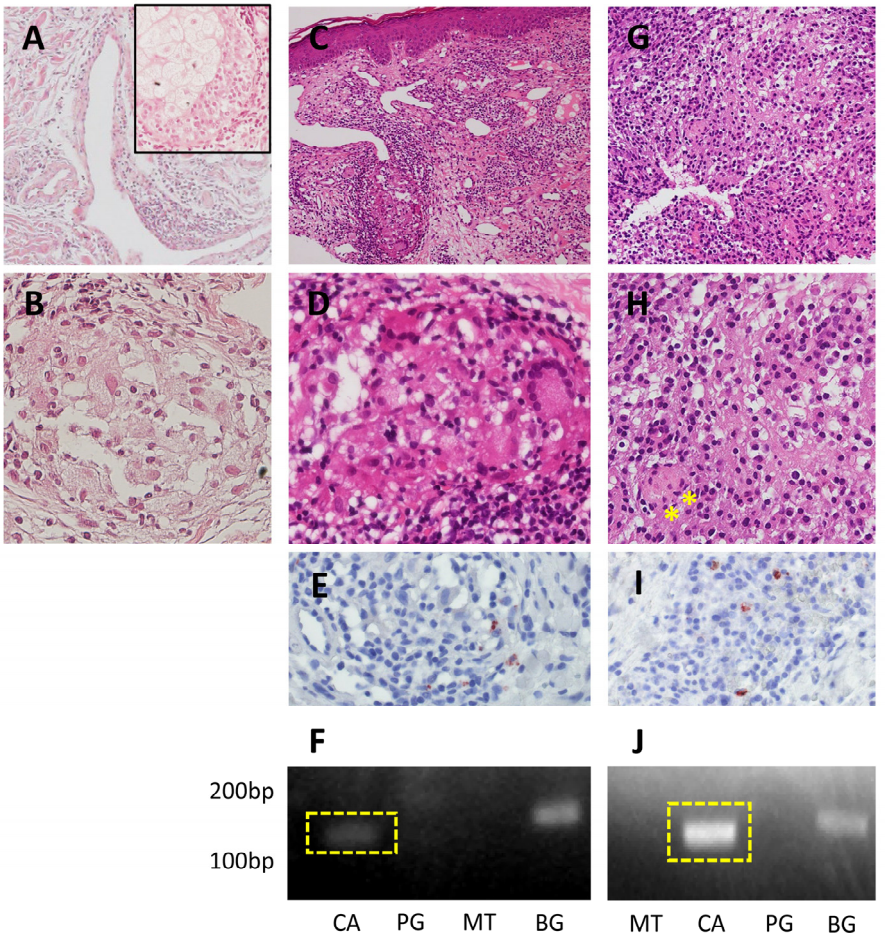

Fig. 2. Histopathologic and ancillary evaluation of the biopsy specimens (A-B, primary facial skin specimen; C-F, second labial skin specimen; G-J, apical inflammatory tissue of #36 tooth).

A. The overall specimens revealed edematous inflamed dermal tissue with perivascular chronic inflammation and foci of granulomatous inflammation. There were no hair follicles in the present specimen and some of the skin appendages showed mild inflammation (inset) but were located at a distance from the core inflammatory lesion (hematoxylin and eosin, original magnification, 100x; inset, x 200).

B. Non-caseating tuberculoid granulomas composed of organized transformed macrophages and peripheral lymphocytes, no signs of foreign materials (hematoxylin and eosin, original magnification, 400x).

C. Diffuse chronic inflammation in the edematous dermis with prominent lymphovascular ectasia. Granulomatous inflammatory foci show perivascular concentration (hematoxylin and eosin, original magnification, 100x).

D. Non-caseating tuberculoid granulomas organized with epithelioid histiocytes, multinucleated giant cells, activated macrophages, and peripheral lymphocytes (hematoxylin and eosin, original magnification, 400x).

E. PAB antibody-positive cytoplasmic granules in macrophages implying intracellular *C. acnes* infection within the granuloma. The PAB-positive stains were only observed in mononuclear macrophages (immunohistochemical staining, original magnification, 400x).

F. Gel electrophoresis results of PCR analysis. *C. acnes*, but not *P. granulosum* or *M. tuberculosis* was detected in the facial dermis specimen (CA: *Cutibacterium [Propionibacterium] acnes*; PG: *Propionibacterium granulosum*; MT: *Mycobacterium tuberculosis*; BG: beta globin).

G. Edematous and fibrous chronic inflammation were observed in the apical soft tissue, consistent with apical periodontitis (hematoxylin and eosin, original magnification: 200x).

H. The inflammation was mainly composed of lymphocytes, plasma cells, and activated macrophages. A few cells resembled transformed multinuclear giant cells (yellow asterisks) but no definite findings of mature granulomas (hematoxylin and eosin, original magnification: 400x).

I. The apical specimen revealed PAB-positive cytoplasmic granules in the macrophages, suggesting intracellular *C. acnes*-infection of the phagocytes (immunohistochemical staining, original magnification: 400x).

J. Gel electrophoresis results of PCR analysis. *C. acnes*, but not *P. granulosum* or *M. tuberculosis,* was detected in the apical specimen (CA: *Cutibacterium [Propionibacterium] acnes*; PG: *Propionibacterium granulosum*; MT: *Mycobacterium tuberculosis*; BG: beta globin).

Ⅲ. RESULTS

To reassess the pathogenic course of the disease, we performed a second biopsy on lower lip lesions. Both the initial and second biopsies revealed diffuse inflammation infiltrating the edematous superficial and mid-dermis (Fig. 2A, 2C, respectively). The inflammatory infiltrates were organized into non-caseating tuberculoid granulomas, concentrated along numerous dilated vascular and lymphatic structures (Fig. 2B, 2D), likely contributing to the rosacea-like clinical manifestations. The tuberculoid granulomas were composed of epithelioid histiocytes and Langhans-type multinucleated giant cells, surrounded by rich collections of lymphocytes.

Although these lesions were inflammatory tuberculoid granulomas rather than 'naked' sarcoid granulomas, we conducted ancillary tests targeting *C. acnes* to rule out the possibility of cutaneous or systemic sarcoidosis[10-12]. Periodic acid-Schiff (PAS) and acid-fast stains were negative, excluding fungal organisms and mycobacterium, respectively. To our surprise, the biopsy specimen stained positive using a PAB antibody, which specifically reacts to the lipoteichoic acid (LTA) antigens found in the membrane of *C. acnes*[12]. The PAB antibody was positively stained as multiple cytoplasmic aggregates within granuloma-associated mononuclear macrophages, but was not in the multinucleated giant cells (Fig. 2E). To further confirm the presence of bacterium, we performed polymerase chain reaction (PCR) on the biopsy specimens, which detected the 16s rRNA gene of *C. acnes*. It revealed a positive band of *C. acnes*, but neither for *Mycobacterium tuberculosis* nor *Propionibacterium granulosum* (Fig. 2F). These findings suggested that persistent *C. acnes* infection as the potent cause for the acneiform dermal granulomas.

We prescribed minocycline, a tetracycline-class antibiotic commonly used for *C. acnes*-related diseases like sarcoidosis and acne vulgaris[11,14,15]. Although the lesions initially showed mild improvement, but soon recurred, remaining as persistent inflammatory lesions similar to those observed at the patient's first visit (Fig. 1B). We hypothesized that the poor response could be due to either minocycline-resistant or the inability of antibiotics alone to eradicate the underlying infection. Therefore, we searched for an alternative infectious source of *C. acnes* infection throughout the patient's body. The inflamed tooth (lower left first molar) was the only anatomic site showing active inflammatory manifestations. Given the poor bone support of the tooth and the active state of apical periodontitis (Fig. 1E-1G), it was extracted with the patient's consent. The apical lesion was sent to the lab for further investigation.

The odontogenic specimen revealed intermixed edematous and fibrous inflammatory tissue (Fig. 2G). Changes in vascular or lymphatic structure were inconspicuous except for mild angiogenesis within the granulation tissue. The inflammation was composed of lymphoplasmacytic infiltrates, activated macrophages, and a few neutrophils, histopathologic findings commonly seen in odontogenic inflammations. A few of the macrophages were suspected of presenting epithelioid or multinuclear-like morphological transformations, but the macrophages were predominantly mononuclear cells with abundant cytoplasm and indistinct cell margins (Fig. 2H). The specimen lacked evidence of definite mature granuloma formation. Upon PAB antibody staining, positive cytoplasmic aggregates were seen in fractions of the activated macrophages (Fig. 2I), identical to the dermal specimen. On PCR analysis the odontogenic specimen showed consistency with the dermal specimen, positive for *C. acnes* while negative for *M. tuberculosis* and *P. granulosum* (Fig. 2J). The distantly located facial (dermal) and odontogenic (dental) inflammations, regarded as solitary and distinct lesions, both contained activated macrophages with intracellular *C. acnes*, a bacterium known for its phagocytic re-

sistance and granuloma formatting abilities[16-18].

The facial acneiform eruptions, redness, and swelling showed significant improvement at 2 months after tooth removal (Fig. 1C). By 10 months post-extraction, the skin lesions had nearly resolved, leaving only a few faint red streaks on the chin (Fig. 1D). The extraction socket healed normally without any postoperative complications. Minocycline was continued throughout the surgical intervention and follow-up period, with no additional side effects reported[19].

Ⅳ. DISCUSSION

Chronic inflammatory disease associated with *C. acnes* is a recognized pathogenic event, yet our case provides new insight into *C. acnes'* pathogenesis and the potential role of an oral-skin microbiome axis. This case suggests that persistent infections in the skin and oral cavity may not only share a common causative microorganism but may also interact along this axis, influencing clinical outcomes. It is well known that intraoral agents can induce cutaneous manifestations through direct anatomical connection, such as in orofacial fistulas, or diffuse hypersensitive immune reactions that involve vast regions in the head and neck region[19,20]. In contrast, our case had separate *C. acnes*-infected chronic inflammatory diseases which were regarded as clinically unrelated.

Determining whether the skin or oral cavity can be the infectious origin for the other side remains a difficult and controversial issue. *C. acnes* is a commensal anaerobe in both the skin and oral cavity, so shared bacterial involvement in both lesions may be regarded as a coincidence[18,21-24]. Previous study has found *C. acnes* to be the prevalent microorganism in apical periodontitis with 'open communication' to the oral cavity, unlike in isolated apical infections[24]. The apical lesion in this case was open to the gingival surface, with evidence of periodontal pus discharge and had a history of root canal treatment, consistent with other *C. acnes*-related apical infections[24,25]. *C. acnes* of skin commensals and refractory apical periodontitis also share dominant phylogenetic strain types, particularly type I, which makes skin and oral strain distinguishment more challenging[24]. While some reports suggest that *C. acnes* in apical periodontitis could be a nosocomial contaminant introduced during dental procedure, cutaneous granulomas may have acquired their intracellular *C. acnes* from direct lymphatic transmissions or through phagocytic carriers[12,24-29].

Regardless of whether causality exists between oral and skin infections and their progressive direction, our case implies that there may be an oral-skin-*C. acnes* axis which critically influences clinical outcomes on both anatomical sites. Notably, the facial granulomatous inflammation remained refractory to minocycline until the infected tooth was removed. This finding highlights the importance of managing odontogenic infections through invasive dental interventions, such as root canal therapy, curettage or tooth extraction, especially since the antibiotics alone may be ineffective in communicated odontogenic infections[29-32]. Root canals, particularly necrotic or avascular (due to root canal filling) in apical periodontitis, provides a sanctuary for anaerobic bacterium[33-36]. An infected root canal may constantly supply pathogenic bacterium to the adjacent soft tissue because of its poor access to systemic and local antibiotic delivery. The removal of the inflamed tooth, a potential bacterial chamber, seemed to accelerate healing in both facial and oral infections and normalize the antibiotic effects of minocycline therapy.

Based on our findings, treating relevant odontogenic infections could improve the clinical outcomes of antibiotic therapy in chronic inflammatory skin diseases, especially those affecting the lower face. Further clinical studies and molecular investigation are needed to clarify the role of *C.*

acnes pathogenesis in the oral-skin-microbiome axis and acneiform skin diseases. We advise dermatologists and dentists to include a dental examination in idiopathic facial dermatitis and granulomatous inflammations refractory to regular antibiotic therapeutics.

Ⅴ. CONCLUSION

Our case highlights a possible oral-skin-*C. acnes* axis, suggesting that persistent infections in the oral cavity can influence the clinical course of facial granulomatous acneiform eruptions. Minocycline alone was insufficient to resolve the patient's skin lesions until the infected tooth was extracted, emphasizing the importance of evaluation and managing odontogenic infections in tandem with dermatologic area.

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Declaration of Interest Statement

The authors report there are no competing interests to declare

Author Contributions Statement

Dawool Han: Investigation, Writing-Original Draft
Sang Hyun Song: Investigation, Writing-Original Draft
Seung Yong Han: Validation, Investigation
Na Yeong Cho: Resources, Validation
Jong In Yook: Conceptualization, Methodology
Jung Seok Lee: Conceptualization, Methodology
Eunae Sandra Cho: Conceptualization, Writing-Review & Editing, Supervision

Data Availability Statement

The data supporting this paper are not openly available due to reasons of sensitivity and privacy of patient, and are available from the corresponding author upon reasonable request.

Ethics Declarations

In our institution, case report that do not contain personally identifiable information are exempt from IRB review and patient consent. This exemption has been approved by Institutional Review Board of our Institution (2-2022-0058).

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