Drug-induced pemphigus–like lesion accompanied by severe gingival enlargement
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Pemphigus-like gingival lesions are common in elderly individuals who are on long-term systemic medications. We report the case of a patient with drug-induced pemphigus–like lesion with severe gingival enlargement who was examined using histological and immunohistochemical methods. A 67-year-old woman with a history of breast cancer and on antihypertensive therapy complained of tumorous gingival enlargement in the left premolar and molar regions of both arches. The involved teeth showed extensive bony destruction, and a malignant tumor was suspected. Cytological examination revealed several round-to-polygonal acantholytic keratinocytes with normal nuclei. Severe gingival inflammation accompanied by extensive acantholysis of the surface epithelium caused multiple erosions and ulcerations in the absence of tumor growth. ß-catenin was weakly expressed in the erosive epithelium, whereas LC3 and GADD45 were found to be strongly positive. These findings suggested that the erosive epithelium had slowly degenerated via autophagy and cellular growth arrest. Thus, the erosive epithelium was suspected to be chronically damaged by certain drugs rather than by acute cytotoxic changes. Following drug cessation, the gingival hyperplasia rapidly regressed with simple oral hygiene care and partial gingivectomy. Drug-induced pemphigus–like lesions can be diagnosed using detailed medical history and pathological examinations and should be followed by a conservative treatment.

Key Words: Acantholysis, Drug-induced pemphigus–like lesion, Gingival enlargement

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Introduction

Drug-induced pemphigus was first recognized 20 years ago; however, the mechanisms leading to epithelial acantholysis are still unclear [1–4]. Penicillamine, captopril, and thiopronin can cause acantholytic lesions by a direct toxic or biochemical effect in human skin explants. Additionally, piroxicam, a new non-steroidal anti-inflammatory drug, is also associated with a pemphigus vulgaris–like eruption [5]. Several patients of drug–induced gingival hyperplasia with mild-to-moderate clinical features report in outpatient clinics, but most lesions usually regress after adequate oral hygiene maintenance. Therefore, drug-induced pemphigus is a diagnostic challenge, as no definite clinical feature can differentiate it from its idiopathic counterpart [6,7].

Gingival hyperplasia is seen in 8% to 85% patients treated with cyclosporine [7]. Furthermore, fosinopril, an angioten-
sin-converting enzyme inhibitor commonly used in anti-
hypertensive therapy, frequently induces a pemphigus-like skin eruption [8]. Another angiotensin-converting enzyme inhibitor, enalapril, a widely used antihypertensive drug, has shown a powerful in-vitro acantholytic effect with a potential to induce pemphigus in genetically predisposed individuals [9]. Skin susceptibility to nifedipine is mostly genetically determined, with some nifedipine-treated patients developing an acantholytic reaction, while others a subepidermal bullous eruption [4].

Drug-induced pemphigus is a heterogenous group of disorders in which some drugs induce acantholysis. Few patients have detectable autoimmune antibodies, and the eruptions usually resolve with the discontinuation of the associated drug [10]. However, the mechanism of progression in drug-induced pemphigus leading to epithelial acantholysis has not been elucidated yet. In this case report, to differentiate between drug-induced pemphigus and true oral pemphigus of autoimmune origin, we have used the term drug-induced pemphigus-like lesion.

In this report, we present a case of drug-induced pemphigus-like lesion with severe gingival enlargement mimicking a malignant gingival lesion, which showed spontaneous remission after simple oral hygiene care and partial gingivectomy. We document the detailed clinical features and histopathological and immunohistochemical findings with a review of the literature.

Case

A 63-year-old women visited the Department of Oral and Maxillofacial Surgery at Gangneung-Wonju National University Dental Hospital with a complaint of tumorous gingival growth. Intraoral clinical examination revealed severe gingival hyperplasia in the left premolar and molar regions of both arches, accompanied by the presence of inflammatory exudate and calculus deposition around the gold fixed dental prosthesis in the left maxillary posterior region. The gingiva was severely edematous and enlarged in the interdental region. The patient first noticed the enlargement four months ago, due to severe gingival bleeding and tooth mobility. However, it did not subside with careful tooth brushing and anti-inflammatory therapy. The patient was concerned regarding the possible recurrence of breast cancer, which had manifested seven years ago.

The patient reported that the breast cancer was treated by surgery, followed by chemotherapy. Thereafter, she was prescribed therapeutic drugs for diabetes mellitus and was on antihypertensive therapy using high doses of the calcium-channel blockers nifedipine (Adalat) for more than seven years. The gingival ulceration and enlargement were first evident four months ago, which have progressed gradually since then.

The enlarged gingival region was diffusely erosive with multifocal ulcerations (Fig. 1A, B). Cone-beam computed tomography revealed severe enlargement of the gingiva of left maxillary posterior region, measuring 28 mm×34 mm×42 mm, with enlarged cervical lymph nodes, strongly suggestive of a malignancy (Fig 1C). Orthopantogram revealed extensive alveolar bone resorption in the left maxil-

![Fig. 1.](image-url)
lary posterior region, resulting in ‘floating’ left maxillary second molar (Fig. 1D).

The exfoliated keratinocytes were smeared and observed under a microscope: they were mostly acantholytic, separate from each other, and polygonal in shape, but their nuclear chromatin patterns were almost normal (Fig. 2). These cytological findings were not adequate for establishing a definitive diagnosis; therefore, an incisional biopsy was performed to examine the tumorous gingival lesion.

Histopathological analysis revealed that the gingival epithelium was diffusely erosive, and individual keratinocytes were gradually shed with variable features of acantholysis in the spinous cell layer and cleft formation in the superficial cell layer, which was followed by epithelial detachment. However, these epithelial cells showed no atypical nuclear changes (Fig. 3). The underlying connective tissue

![Image](image1.png)

**Fig. 2.** Spontaneous remission of the gingival enlargement after simple oral hygiene care and partial gingivectomy. (A, D) Results after simple oral hygiene care with no surgical intervention. (B, C) Results after extraction of the involved teeth (#27) and partial gingivectomy. Almost complete gingival healing is evident.

![Image](image2.png)

**Fig. 3.** Smeared specimen from the gingival lesion showing severe epithelial acantholysis. (A-D) Hematoxylin- and eosin-stained sections. (A) Round- to polygonal-shaped exfoliated keratinocytes, almost separate from each other. (B-D) Under high magnification, exfoliated keratinocytes showing abundant cytoplasmic content, but normal nuclear chromatin patterns (arrow).
showed diffuse fibrosis, with the presence of thick collagen bundles, accompanied by a mild inflammatory reaction. In contrast, the erosive and ulcerated gingival areas showed marked chronic inflammatory cell infiltration, suggestive of a granulomatous lesion. No features of neoplastic proliferation were evident in the fibroepithelial gingival lesion.

Immunohistochemical analysis for the expression of different proteins in the erosive/ulcerated gingival epithelium revealed that β-catenin was rarely expressed in the erosive epithelium (Fig. 4A), weakly expressed in the detached epi-

Fig. 4. Photomicrographs of the drug-induced pemphigus-like gingival lesion. (A-I) Hematoxylin- and eosin-stained sections. (A) Low magnification view of the gingival lesion showing fibro-epithelial tissue but no evidence of tumor-like growth. Markedly erosive and ulcerated surface epithelium (arrows). (B, C) High magnification of panel A, shed involved epithelium due to the presence of frequent supra basal clefts (arrows), but no inflammatory reaction. (D, E) Severely degenerated and detached epithelium (arrow heads), with presence of granulomatous chronic inflammation. (F) High magnification of panel E, heavy infiltrations of plasma cells, macrophages, and lymphocytes. (G-I) High magnification of surface epithelium in panel A, (G) Superficial cell layer showing vacuolated keratinocytes with pyknotic nuclei (arrows). (H) Spinous cell layer showing markedly increased intercellular spaces (arrows) undergoing acantholysis. (I) Supra basal cell layer showing severe acantholytic dilation of the intercellular spaces (arrows).
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Epithelium in the periphery of the ulcer (Fig. 4B), and strongly expressed in the normal epithelium in areas remote from the ulcer (Fig. 4C). The gradual loss of β-catenin staining ability indirectly correlated with the occurrence of epithelial acantholysis in this case.

The intracellular degradative enzyme, cathepsin G was

![Figure 5](image_url)

**Fig. 5.** Immunohistochemical analyses for drug-induced pemphigus-like gingival lesion. (A1-F1) Low magnification. (A2-F2) High magnification. (A-C) rare expression of β-catenin (arrows) in the erosive epithelium (A), weak expression in the detached epithelium (B), and strong expression in the normal epithelium (C). The gradual loss of β-catenin staining ability was closely associated with epithelial acantholysis. (D) Strongly localized cathepsin G in macrophages infiltrated in the ulcerated epithelium. (E) Strong expression of GADD45, a biomarker for growth arrest, in the spinous layer of the epithelium (arrows). (F) diffuse expression of LC3, a biomarker for autophagy, in the suprabasal and lower spinous layer of the detached epithelium (arrows).
strongly localized in the neutrophils infiltrated in the ulcerated epithelium (Fig. 4D). The biomarker of cellular growth arrest, GADD45 was strongly expressed in the entire spinous layer of the epithelium (Fig. 4E). Furthermore, the biomarker of autophagy, LC3 was diffusely localized in the suprabasal and lower spinous layers of the detached epithelium (Fig. 4F). In contrast, PCNA, HSP-70, and p38 were entirely negative in the erosive and ulcerated epithelium (Fig. 4G-I).

Taken together, the gingival lesion in this case showed severe epithelial acantholysis, concurrent with the loss of β-catenin expression, and intracellular autophagy, indicated by increased expressions of cathepsin G and LC3. These findings indicate that the cellular damage was caused by certain drugs prescribed for systemic diseases, such as hypertension. As the findings of this case were strongly associated with the intake of antihypertensive drugs, the case was finally diagnosed as drug-induced pemphigus-like lesion with gingival hyperplasia.

For the treatment of the gingival lesions, the patient was asked to stop the antihypertensive drug temporarily, after consultation with the patient’s physician. The gingival swelling subsided in a week by simple oral hygiene care. The tumorous gingival overgrowth was excised through partial gingivectomy with extraction of the involved teeth. The postoperative wound healing was uneventful, and most of the gingival hyperplasia had regressed by the five-month follow-up visit.

Fig. 6. Immunohistochemical analyses for drug-induced pemphigus-like gingival lesion. (A) HSP-70, weakly expressed in the epithelium. (B, C) PCNA, p38, respectively. (D) TGF-β1, positively expressed in the stromal fibroblasts. (B, C, E, F) Almost negatively expressed PCNA, p38, bFGF, and BCL2, respectively.
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Discussion

In this case, severe gingival enlargement was evident in both jaws, which appeared aggressive in radiological analysis as extensive bony destruction around the involved teeth. The areas of gingival enlargement exhibited an erosive epithelium, and were closely associated with the ill-fitting gold prosthesis, which showed poor maintenance of oral hygiene.

The marginal gingiva was erosive and ulcerated, with chronic granulomatous inflammatory reaction, resulting in severe submucosal fibrosis. However, the submucosal connective tissues of the gingival lesions showed no evidence of neoplastic growth but exhibited granulomatous inflammation and subsequent bone resorption.

Therefore, we speculate that the gingival hyperplasia might have been originated from the erosive and ulcerated gingival epithelium, which was secondarily infected, followed by stimulation of submucosal fibrosis. Additionally, the drug-induced acantholytic destruction of the epithelial architecture could have been the pivotal factor for the progression of gingival hyperplasia to tumorous growth in this case.

The immunoreaction to β-catenin was rarely expressed in the erosive and ulcerated gingival epithelium, while it was conspicuously expressed in the normal mucosal epithelium near the gingival lesion. Therefore, the gradual loss of β-catenin could be related to the occurrence of epithelial acantholysis in the gingival lesion of this case.

Different protein expressions were observed through immunohistochemical staining: the epithelium of the drug-induced pemphigus-like lesions showed severe acantholysis (loss of β-catenin) with activation of autophagy and growth arrest (positive for LC3 and GADD45, respectively). These features differ from those of ordinary cytotoxic damage, such as cellular apoptosis or necrosis, heat-shock protein activation, and cellular survival signaling. Therefore, we propose that the epithelial changes in this case might be more closely related to drug-induced cellular damage than to ordinary cytotoxic damage. Additionally, the clear immunoreaction to TGF-β1 in the stromal fibroblasts might correlate with the severe tumorous gingival hyperplasia observed in this case (Fig. 5).

Strong positive immunoreactions to cathepsin G, GADD45, and LC3 were evident in the erosive/ulcerated epithelium in this case, while the immunoreactions to PCNA, HSP-70, and p38 were entirely negative. Therefore, it can be presumed that the epithelial cells were still active and recovering from stressful cellular conditions by the infiltration of macrophages (Fig. 6).

In summary, we presented a representative case of drug-induced pemphigus-like lesion that progressed to severe tumorous gingival hyperplasia. The gingival hyperplasia regressed rapidly by simple oral hygiene care after the cessation of the antihypertensive drug intake, and subsided completely after partial gingivectomy. The histological features of extensive acantholysis and the results of immunohistochemical staining prompted the diagnosis of drug-related pemphigus like gingival lesion. Inflammatory gingival ulceration

Fig. 7. Schematic representation of molecular signaling pathways. The present immunoreactions of β-catenin, TGF-β1, LC3, GADD45, PCNA, and Ki-67 (red arrows) were identical to the immunoreactions found in the cases caused by drug induced damage as reported in the literatures (blue arrows), while the present immunoreactions of PARP, HSP-70, p38, and pAKT (red arrows) were contrast to the immunoreactions found in the cases caused by cytotoxic damage as reported in the literatures (blue arrows). Therefore, the present case was finally diagnosed as a drug-induced pemphigus-like lesion with tumorous gingival hyperplasia.
drug-induced pemphigus-like lesion with severe gingival hyperplasia. The pathogenic mechanism was speculated as acantholysis (down-regulation of β-catenin), autophagy activation (up-regulation of LC3), growth arrest (up-regulation of GADDH), and diffuse stromal fibrosis (up-regulation of TGF-β1) (Fig. 7). The accurate diagnosis of drug-induced pemphigus-like lesion is possible through detailed medical history and pathological examinations, and should be followed by conservative treatment [11].

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Conflicts of Interest

The authors declare that they have no competing interests.

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