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CASE REPORT

Oral mucosal melanoma: clinicopathological analysis and narrative review of a case with heterogeneous clinical presentation

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Abstract:

Oral mucosal melanoma is a rare and aggressive malignant neoplasm, frequently associated with delayed diagnosis and unfavorable prognosis. This study aims to report a case of oral mucosal melanoma located at a non-palatal site, presenting as an extensive pigmented lesion affecting the lower gingiva and extending to the floor of the mouth, a topography less frequently described for this neoplasm, as well as to present a narrative review of the literature. An adult patient presented with a pigmented lesion in the lower gingival region extending to the floor of the mouth. The diagnosis was established through histopathological and immunohistochemical examination, confirming oral mucosal melanoma. The literature review addressed clinical, diagnostic, and prognostic aspects of oral mucosal melanoma, highlighting the influence of anatomical location and the biological particularities of this neoplasm in comparison with cutaneous melanoma. It is concluded that the recognition of atypical melanocytic lesions in less common sites of the oral cavity is essential for early diagnosis and appropriate clinical management of oral mucosal melanoma.

Keywords: Melanoma; Mouth neoplasms; Gingiva; Mouth floor; Case reports.

INTRODUCTION

Melanoma is the third most common cutaneous malignancy, following basal cell carcinoma and squamous cell carcinoma, although it accounts for only 3–5% of all cutaneous malignancies. In the oral cavity, its occurrence is even rarer, ranging from 0.2 to 8% of all melanomas described[1].

Mucosal melanoma (MM) is a malignant neoplasm originating from melanocytes present on mucosal surfaces. Its etiology remains undefined, although it frequently exhibits characteristic cytogenetic alterations. Approximately 55% of cases involve the head and neck region, followed by the anogenital region[2]. It is a rare variant of melanoma, representing less than 1.3% of all cases[3].

MM demonstrates aggressive behavior and high clinical complexity, factors that hinder its management, especially due to its low prevalence. Its epidemiological and clinical characteristics differ substantially from those observed in cutaneous melanoma (CM). Whereas CM tends to occur in younger individuals, MM predominantly affects older age groups, with a median age at diagnosis of approximately 70 years, compared with about 55 years in CM cases[4].

Statement of Clinical Significance
The clinical heterogeneity of oral mucosal melanoma includes presentations with extensive pigmentation alongside non-pigmented nodular lesions, increasing risk of diagnostic misinterpretation and delay. These features highlight the importance of careful clinical observation and early histopathological assessment of persistent mucosal changes.

Risk factors associated with the development of MM are not yet fully established. Unlike CM, there is no evidence of an association between ultraviolet radiation exposure and its occurrence[5].

Oral mucosal melanoma (OMM) corresponds to a rare subtype of MM, resulting from the neoplastic transformation and clonal proliferation of melanocytes in the oral cavity. It represents approximately 0.5% of oral malignant neoplasms[6]. The highest incidence of OMM is observed between the fourth and sixth decades of life, with a male predominance, at an approximate ratio of two men for every woman[7].

Classified as a "non–sun-related" melanoma, OMM shows no association with UV radiation or with known carcinogenic agents. There is also no evidence that repeated trauma, chronic inflammation, or tobacco

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use contribute to its development mechanism. Its pathogenesis is complex and poorly understood, involving genetic and molecular alterations that affect melanogenesis, the cell cycle, and apoptosis. Recent evidence suggests that its origin may lie in the transformation of melanocytic stem cells or mature melanocytes, contributing to its heterogeneity[8,9].

OMM presents a wide clinical spectrum, usually manifesting as a brown macule, patch, or nodular lesion, often displaying shades of gray, red, purple, or areas of depigmentation. Clinically non-pigmented or hypopigmented melanomas have also been described[10]. These lesions may present as pink, erythematous, or whitish macules, papules, or nodules and are frequently associated with delayed diagnosis because they may mimic benign or reactive conditions[11].

As most oral melanocytic lesions are initially asymptomatic, diagnosis is frequently delayed and established only after ulceration or tumor growth capable of producing symptoms. Therefore, early detection is essential to enable effective treatment and represents the primary strategy to improve patient survival and prognosis, considering the aggressive behavior and generally unfavorable outcome of OMM[12].

OMM exhibits a molecular profile distinct from that observed in cutaneous melanoma, with a low frequency of mutations in genes classically associated with ultraviolet radiation, such as BRAF and NRAS. In contrast, KIT alterations are described in a limited subset of cases, reflecting the genetic heterogeneity and still poorly understood pathogenesis of this neoplasm. This molecular diversity contributes to the aggressive behavior of the tumor and limits the application of targeted therapies widely used in cutaneous melanoma[13].

Prognostic factors for oral mucosal melanoma (OMM) are not yet fully defined. A recent systematic review and meta-analysis sought to identify predictors influencing patient survival. The overall 5-year survival rate was 34%. Among the main factors associated with poorer prognosis were tumors larger than 4 cm, the presence of lymph node metastasis, and tumor location outside the palate. Conversely, palatal lesions demonstrated better survival, with an estimated 2-year survival rate of 85%[14].

Given the rarity and heterogeneous clinical behavior of oral melanoma, the present study describes a case with different clinical characteristics, contributing to the understanding of this uncommon neoplasm.

CASE REPORT

A 74-year-old female patient, melanoderma, with no systemic history, presented in good general health. She denied known comorbidities, deleterious habits (smoking and alcohol consumption), or continuous medication use. The chief complaint referred to the appearance of a nodular lesion on the gingiva, described by the patient in lay terms as a "small lump." She reported that the lesion had begun insidiously and exhibited progressive growth over approximately one year, becoming gradually more evident and producing a sensation of increased volume in the lower gingival ridge. Although she did not report significant pain, she mentioned mild local discomfort, particularly during mastication.

On intraoral clinical examination, the lesion exhibited a nodular morphology, fibrous consistency, and pedunculated implantation. Due to these characteristics, the initial diagnostic hypothesis was of a benign or reactive alteration, which led the first professional to perform an excisional biopsy without suspicion of malignancy. The patient was unable to inform whether the specimen had been submitted for histopathological examination. However, she reported recurrence of the lesion at the same site approximately one month after the procedure.

The patient did not seek immediate care and remained with the recurrent lesion for approximately ten months. Only after this period did she seek dental evaluation again and, given the persistence and growth of the lesion, she was referred to a specialized Oral Medicine service.

During clinical examination by the oral medicine specialist, an extensive area of dark pigmentation was observed on the lower gingiva, predominantly affecting the vestibular region and also extending to the floor of the mouth. The pigmentation present on the oral mucosa had gone unnoticed by both the patient and the professionals who had previously treated her, possibly due to her higher phototype, which may have led to an erroneous interpretation as physiologic racial melanotic pigmentation. No perceptible enlargement of cervical lymph nodes was observed at the time of evaluation. Imaging examinations were not available at the time of diagnosis, and no clinical evidence of regional metastasis was observed during the initial evaluation.

The coloration ranged from dark brown to black, exhibiting irregular borders and poorly defined margins throughout its extension. Clinical photographs (Figure 1) demonstrate the extent of the pigmented area,

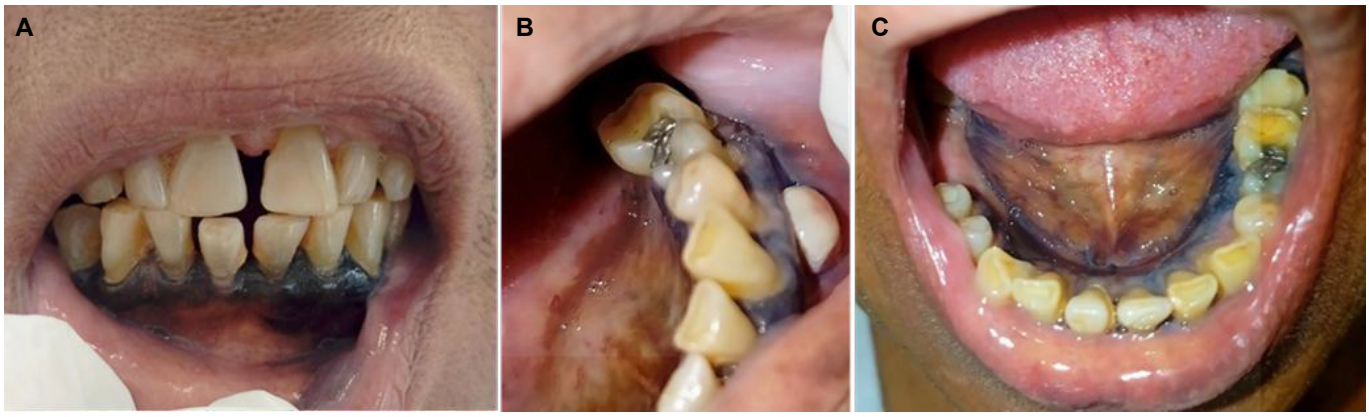

Figure 1. (A) Lower vestibular gingiva showing extensive diffuse dark pigmentation. **(B)** Posterior region of the lower gingiva demonstrating a well-defined white nodular lesion associated with an adjacent pigmented area. **(C)** Lingual aspect of the lower gingiva evidencing diffuse dark pigmentation along the alveolar ridge and floor of the mouth.

where the presence of a nodule with a whitish surface, fibrous consistency, and pedunculated base was also observed, measuring approximately 4 mm in diameter, with an initially uncertain etiology.

Given the clinical suspicion of a malignant melanocytic neoplasm, an incisional biopsy of the gingival nodular lesion was performed. Histopathological examination revealed a proliferation of atypical melanocytes arranged in nests, infiltrating the underlying connective tissue stroma. The cells exhibited marked pleomorphism, enlarged hyperchromatic nuclei, and frequent presence of brownish pigment consistent with melanin. At the epithelial–connective tissue interface, evident junctional activity was observed, characterized by isolated or grouped atypical melanocytes, confirming the diagnosis of oral melanoma. For diagnostic confirmation, an immunohistochemical study was performed, revealing positivity of the neoplastic cells for S-100, Melan-A, and HMB-45.

Although histopathological confirmation was obtained only from the gingival nodular lesion, the extensive adjacent pigmented areas involving the gingiva and floor of the mouth exhibited continuous clinical features highly suggestive of melanocytic involvement associated with the primary lesion. No additional biopsies were performed in these areas.

The immunoexpression profile, associated with the previously described morphological findings, established the definitive diagnosis of oral mucosal melanoma in the biopsied gingival lesion (Figure 2).

At the time of manuscript preparation, no evidence of regional lymph node involvement or distant metastasis had been identified.

DISCUSSION

Malignant mucosal melanomas of the head and neck represent a rare neoplastic entity, accounting for a small fraction of all melanomas, with oral cavity involvement being particularly uncommon. Despite their low incidence, these neoplasms exhibit highly aggressive biological behavior, characterized by high rates of local recurrence, metastatic dissemination, and poor five-year survival, underscoring their clinical relevance and unfavorable prognostic impact[15].

Oral mucosal melanoma (OMM) occurs more frequently in Asian, African, Hispanic, and Indian populations, predominantly affecting the hard palate and maxillary gingiva, followed by the buccal mucosa, lips, tongue, and floor of the mouth. Clinically, it may present as an asymmetric macule, plaque, or nodule, with coloration ranging from brown to gray or black tones, and is generally asymptomatic in its early stages. This subtle clinical presentation contributes to delayed diagnosis, often established in advanced stages of the disease, unlike cutaneous melanoma, which is reflected in the low estimated five-year survival rate of approximately 15%[16].

In the present case, the lesion involved the mandibular gingiva associated with the floor of the mouth, a less frequently reported topography classified as a non-palatal site. Tumor location has been recognized as an important prognostic factor in oral mucosal melanoma, with several studies indicating that palatal lesions tend to present better survival outcomes than non-palatal sites. Consequently, involvement of the mandibular gingiva and floor of the mouth has been associated with less favorable prognostic outcomes[17].

Several prognostic factors have been associated with the survival of patients with oral mucosal melanoma. Among the main unfavorable determinants are increased tumor size and thickness, vascular invasion, lymph node metastasis, distant metastasis, and local recurrence[18].

In addition to disease extent, biological factors also play a relevant role in tumor progression. Loss of BAP1 expression has been associated with more aggressive tumor behavior and poorer prognosis, whereas the absence of tumor-infiltrating lymphocytes reflects an ineffective antitumor immune response, favoring neoplastic progression. Conversely, preserved expression of proteins involved in cell cycle control and apoptosis, such as BAP1, p53, p16, and BCL2, as well as the presence of tumor-infiltrating lymphocytes, have been associated with improved overall survival. Furthermore, demographic factors, such as younger age and, in some studies, female sex, have also been associated with a more favorable prognosis[19].

From a cytogenetic perspective, mucosal melanomas exhibit a high degree of genomic instability, with multiple complex chromosomal aberrations. The most frequently described alterations include chromosomal gains in 1q, 6p, 7, and 8q, as well as losses in 3p, 6q, 8p, and 9p21, the latter involving the tumor suppressor gene CDKN2A. In addition, gene amplifications are common, particularly involving KIT and CCND1, reinforcing the existence of a molecular profile distinct from that observed in cutaneous melanomas and supporting the hypothesis of specific oncogenic pathways in the pathogenesis of mucosal melanoma[20,21].

These cytogenetic alterations are directly reflected in the biological behavior of oral mucosal melanoma, which is strongly influenced by specific molecular events. In this context, KIT mutations have been reported in approximately 7.0% of cases, whereas BRAF mutations occur less frequently, in approximately 3.5%[22]. Such alterations are associated with the activation of critical intracellular signaling pathways, particularly the RAS–RAF–MEK–ERK (MAPK/ERK) cascade and the PI3K–AKT pathway. Activation of tyrosine kinase receptors, such as c-KIT, may trigger these pathways, promoting cellular proliferation and increased tumor survival even in the absence of classical NRAS and BRAF mutations[23].

Immunohistochemistry plays a fundamental role in the diagnosis of melanocytic lesions, assisting in the distinction between benign and malignant forms and guiding clinical management. Markers such as S-100, HMB-45, Melan-A (MART-1), MiTF, and SOX10 are widely used[24].

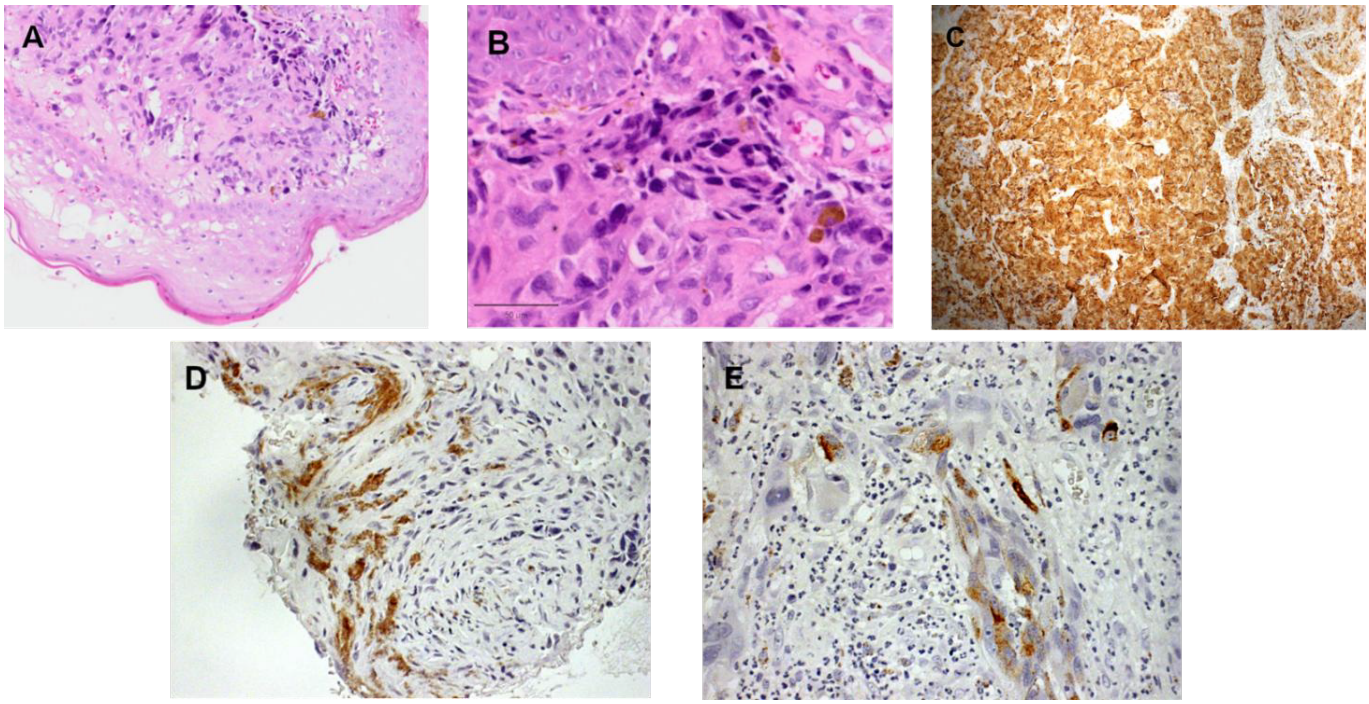

Figure 2. Histopathological examination of the incisional gingival biopsy. **(A and B)** Proliferative neoplastic cells arranged in sheets separated by connective tissue; atypical melanocytes are enlarged, exhibiting marked nuclear pleomorphism and hyperchromatism, with large cells containing dark brown pigment (melanin) observed near the epithelium (H&E, scale bars: A = 100 µm, B = 50 µm). **(C-E)** Immunohistochemical profile showing strong positivity for **(C)** S-100 protein (original magnification 100x), and positivity for **(D)** Melan-A (original magnification 400×) and **(E)** HMB-45 (original magnification 400×).

The main immunohistochemical markers used in the diagnosis of oral melanoma, their functions, and their sensitivity and specificity characteristics are summarized in Table 1.

Mucosal melanomas (MM) may exhibit wide clinical variability, including clinically non-pigmented presentations which frequently mimic benign lesions[25]. In the oral cavity, these lesions may present as whitish or pink exophytic masses with a smooth surface, resembling reactive hyperplasias, thereby contributing to diagnostic errors and treatment delays[26].

In the present case, although the gingiva and floor of the mouth exhibited extensive pigmented areas ranging from dark brown to black, these alterations were not initially recognized, possibly because they were interpreted as physiologic racial pigmentation. The patient's main complaint, however, was related to a whitish fibrous nodular lesion clinically suggestive of benign reactive hyperplasia.

Although the palate is described as the anatomical site most frequently affected by oral mucosal melanoma, few studies have reported the gingiva as the most commonly involved tumor site in patients with malignant oral melanoma, which may contribute to lower clinical suspicion when this topography is involved[27].

Histopathological examination of this area revealed oral mucosal melanoma, highlighting the clinical and morphological heterogeneity of this neoplasm. The coexistence of intensely pigmented areas with clinically non-pigmented nodular lesions reinforces the diagnostic complexity of mucosal melanomas with heterogeneous clinical presentation.

In addition to the rarity of oral mucosal melanoma, the present case exhibited unusual clinical features that increase its diagnostic relevance. The patient's main clinical complaint was a whitish nodular lesion with features suggestive of reactive fibrous hyperplasia, in contrast to the pigmented presentation classically associated with oral mucosal melanoma. This finding reinforces that oral mucosal melanoma may present heterogeneous clinical manifestations, including clinically non-pigmented components capable of masking the initial diagnosis[28].

Previous studies have demonstrated that clinically non-pigmented or partially pigmented melanomas frequently result in delayed diagnosis due to their clinical similarity to benign inflammatory or reactive lesions[29]. In the present report, although extensive pigmented areas involving the gingiva and floor of the mouth were observed, these alterations were not initially recognized clinically, possibly because they were interpreted as physiologic pigmentation. This aspect is consistent with reports demonstrating that oral mucosal melanomas may remain asymptomatic for long periods and only be identified in more advanced stages of the disease[30].

Another relevant aspect concerns the anatomical location of the lesion. Oral mucosal melanoma shows a predilection for the hard palate and maxillary gingiva, which are considered the sites most frequently affected by this neoplasm[31]. In the present case, however, the lesion predominantly involved the mandibular gingiva associated with the floor of the mouth, representing a less common presentation. This finding reinforces the

Table 1. Main immunohistochemical markers used in the diagnosis of oral melanoma, their functions, sensitivity/specificity, and relevant clinical.

Marker	Function / target	Sensitivity / specificity	Observations
S-100	Protein present in cells of the melanocytic lineage	Highly sensitive, low specificity	May react with neural and mesenchymal cells; used as an initial screening marker
HMB-45	Antigen related to melanocyte maturation	Relatively specific for melanocytic lesions	Useful to confirm melanocytic origin, especially in clinically non-pigmented lesions
Melan-A / MART-1	Melanocytic protein	Sensitive and relatively specific for melanocytic lesions	Frequently combined with S-100 and HMB-45 to increase diagnostic accuracy
SOX10	Nuclear transcription factor in melanocytes	Highly sensitive for melanocytic lesions	Excellent for clinically non-pigmented melanomas and small biopsy samples
c-KIT (CD117)	Tyrosine kinase receptor	Moderately sensitive	More common in mucosal melanomas; also indicates a potential therapeutic target
Ki-67	Cellular proliferation marker	Non-specific	Assesses tumor aggressiveness; does not indicate melanocytic origin
MITF	Melanocyte-specific transcription factor	Sensitive and relatively specific for melanocytic lesions	Useful in ambiguous or clinically non-pigmented cases

Source: adapted from Saleem et al.[14] and Sebastian et al.[24].

importance of careful investigation of oral pigmentations occurring at non-classical sites, especially when associated with nodular or ulcerative changes, considering the aggressive behavior and potential for delayed diagnosis of oral mucosal melanoma.

When compared with similar studies, the present case reinforces the diagnostic difficulty of oral mucosal melanoma in its early stages. Several authors have highlighted that the clinical variability of these lesions frequently leads to misdiagnostic hypotheses, including inflammatory hyperplasia, pyogenic granuloma, vascular lesions, and physiologic pigmentation. Therefore, the present report emphasizes the importance of early biopsy in atypical oral lesions, even when they exhibit a clinical appearance suggestive of benignity[32,33].

In this context, pedunculated gingival lesions should not be automatically interpreted as benign processes. In oral mucosal melanoma, clinically non-pigmented nodular presentations may simulate reactive hyperplasias, contributing to diagnostic errors and delayed treatment.

Treatment of mucosal melanoma is primarily based on radical surgical excision with adequate margins. Depending on tumor stage and resectability, adjuvant or systemic therapy may be indicated. Historically, dacarbazine has been widely used as a chemotherapeutic agent, although response rates are generally limited. Radiotherapy has traditionally been considered a palliative approach; however, some reports suggest that it may contribute to local disease control in oral mucosal melanoma. The management of clinically non-pigmented oral melanomas follows the same therapeutic principles as pigmented lesions[34,35].

This case demonstrates that oral mucosal melanoma may exhibit highly heterogeneous clinical behavior, including the coexistence of intensely pigmented areas and clinically non-pigmented nodular components with a benign appearance. This morphological variability represents an important diagnostic challenge and may delay disease recognition. Therefore, the correlation between detailed clinical examination, histopathological analysis, and immunohistochemical investigation is essential for accurate diagnosis and early treatment establishment, potentially contributing to improved prognosis in this recognized aggressive neoplasm.

CONCLUSION

Oral mucosal melanoma is a rare and biologically aggressive neoplasm whose diagnosis may be challenging due to heterogeneous clinical presentations. In the present case, the coexistence of a clinically non-pigmented nodular lesion with extensive adjacent pigmented areas that were initially undervalued highlights the potential for diagnostic confusion and the risk of delayed disease recognition. These findings reinforce the need for careful attention during clinical examination of the oral mucosa and underscore the importance of indicating biopsy whenever persistent alterations are observed.

AUTHORS' CONTRIBUTIONS

FSO: Conceptualization, Clinical investigation, Data curation, Writing – original draft, Writing – review and editing. PSP: Histopathological analysis, Methodology, Writing – review and editing. JSPD: Literature review, Data interpretation, Writing – review and editing. SCOM: Histopathological diagnosis, Investigation, Validation of pathological findings, Writing – review and editing. NNS: Methodological guidance, Critical revision of the manuscript. CAL: Study design, Supervision, Final approval of the manuscript.

CONFLICT OF INTEREST STATEMENT

Funding: No external funding was received for this study.
Competing interests: The authors declare no conflicts of interest.
Ethics approval: This case report was based on data obtained during routine clinical care and involved no experimental intervention. Written informed consent for publication of the clinical information and accompanying images was obtained from the patient.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

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