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Case Report

Maxillary mucormycosis and aspergillosis in post-COVID-19 patients in Mexico: A case series

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ABSTRACT

Background: Fungal infections, during or as a consequence of SARS-CoV-2 infection, associated with uncontrolled diabetes mellitus and indiscriminate use of corticosteroids have been reported. In the jaw, mostly mucormycosis has been diagnosed in hospitals.
Methods: A retrospective, cross-sectional, descriptive study of the clinical, imaging, and histopathologic characteristics of maxillary invasive fungal infection in post-COVID-19 patients diagnosed in a private non-hospital oral pathology service in Mexico during 2020–2022 was conducted.
Results: We found 20 cases of maxillary invasive fungal infections in post-COVID-19 patients, 75% including a diagnosis of mucormycosis and 25% diagnosed as probable aspergillosis. The most common signs and symptoms were exposed necrotic bone followed by tooth mobility, discharge, and pain. On imaging, unilateral maxillary sinus involvement was observed in 6 cases (30%), and bilateral maxillary sinus involvement was observed in 3 cases (15%).
Conclusions: It is essential to consider the association of osteonecrosis of the jaw in post-COVID-19 patients, with aspergillosis, not only mucormycosis, for early diagnosis and appropriate treatment.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome type 2 coronavirus (SARS-CoV-2) that shows an increased incidence of secondary fungal and/or bacterial infections during active disease or as a post-COVID-19 manifestation [1]. The association of uncontrolled diabetes mellitus, SARS-CoV-2 infection, indiscriminate use of corticosteroids, and invasive fungal infections, has been suggested [2]. Mucormycosis, aspergillosis, and candidiasis are the three most common opportunistic infections observed [1–3]

Mucormycosis is an acute, angioinvasive, rapidly progressive disease caused by an opportunistic fungal infection of the class Zygomycetes (order Mucorales), usually, Mucor or Rhizopus, whose main risk factors are type 2 diabetes mellitus, immunosuppression, as well as the administration of drug combinations including corticosteroids, monoclonal antibodies, high-dose broad-spectrum antibiotics; in addition to microbial growth and xerostomia. The most common clinical presentation is rhinocerebral, although pulmonary, gastrointestinal, cutaneous, and disseminated manifestations are known. Diagnosis of mucormycosis includes imaging and histopathologic studies, surgical management, and various drugs used in its treatment [1,4,5].

In the oral cavity, mucormycosis usually presents as a necrotic palate ulcer with blackish exfoliation and bony exposure, tenderness or paresthesia in the maxillary sinus area, and tooth loss [1]. Other manifestations include facial pain, fistula with purulent discharge from the alveoli, nasal discharge, periorbital swelling, and headache [4].

Suresh et al., proposed the term "COVID-19-associated fungal osteomyelitis of the jaws and sinuses" for cases occurring in patients who have recovered from COVID-19 [6].

The studies reported in the literature were conducted in hospital centers, but no investigation was conducted in a non-hospital center or histopathology service. Therefore, this study aimed to describe the

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Table 1
Characteristics of cases of maxillary invasive fungal infections in post-COVID-19 patients.

Year	2020			2021												2022				
Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Sex	F	F	M	M	M	M	F	M	M	M	M	F	F	M	F	M	F	M	M	F
Age	67	82	38	64	66	53	66	37	48	36	58	71	62	47	83	76	59	74	54	54
Signs and symptoms			n/m		n/m	n/m	n/m	n/m					n/m	n/m		n/m				
Pain	+			+						+	+				+		+			
Parestesia	+	+																		
Exposed necrotic bone	+	+		+		+									+			+		+
Discharge				+					+	+							+	+	+	
Tooth mobility				+					+			+					+		+	+
Halitosis																	+			
Oral-nasal communication																	+			
Lesion location by imaging			n/m				n/m	n/m			n/m	n/m	n/m	n/m				n/m		n/m
Maxillary sinus	R	L		R	B	L			R	B					R		L		B	
Ethmoidal sinus	R								R	B						L				
Frontal sinus	R									R										
Nasal cavity	R	L														L				
Orbital region		L																		
Floating teeth					+															
Time since diagnosis of COVID-19 (months)	n/m	n/m	6	2	n/m	n/m	1	n/m	n/m	1.5	12	n/m	n/m	4	n/m	n/m	5	n/m	n/m	n/m
Personal medical history					n/m	n/m	n/m	n/m	n/m					n/m			n/m	n/m	n/m	
T2DM	+	+	+	+						+		+	+							+
SAH	+	+		+						+		+	+							
Others											Maxillary sinusitis		Acute cerebrovascular accident, pneumonia, perforated corneal ulcer		Breast carcinoma	Squamous cell carcinoma in the left maxilla				Hypothyroidism
Clinical diagnosis					n/m			n/m			n/m									n/m
Osteonecrosis of the jaw	+	+				+			+			+		+	+			+		
Mucormycosis		+		+			+		+	+		+	+	+	+	+	+		+	
Aspergillosis		+													+		+			
Maxillary abscess			+																	
Osteoradionecrosis																+				
Osteomielitis																	+			
Biopsy site																				
Maxilla	R	L	B	R	B	L	L	+	R	B	+	+	+	+	R	B	L	L	B	+
Nasal cavity							L													
Orbital region							L													
Type of biopsy																				
Incisional	+	+	+	+	+	+		+		+		+			+		+	+	+	+
Maxillary resection							+		+		+		+	+		+				
Histopathological diagnosis																				
Probable mucormycosis	+	+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Probable aspergillosis			+					+				+			+	+				

+, present; B, bilateral; F, female; L, left side; M, male; n/m, not mentioned; R, right side; SAH, systemic arterial hypertension; T2DM, type 2 diabetes mellitus.

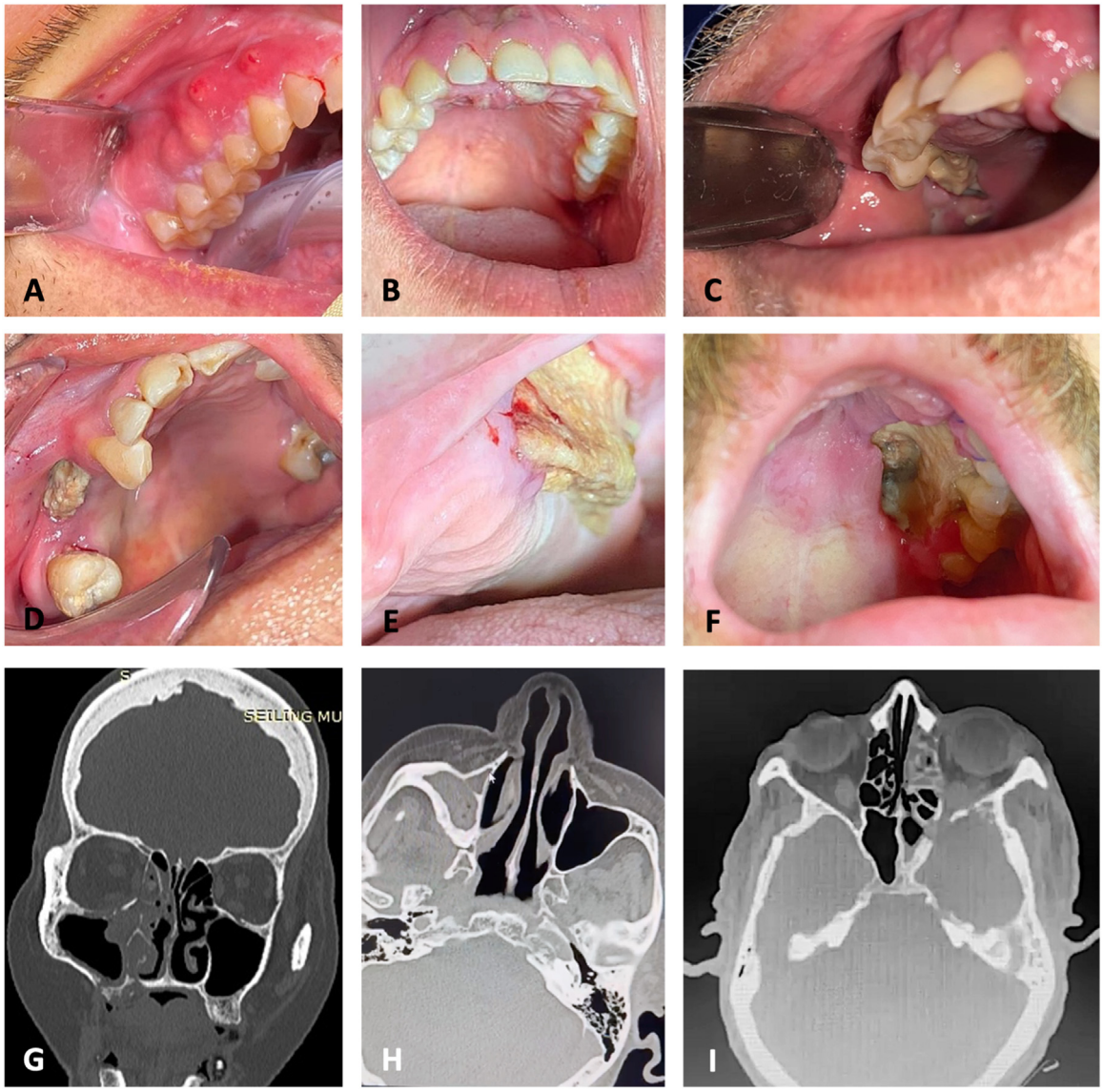

Fig. 1. Clinical features. [A, B] Gingival fistulas (cases 9 and 10). [C to F] Exposed necrotic bone (cases 4, 1, 2, and 6). Imaging features. [G to I] Involvement of paranasal sinuses such as maxillary, ethmoidal, and frontal sinuses (cases 1, 15, and 16).

clinical, imaging, and histopathologic characteristics of invasive fungal infections of the jaws in post-COVID-19 patients diagnosed in a private non-hospital oral pathology service in Mexico.

2. Materials and methods

This is a retrospective, descriptive, cross-sectional study that included all cases of invasive fungal infections of the jaws in patients with a previous diagnosis of COVID-19 reported in a private oral pathology service in Mexico from January 2020 to December 2022.

Data were collected on the patient sex and age, clinical and imaging features, symptomatology, and personal health history. All histologic sections of the cases were analyzed by hematoxylin-eosin (H&E) staining. In addition, histomorphology was evaluated by histochemical techniques such as periodic acid-Schiff (PAS) staining and Grocott-Gomori methenamine silver (GMS) staining. Modified European Organization for Research and Treatment of Cancer Mycosis Study Group (EORTC/MSG) criteria were used to diagnose mycosis [7]. Probable mucormycosis was defined as histologic evidence of tissue invasion that included non-septate, right-angled branching filamentous fungi. Probable aspergillosis was defined as histologic evidence of tissue invasion, including septate, acute-branched filamentous fungi.

3. Ethical approval

The subjects were informed about the investigation and signed informed consent forms agreeing to participate in the study. The study was approved by the Ethics Committee of the Women's Hospital, Secretariat of Health (No. 202,306–18). It was conducted following the ethical principles of the World Medical Association Declaration of Helsinki.

4. Results

Twenty cases of invasive fungal infections of the jaws were diagnosed in post-COVID-19 patients. Table 1 summarizes these cases' clinical, imaging, and histopathologic characteristics. Three of the 20 cases were diagnosed in 2020, twelve in 2021, and five in 2022. The mean age of the patients was 59.7 ± 14.0 years, with an age range of 36 to 83 years; the male sex was more common, with a ratio of 1.5:1.

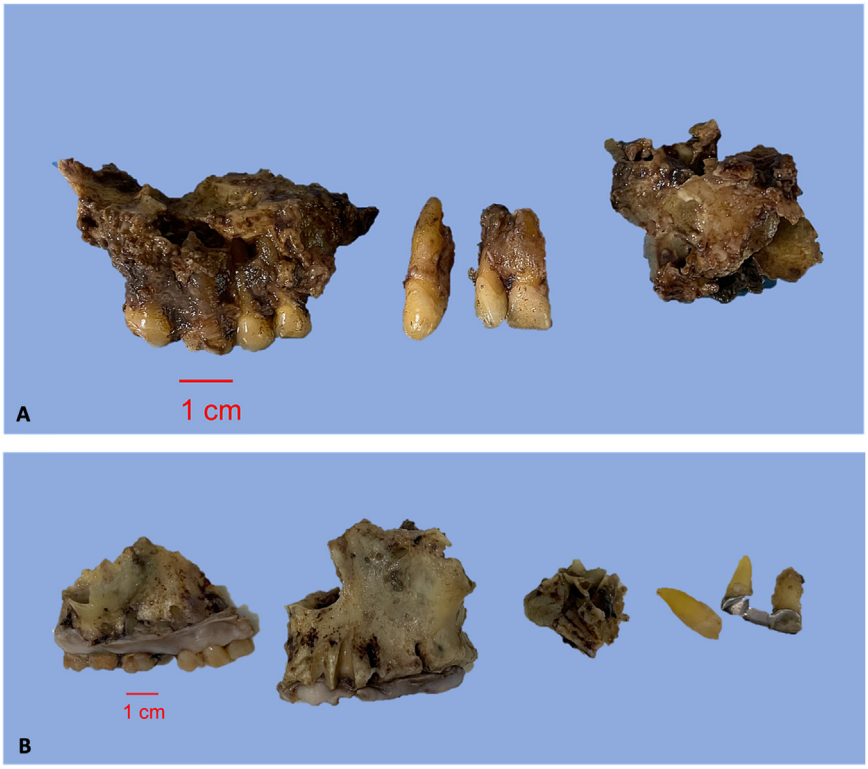

Fig. 2. Macroscopic features. [A, B] Necrotic maxillary bone and teeth with loss of periodontal support (cases 9 and 13).

All cases involved the maxilla. Among the imaging features, bilateral paranasal sinus involvement was observed in four patients (20%), three corresponding to maxillary sinus; unilateral maxillary sinus involvement was observed in 6 cases (30%). The most commonly reported signs and symptoms were: exposed necrotic bone (n = 7, 35%), pain (n = 6 cases, 30%), tooth mobility (n = 6 cases, 30%), discharge (n = 6 cases, 30%), and paresthesia (n = 2 cases, 10%) (Fig. 1).

All cases had a history of COVID-19 from 1 month to 12 months prior. However, in 13 cases, the time between the diagnosis of COVID-19 and the onset of oral/maxillary manifestations could not be determined. Eight cases (40%) had a history of type 2 diabetes mellitus, 6 cases (30%) had systemic arterial hypertension, 2 cases (10%) had a history of cancer (1 case with squamous cell carcinoma in the left maxilla and 1 case with breast carcinoma without specifying the type), 1 case (5%) had maxillary sinusitis, and 1 case (5%) had hypothyroidism. In addition, twelve cases (60%) were referred to the oral pathology service with a previous presumptive clinical diagnosis of invasive fungal infection.

The oral pathology service received incisional biopsy specimens from 14 cases (70%) and maxillary resection specimens from 6 cases (30%) (Fig. 2). Of the 20 cases, 15 (75%) received a histopathologic diagnosis of probable mucormycosis, with histologic evidence of tissue invasion that included non-septate, right-angled, filamentous fungi arranged on a necrotic background. Three cases (15%) included a differential diagnosis of probable mucormycosis versus probable aspergillosis because they also had fine septate hyphae branching at acute angles. Finally, 2 cases (10%) were diagnosed as probable aspergillosis, with histologic evidence of tissue invasion that included abundant acute-branching septate hyphae (Figs. 3 and 4).

Regarding patient follow-up, the clinicians who sent the specimen for histopathologic examination reported continuing their treatment in a hospital setting.

5. Discussion

Cases of maxillary invasive fungal infections in post-COVID-19 patients usually present with exposed necrotic bone, tooth mobility, pain, and discharge of purulent material. In addition, palatal ulceration, foul odor, and nonpurulent gingival inflammation as the initial suspicious signs leading to the diagnosis of mucormycosis have been reported in other studies [8–12].

The clinical presentation of invasive fungal infections may suggest the diagnosis of a malignant neoplasm due to its aggressive course, which can rapidly involve and invade adjacent oral structures [13]. In our study, involvement of the left or right maxillary sinus or both was the most common presentation by imaging, and involvement of the other paranasal sinuses was less often observed. Similarly, Gupta et al. reported that maxillary sinuses were involved in 94% of cases of rhino-orbit-cerebral mucormycosis, being the most common site, followed by the ethmoidal, frontal, and sphenoidal sinuses [4]. Mucormycosis diagnosis 1 to 2 months after testing positive for COVID-19 has been reported [4]. Unfortunately, in 65% of our cases, the time elapsed since COVID-19 diagnosis and initial manifestations of the invasive fungal infection were not mentioned.

Regarding personal medical history, type 2 diabetes mellitus was present in 8 cases (40%). Suresh et al. found that hyperglycemia was the main predisposing factor for fungal osteomyelitis of the jaws and sinuses associated with COVID-19 [6]. In the case series of Nehara et al., all patients had a history of diabetes mellitus and were treated with intravenous steroids for COVID-19 infection [14]. In this sense, the increased likelihood of fungal co-infections in COVID-19 patients with pre-existing conditions and the need for reasonable, evidence-based use of immunomodulatory medications in these patients have been emphasized [14–17].

In the present study, 12 males (60%) and eight females (40%) had invasive fungal infections associated with COVID-19; all cases were located in the maxilla. Similarly, Kamat et al. observed that COVID-19-associated mucormycosis affected more males (73.9%) than females (26.1%) [3]. Cases of mandibular fungal osteomyelitis in post-COVID-19 patients have been described [18,19]. However, whether this was an invasive fungal infection or the fungus was only superficially localized without invading the deep bony trabeculae or soft tissue blood vessels was not specified.

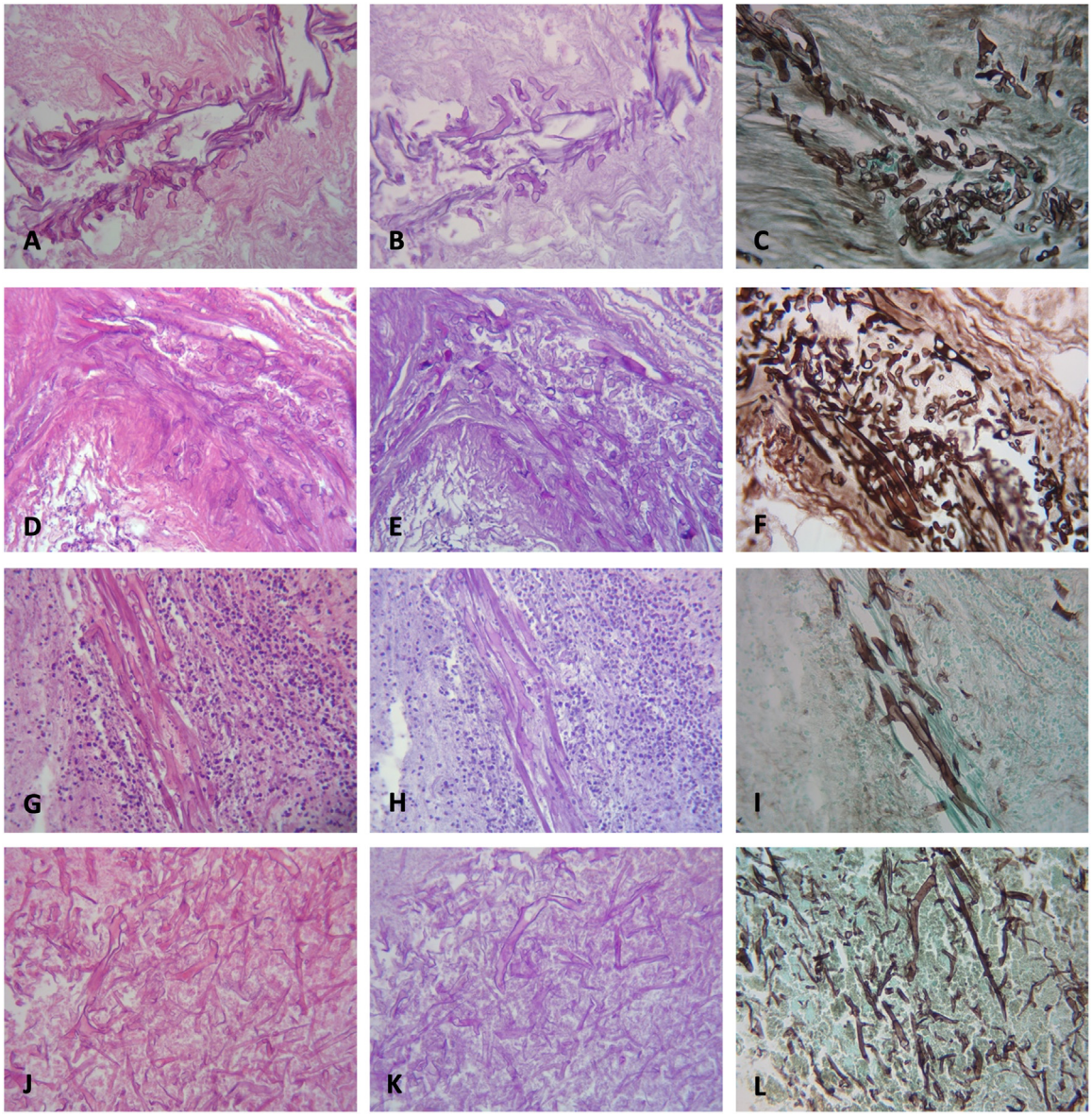

Fig. 3. Microscopic features of cases with probable mucormycosis. Tissue invasion with the presence of non-septate, right-angled filamentous fungi. Case 13 [A] H&E, [B] PAS, [C] GMS, ×400. Case 7 [D] H&E, [E] PAS, [F] GMS, ×400. Case 9 [G, J] H&E, [H, K] PAS, [I, L] GMS, 400X.

Histopathologic evaluation is the gold standard for diagnosing these diseases [5,6,20].

In addition, the presence of a fungus should be confirmed by other complementary methods (culture, molecular, or *in situ* identification techniques). In the present study, the diagnosis of probable mucormycosis was the most common, although probable aspergillosis should be considered a frequent differential diagnosis. Moreover, in cases of invasive fungal infections of the jaws in COVID-19 patients, dual fungal infections (aspergillosis and mucormycosis) and mixed infections (mucormycosis, actinomycosis, and candidiasis) have been identified [1,21].

To our knowledge, this is the first study to describe the clinical, imaging, and histopathologic features of cases of invasive fungal infections of the jaws in post-COVID-19 patients from a private, non-hospital oral pathology service in Mexico. This highlights the vital role of dental/maxillofacial health professionals in identifying the initial manifestations of these conditions.

6. Conclusion

It is essential to consider the association of osteonecrosis of the jaw in post-COVID-19 patients, with invasive fungal infections such as aspergillosis, not only mucormycosis, for early diagnosis and appropriate treatment.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval statement

Patient consent statement: The study conforms to the tenets of the Declaration of Helsinki. The manuscript is based on the biopsy specimen obtained from a private oral pathology service with no physical, psychological, or financial commitment to the patient.

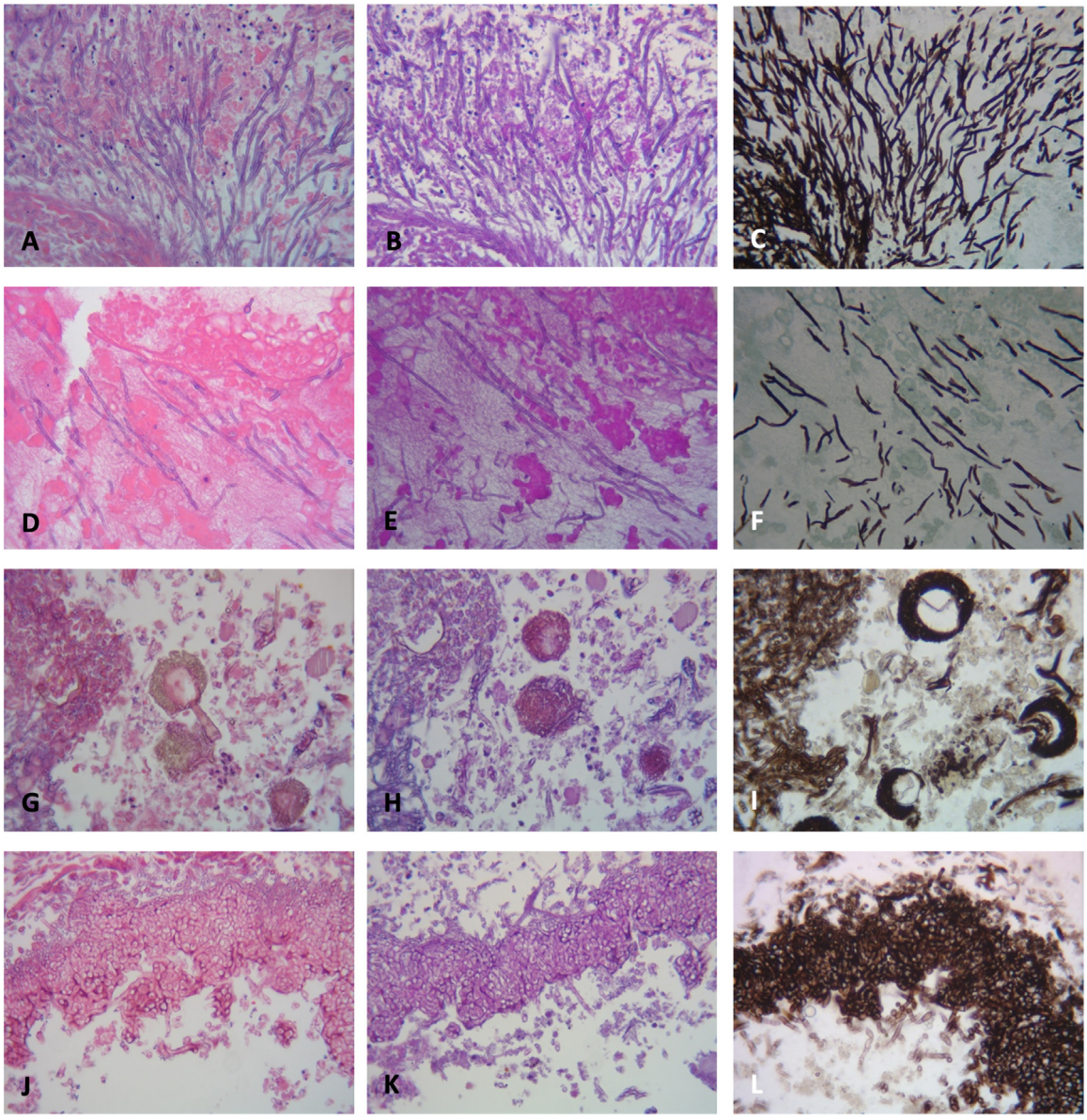

Fig. 4. Microscopic features of cases with probable aspergillosis. Tissue invasion with septate and acutely branching filamentous fungi. Case 8 [A, D] H&E, [B, E] PAS, [C, F] GMS, ×400. Case 3 [G, J] H&E, [H, K] PAS, [I, L] GMS, ×400.

Appropriate informed consent was obtained from the patients to include intraoral photography and/or imaging studies, and the patients were aware that their identities would remain anonymous. The study was approved by the Ethics Committee of the Women's Hospital, Secretariat of Health (No. 202,306–18)

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Cynthia M. Urias-Barreras: Conceptualization, Supervision, Writing – original draft, Writing – review & editing, Investigation, Supervision. **Alberto Rodríguez-Archilla:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Adrian Canizalez-Roman:** Data curation, Methodology. **Daniela A. Bastidas:** Writing – original draft. **Nidia M. León-Sicairos:** Writing – original draft, Supervision, Visualization, Writing – review & editing.

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