Atypical ulceration of the hard palate

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CLINICAL PRESENTATION

A 20-year-old female presented to the Department of Oral and Maxillofacial Surgery at the Pretoria Oral and Dental Hospital complaining of foul smelling oral odour with painful and bleeding gums for a duration of two weeks. The patient reported no previous history of systemic diseases, trauma or prior management.

Upon intraoral examination, a large, necrotic and foul smelling lesion involving most of the anterior hard palate was observed. The lesion in the palate extended from the right permanent canine involving the premaxilla, crossed the midline in the mid-palatal region and extended to involve the entire left half of the hard palate up to the posterior border (Figure 1). The alveolar bone and gingiva of the dentition in the described area were also severely involved, leading to gross teeth mobility and a loss of periodontal support. The underlying bone was completely denuded with exposure of the nasopalatine foramina and the foramen of the greater palatine neurovascular bundle. The surrounding non-necrotic palatal mucosa was erythematous with markedly undercut borders leading to the denuded bone and necrotic centre.

Radiological evaluation of the Conebeam Computer Tomography (CBCT) revealed bony erosion of the cortex on the palatal aspect of the hard palate at the level of the incisive foramen and the alveolar bone on the left (Figure 2).

DIFFERENTIAL DIAGNOSES

The differential diagnoses for a destructive mid-palatal lesion included a variety of infective lesions as well as neoplasms. A deep fungal infection was considered to be the most likely, with Mucormycoses, Aspergillus, Cryptococcus and Histoplasma as the possible causative species. Human Herpesvirus 8 (HHV8), Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were also considered as possible viral aetiological agents.

Deep fungal infections, when suspected, can be highlighted by special histochemical stains such as Periodic acid-Schiff (PAS) stain and Grocott-Gomori's methenamine silver stain. Depending on the growth characteristics, fungi can appear as multicellular filaments, individual cells or yeasts. Yeasts appear round-to-oval due to their cell walls and mainly reproduce by budding. An important feature of some fungi is their ability to grow as a yeast in human tissue but as hyphae under laboratory conditions, termed dimorphism. In some cases definitive identification of fungal species requires tissue culture.

Mucormycosis is an opportunistic infection caused by bread mold fungi. Disease occurs following inhalation of spores, usually in immunocompromised patients or poorly controlled diabetics. The infection is initially localized in the paranasal sinuses, but often spreads to the brain, giving rise to rhinocerebral mucormycosis, with a high mortality rate. Most reported cases of oral mucormycosis have been described in patients with leukemia or diabetes, with primary localization involving the palate or a secondary localization following pulmonary infection.[1] The organism causes local tissue necrosis, characteristically invades arterial walls, and penetrates the periorbital tissues and cranial vault. Mucormycetes form non-septate hyphae with a width ranging from 6 to 50 μm and demonstrate frequent right angle branching, distinct from *Aspergillus* hyphae.

Aspergillus is a ubiquitous mold that causes allergic bronchopulmonary aspergillosis in healthy individuals and serious sinusitis, pneumonia, and invasive disease in immunocompromised individuals. Oral aspergillosis is rare and usually affects hosts at particular risk or with underlying immunosuppression.[1] *Aspergillus* forms so-called fruiting bodies consisting of septate filaments, 5 to 10 μm thick, branching at an acute angle of 40 degrees.

Cryptococcosis is a chronic fungal disease that primarily involves the lungs, although the central nervous system, skin and oral mucosa may occasionally be affected. The disease

occurs worldwide, with the causative agent, *C. neoformans*, found in bird droppings. The organism is best appreciated on mucicarmine histochemical staining, which highlights numerous budding, yeast-like organisms with prominent thick capsules. This morphology and staining characteristics are virtually pathognomonic for *Cryptococcus* species.[2]

Histoplasmosis causes chronic disseminated forms or acute forms with a fatal outcome, especially in newborns or in immunocompromised patients. The fungus, *H. capsulatum*, is an intracellular pathogen that is found mainly in phagocytes. In rare cases the fungus can spread from the lungs to involve the skin and oral cavity. Histopathology usually shows pseudoepitheliomatous hyperplasia, with an underlying granulomatous chronic inflammatory process.[1] The organism appears as thin-walled yeast forms, 3 to 5 μm in size.

KS is a vascular neoplasm of intermediate-grade caused by HHV8 infection, which is strongly associated with HIV/AIDS. It progresses through three clinical phases, namely patch, plaque and nodular phases. Histologically, this tumour demonstrates sheets of plump, proliferating spindle cells that form vascular-like slit spaces often containing extravasated red blood cells.[3] Immunohistochemical staining for HHV8 is diagnostic, as well as other endothelial markers. Kaposi's sarcoma, occurring as a solitary hard palate lesion without evidence of cutaneous involvement, is a rare occurance.[4]

CMV infection may produce a variety of disease manifestations, which depend on the host's age and immune status.[5] Infected cells are enlarged, often with a diameter of 40 μm with both cellular and nuclear pleomorphism. Prominent intranuclear basophilic inclusions are noted surrounded by a clear halo. Disseminated CMV causes focal necrosis with minimal inflammation in virtually any organ. A diagnosis of CMV infection may be made by demonstration of characteristic morphological alterations in tissue sections, detection of CMV antigens, viral culture or PCR-based detection of CMV DNA.

A possibility of an extranodal NK T-cell lymphoma, nasal type (ENKL) was also considered due to its aggressive and destructive growth in the mid-facial area.[6] The oral cavity is usually secondarily involved following palate midline destruction. This neoplasm is often seen in immunosuppressed patients and has a strong relationship with EBV. Histologically, this neoplasm appears hypercellular and consists of large, immunoblast-like cells with adjacent small lymphocytes. A striking feature of this neoplasm is its prominent angiocentric distribution with associated angiodestruction, mimicking a vasculitis.[7] The diagnosis of NK/T-cell lymphomas can be challenging, particularly in cases of unusual clinical presentation.[6]

EBV-positive mucocutaneous ulceration (EBV MCU) represents a rare form of lymphoproliferative disorder that arises in the setting of immunosuppression. Previously published cases of EBV MCU involving the oral mucosa occurred in patients receiving immune-suppressive medication and in the elderly with age-related immune senescence. EBV MCU presents with localized, solitary areas of mucosal ulceration commonly affecting the oropharynx.[8] Histologically, this lesion is characterised by areas of ulceration with an associated polymorphous inflammatory infiltrate. In many instances the infiltrate contains a predominance of eosinophils and plasma cells. Characteristically, scattered large pleomorphic immunoblasts reminiscent of Reed-Sternberg cells are usually present in variable numbers.[9] Epstein-Barr encoding region (EBER) in situ hybridization is the methodology of choice for the detection of the EBV encoded mRNA in tissue sections.

Other less likely clinical differential diagnoses included an aggressive salivary gland malignancy, nasopharyngeal and oral carcinomas, necrotizing sialoadenitis, cancrum oris and a secondarily infected nasopalatine cyst.

DIAGNOSIS AND MANAGEMENT

An incisional biopsy of the palatal mucosa was performed and submitted for histological examination. An additional soft tissue fragment was submitted for microscopy, culture and sensitivity (MC&S). Following the incisional biopsy, a total debridement of the necrotic tissue was performed to stimulate bleeding and initialise the healing response. The site was thoroughly rinsed with 0.2% Chlorhexidine Gluconate and a Saline solution. The denuded bone was covered with a generous layer of Bismuth Iodine Paraffin paste infused lint gauze (BIPP gauze) and secured with Polyglactin 910, size 4/0, creating a net-like configuration and securing the BIPP to the palate. This was done to stimulate granulation tissue formation and to prevent re-infection of the curetted denuded bone. Oral antibiotics were prescribed, Augmentin 625mg three times daily for ten days and Metronidazole 400mg three times daily for five days as empirical therapy, with analgesics to manage pain.

Due to the clinical presentation and the age of the patient, a possibility of a compromised immune system was suspected. Haematological studies which included a full blood count (FBC), urea and electrolytes as well as a HIV-rapid test and a Treponema Pallidum hemagglutination assay (TPHA) were performed. The HIV-rapid and confirmatory serology ELISA results were positive and the patient was subsequently diagnosed with HIV infection.

Histological examination of the incisional biopsy specimen showed a soft tissue fragment surfaced partially by an ulcerated, parakeratinizing stratified squamous epithelium with elongated rete ridges. The adjacent epithelium showed areas of inflammatory cell exocytosis with numerous neutrophils present superficially. The ulcer bed was comprised of granulation tissue with an extensive mixed acute-on-chronic inflammatory cell infiltrate (Figure 3A). The lamina propria consisted of fibrous connective tissue with numerous areas of necrotic tissue with a dense, mixed inflammatory cell infiltrate consisting predominantly

of neutrophils and histiocytes (Figure 3B). There were several blood vessels present with associated fibrin thrombi, related to areas of infarction (Figure 3C).

PAS and Grocott-Gomori's methenamine silver histochemical stains were performed, both of which failed to highlight fungal microorganisms. Similarly the CMV immunohistochemical stain was negative for viral inclusions. A Warthin-Starry special stain was then performed, highlighting the presence of numerous coiled spirochetes within the epithelium, as well as within the lamina propria and fibrin thrombi in the blood vessels (Figure 3D). The diagnosis of syphilis was made.

Upon availability of results, the patient was subsequently referred to the local clinic of infectious diseases for further HIV-counselling, the initiation of highly active antiretroviral therapy (HAART) and the administration of 2.4 million units benzathine penicillin (IM).[10] The BIPP dressing was removed and granulation tissue formation and epithelialisation was seen at the previously necrotic site (Figure 4).

DISCUSSION

Syphilis is a systemic infection caused by the anaerobic spirochete *Treponema pallidum*. It is acquired predominately via sexual transmission but may be vertically transmitted, resulting in congenital disease.[11] This microorganism has positive tropism for several human organs and tissues, with complex clinical implications.[12] The advent of antibiotic usage and the implementation of prevention campaigns have resulted in a rapid decline in the prevalence and incidence of the disease.[13] However, in the last decade, there has been a notable resurgence of the disease. The recent increased incidence has been attributed to the general lack of public education regarding sexually transmitted infections (STIs), the concept that STIs are curable, the belief that oral sex is a safe practice, and a culture that endorses multiple sexual partners.[11]

Concurrent syphilis and HIV co-infection is also on the increase. An underlying immune dysfunction in HIV-positive patients may predispose patients to syphilis co-infection.[13] Syphilis facilitates the transmission of HIV through the disruption of the natural barriers by the primary genital ulcerative lesions or chancres. This facilitates bidirectional spread through biological contact, the upregulation of target cells for HIV through the influx of CD4 T-lymphocytes seen in syphilitic lesions, and the induced overexpression of CCR5 on macrophages due to the stimulation CD14 monocytes by treponemal lipoproteins.[14] Both syphilis and HIV affect the same biological parameters. Syphilis showed a decrease in the CD4 count and an increase of the HIV viral load in co-infected patients.[15,16]

Syphilis is subdivided in stages based on the activity and infectivity of the lesions as primary, secondary, latent (early and late) and tertiary syphilis.[11] Oral involvement may present in any of the stages, but is frequently a feature of the secondary stage.[13] All areas of the oral cavity can be affected.

Primary syphilis is generally localised to the site of infection where contact with an active lesion occurs. Thus, the genital area is most frequently involved with oral involvement representing the most common extragenital site.[11] The initial presentation consists of a painless papule that develops at the site of inoculation following an incubation period of two to three weeks. The papule becomes indurated and ulcerated resulting in a classical syphilitic chancre. Intra-oral chancres on the tongue and lips are well documented when oral sex is implicated in disease transmission.[11] Regional lymphadenopathy is an additional useful diagnostic tool in the case of primary syphilis infection. Chancres generally resolve spontaneously within weeks and in many instances may go unnoticed by patients.[13]

Secondary syphilis results from lymphovascular spread of the spirochetes from the primary site of involvement. This stage presents with the greatest diagnostic challenge due its diverse clinical presentation. The diagnosis of secondary syphilis requires a high index of

clinical suspicion as the primary stage may have gone undiagnosed.[17] Clinical symptoms are usually non-specific with patients complaining of headaches, low-grade fever, myalgia, generalised lymphadenopathy and pharyngitis. A mucocutaneous maculopapular rash located predominantly on the trunk and extremities often with both palmar and plantar involvement is a consistent feature.[11]

Several clinical manifestations of secondary syphilis infection involving the oral mucosa have been described. The most common are "mucous patches" which may be further divided into-two subtypes: slightly elevated-type plaques which are occasionally ulcerated and covered with a gray or white pseudomembrane; or multiple mucous patches that may coalesce to give rise to serpiginous lesions, described as snail track ulcers. White plaques with verrucous aspect, so-called "leukoplakia like" are also described as another frequent form of disease.[18] Lesions can however be clinically and histopathologically unspecific, and may mimic other entities.[13] The current case highlights this fact that some cases can manifest atypically, and the diagnosis may hence be delayed or even missed.

If left untreated, one third of patients will progress to the tertiary stage of syphilis. Tertiary syphilis is associated with the greatest morbidity and mortality due to neurological and cardiovascular complications. The characteristic syphilitic lesion during this stage is the non-infective gumma, which refers to an area of necrotising granulomatous inflammation of which the occurrence in the oral cavity is well documented. Gummatous foci involving the hard palate and tongue are typical. The palatal lesions often result in destruction of bone resulting in an oro-antral communication. Tongue lesions tend to heal with pronounced scarring and muscular contracture.[11,19]

HIV patients with syphilis co-infection have been studied in past decades. The infection can present with the typical oral lesions or as painless mucous patches. However, HIV co-infection may dramatically alter the clinical appearance and is associated with a more

aggressive disease course. Moreover, some cases present difficulty in delineating the differential diagnosis.[12,19]

Histologically, syphilis often shows an intense subepithelial plasma cell infiltration that should be differentiated from idiopathic plasmacytosis, IgG4-related sclerosing disease, contact stomatitis, candidiasis, inflammatory pseudotumor, and plasmacytoma. Primary and secondary syphilis is characterized by a plasma cell infiltration that extends deeply beyond the lamina propria, surrounding capillaries and nerve bundles. The plasma cells may be arranged with lymphocytes and macrophages in a band-like pattern within the superficial lamina propria resembling that of a lichenoid reaction. Pseudoepitheliomatous hyperplasia and granulomatous inflammation with a central zone of acellular necrosis, accompanied by histiocytes and multinucleated giant cells is characteristic of tertiary oral syphilis. Obliterating endarteritis may be seen in all stages of the disease.[20]

Histochemical staining with a Warthin-Starry stain can be done to identify spirochetes within the specimen; however in some instances the presence of bacterial colonies in oral mucosal biopsies impairs the interpretation of the results. Immunohistochemical stains specific for *T. pallidum* are available and should be utilised to assist the pathologist in making a diagnosis.[19,20] Recent studies show that immunohistochemistry has a higher sensitivity (71%) than Warthin-Starry staining (41%) for the assessment of secondary syphilis lesions.[20]

Syphilis may also be diagnosed with serology tests, which include the non-treponemal and treponemal assays. The non-treponemal tests are cost effective and are useful for screening patients and monitoring patients' response to treatment, by detecting antibodies that are not specifically directed against the *Treponema pallidum* bacterium. Treponemal assay tests which are available include the Venereal Disease Research Laboratory (VDRL) test and the Rapid Plasma Reagin (RPR) test, which are reported as a titre reflecting both IgM and IgG antibodies. This test may be utilized following treatment to demonstrate treatment

response.[19,20] Treponemal tests are however more specific and are of a more qualitative nature. Several treponemal serologic tests are available for confirmation, including the FTA-ABS as well as T. pallidum particle agglutination (TP-PA) tests and enzyme immunoassay (EIA). Once a patient tests positive for the treponemal test, it remains positive for the duration of the patient's lifetime. Patients diagnosed with syphilis with concomitant HIV-coinfection should be treated in accordance to the recommendations of the Centre of Disease Control (CDC), which is the same regime as for HIV infected patients.

The preferred treatment for syphilis remains benzathine penicillin G (2.4 million Units IM); however, treatment is greatly dependent on the stage of the disease.[21]

CONCLUSIONS

Syphilis and HIV-coinfection is on the rise and may complicate and delay early and accurate diagnosis. Hence, HIV serology is recommended following a positive diagnosis of syphilis. Clinicians should consider secondary syphilis in the differential diagnosis of white and ulcerative oral lesions, irrespective of site, and especially in a background of HIV-infection. A detailed medical history and clinical examination are of great importance in ascertaining the correct diagnosis.

Serological tests are the mainstay in the diagnosis of syphilis. It must be emphasised that suspicion needs to be maintained by both clinicians and pathologists, as the clinical and histologic findings may be subtle and mistaken for other more common diagnoses.

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LEGENDS

Fig. 1. Initial presentation of lesion at consultation.

Fig. 2. CBCT: Coronal bony window at the level of the premolars. Bony erosion and the loss of the cortex on the palatal aspect of the alveolar ridge are visible on the left.

Fig. 3. (A) A low-power haematoxylin and eosin-stained section showing the incisional biopsy specimen with an ulcerated surface epithelium (original magnification x100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05515*. (B) Haematoxylin and eosin-stained section demonstrating fibrous connective tissue with numerous areas of necrotic tissue with a dense, mixed inflammatory cell infiltrate (original magnification x200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05515.* (C) Haematoxylin and eosin-stained section demonstrating a blood vessel with associated fibrin thrombi and surrounding necrosis (original magnification x200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05515.* (D) A Warthin-Starry special stain showing the presence of numerous coiled spirochetes, some invading a bloodvessel (original magnification x400). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05516.*

Fig. 4. Presentation at two-week follow-up.

Figure 1

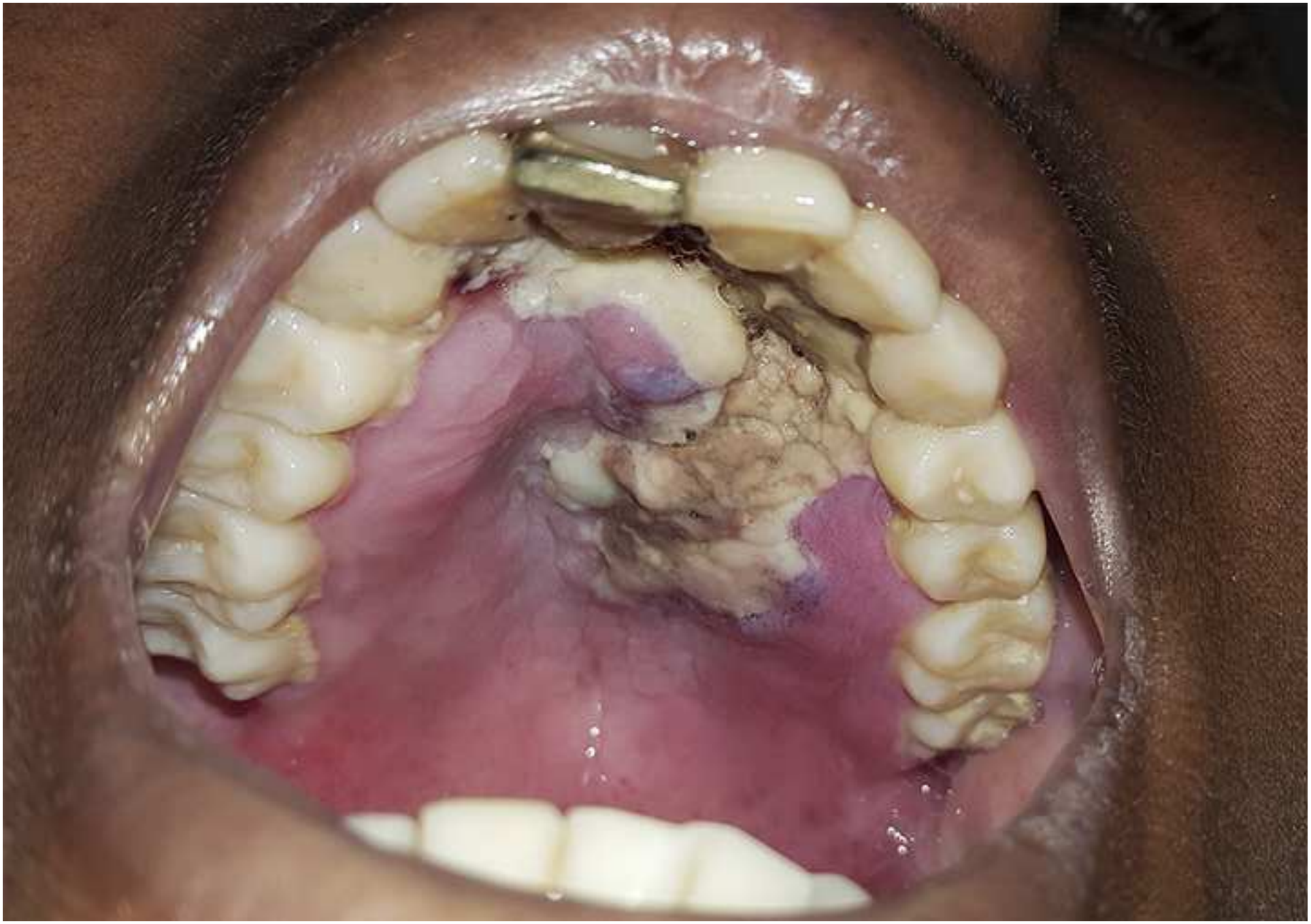

Figure 2

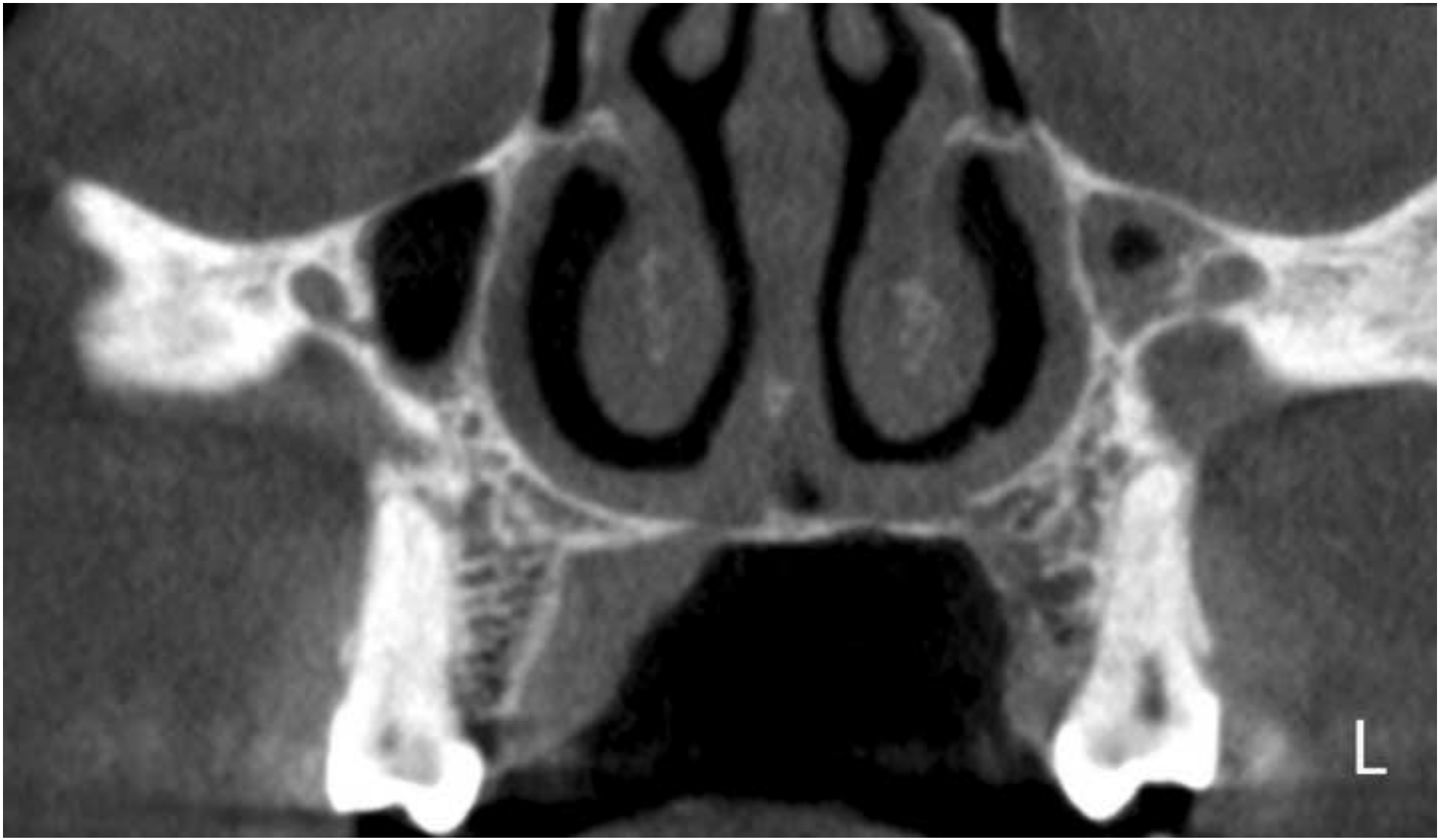

Figure 3

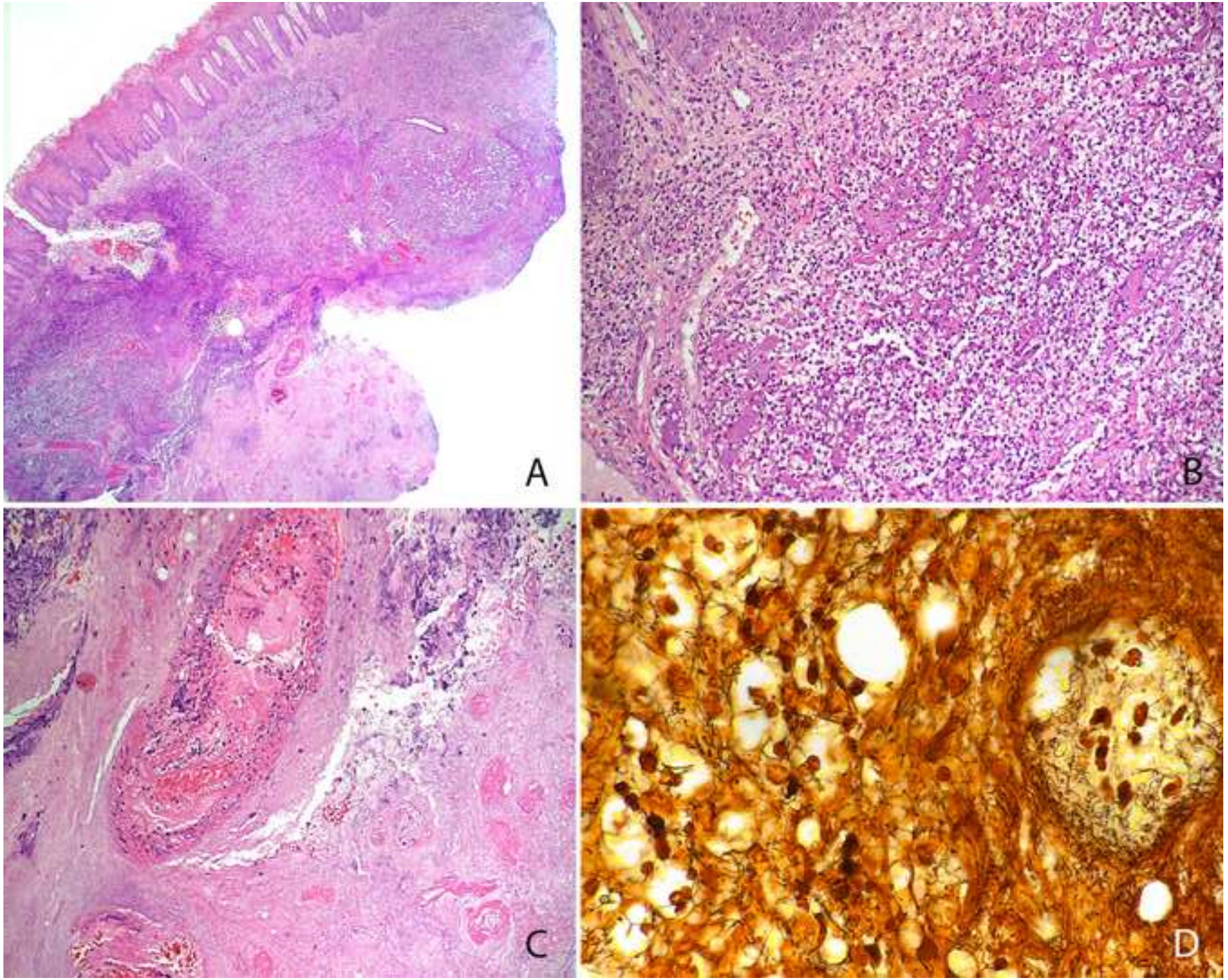

Figure 4