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 (Pretoria, South Africa) complaining of foul-smelling oral odor and painful, bleeding gums for a duration of 2 weeks. The patient reported no previous history of systemic diseases, trauma, or prior treatment.

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 midpalatal region, and extended to involve the entire left half of the hard palate up to the posterior border (Figure 1). The alveolar bone and the gingiva of the dentition in the described area were also severely involved, leading to gross teeth mobility and 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 nonnecrotic palatal mucosa was erythematous, with markedly undercut borders leading to the denuded bone and necrotic center.

Radiologic evaluation with cone beam computed tomography 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 the destructive midpalatal lesion included a variety of infective lesions as well as neoplasms. A deep fungal infection was considered most likely, with fungi of the order Mucorales, as well as *Aspergillus*, *Cryptococcus*, and *Histoplasma*, as the possible causative agents. Human herpesvirus 8 (HHV8), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) were also considered as possible viral etiologic agents.

Deep fungal infections, when suspected, can be highlighted by special histochemical stains, such as periodic acid−Schiff stain and Grocott-Gomori's methenamine silver stain. Depending on their growth characteristics, fungi can appear as multicellular filaments, individual cells, or yeasts. Yeasts appear round-to-oval because of 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, a characteristic termed *dimorphism*. In some cases definitive identification of fungal species requires tissue culture.

Mucormycosis is an opportunistic infection caused by fungi that cause bread mold. Disease occurs after inhalation of spores, usually in immunocompromised patients or those with poorly controlled diabetes. The infection is initially localized in the paranasal sinuses but often spreads to the brain, giving rise to rhinocerebral mucormycosis, which has 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 after pulmonary infection.[1] The organism causes local tissue necrosis, characteristically invades arterial walls, and penetrates the periorbital tissues and the cranial vault. Mucormycetes form nonseptate hyphae, with 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 the 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 *Cryptococcus 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 the *Cryptococcus* species.[2]

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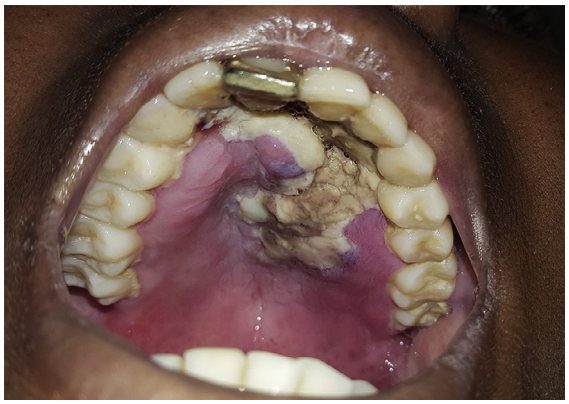

Fig. 1. Initial presentation of lesion at consultation.

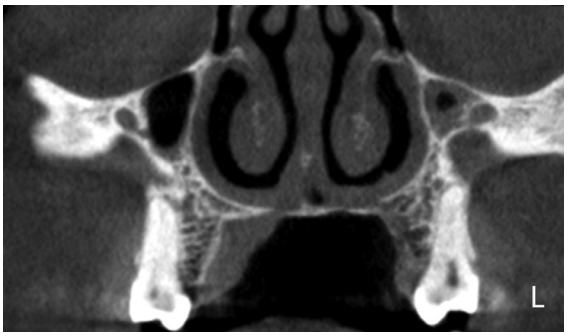

Fig. 2. Cone beam computed tomography. Coronal bony window at the level of the premolars. Bony erosion and the loss of the cortex on the palatal aspect of the alveolar ridge are visible on the left.

Histoplasmosis manifests as chronic disseminated forms or as acute forms with a fatal outcome, especially in newborns and immunocompromised patients. The fungus *Histoplasma 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 the 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.

Kaposi sarcoma is a vascular neoplasm of intermediate-grade caused by HHV8 infection, which is strongly associated with HIV/AIDS. It progresses through 3 clinical phases, namely patch, plaque and nodular phases. Histologically, this tumor demonstrates sheets of plump, proliferating spindle cells that form vascular-like slit spaces often containing extravasated red blood cells.[3] Immunohistochemical staining for HHV8, as well as other endothelial markers, is diagnostic. Kaposi sarcoma rarely occurs as a solitary hard palate lesion without evidence of cutaneous involvement.[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, surrounded by a clear halo, are noted. Disseminated CMV causes focal necrosis with minimal inflammation in virtually any organ. A diagnosis of CMV infection may be made through demonstration of characteristic morphologic alterations in tissue sections, detection of CMV antigens, viral culture, or polymerase chain reaction−based detection of CMV DNA.

The possibility of an extranodal natural killer (NK) T-cell lymphoma, nasal type was also considered because of its aggressive and destructive growth in the midfacial area.[6] The oral cavity is usually secondarily involved after 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 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 immunosuppressive medication and in older adults with age-related immune senescence. EBV MCU presents with localized, solitary areas of mucosal ulceration commonly affecting the oropharynx.[8] Histologically, this lesion is characterized 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 in situ hybridization is the methodology of choice for the detection of the EBV-encoded messenger RNA in tissue sections.

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

DIAGNOSIS AND MANAGEMENT

An incisional biopsy of the palatal mucosa was performed and the tissue submitted for histologic examination. An additional soft tissue fragment was submitted for microscopy, culture, and sensitivity. After the incisional biopsy, total debridement of the necrotic tissue was performed to stimulate bleeding and initialize 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 (BIPP)—infused lint gauze and secured with polyglactin 910, size 4/0, creating a netlike configuration and securing the BIPP gauze to the palate. This was done to stimulate granulation tissue formation and to prevent reinfection of the curetted denuded bone. Oral antibiotics were prescribed—augmentin, 625 mg 3 times daily for 10 days, and metronidazole, 400 mg 3 times daily for 5 days—as empirical therapy, with analgesics to manage pain.

Because of the clinical presentation and the age of the patient, the possibility of a compromised immune system was suspected. Hematologic studies, which included a full blood count, urea, and electrolytes, as well as a HIV-rapid test and a *Treponema pallidum* hemagglutination assay, were performed. The HIV-rapid and confirmatory serology enzyme-linked immunosorbent assay results were positive, and the patient was subsequently diagnosed with HIV infection.

Histologic 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 comprised 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 and a dense, mixed inflammatory cell infiltrate consisting predominantly of neutrophils and histiocytes (Figure 3B). Several blood vessels were present, with associated fibrin thrombi, related to areas of infarction (Figure 3C).

Periodic—acid Schiff and Grocott-Gomori's methenamine silver histochemical staining failed to highlight fungal microorganisms. Similarly, CMV immunohistochemical staining yielded a negative result for viral inclusions. Warthin-Starry special staining 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 for infectious diseases for further HIV counselling, the initiation of highly active antiretroviral therapy, and intramuscular administration of 2.4 million units of benzathine penicillin.[10] The BIPP gauze dressing was removed, and granulation tissue formation and epithelialization were 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 use 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, which has been attributed to the general lack of public knowledge regarding sexually transmitted infections, the misconception that all sexually transmitted infections are curable, the erroneous belief that oral sex is safe, and the prevailing culture that endorses having multiple sexual partners.[11]

Coinfection with syphilis and HIV is also on the rise. An underlying immune dysfunction in HIV-positive patients may predispose them to coinfection with syphilis.[13] Syphilis facilitates the transmission of HIV through the disruption of natural barriers via primary genital ulcerative lesions or chancres. This facilitates bidirectional spread through biologic 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 caused by the stimulation CD14 monocytes by treponemal lipoproteins.[14] Both syphilis and HIV affect the same biologic parameters. Syphilis demonstrates a decrease in the CD4 count and an increase of the HIV viral load in patients infected by both entities.[15,16]

Syphilis is subdivided into stages on the basis of the activity and infectivity of 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 localized to the site where contact with an active lesion occurs. Thus, the genital area is most frequently involved, with oral sites representing the most common extragenital site.[11] The initial presentation consists of a painless papule that develops at the site of inoculation after an incubation period of 2 to 3 weeks. The papule becomes indurated and ulcerated, resulting in the classic syphilitic chancre. Intraoral 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

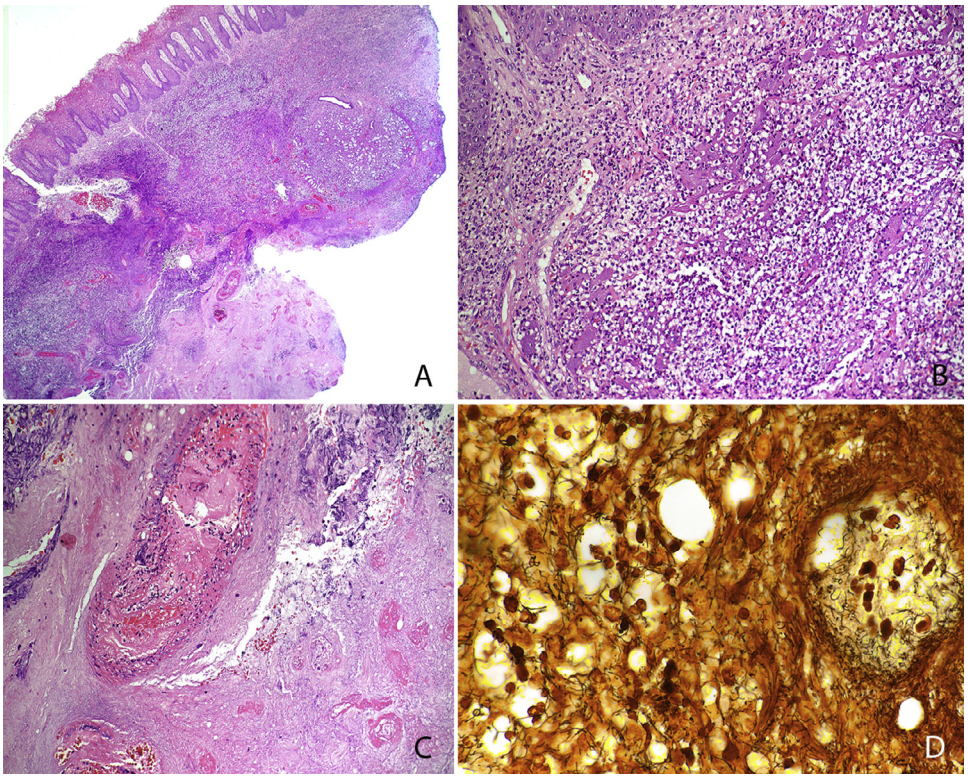

Fig. 3. **(A)** A low-power hematoxylin and eosin (H&E)−stained section showing the incisional biopsy specimen with an ulcerated surface epithelium (original magnification × 100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05515.* **(B)** H&E-stained section demonstrating fibrous connective tissue with numerous areas of necrotic tissue with a dense, mixed inflammatory cell infiltrate (original magnification × 200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05515.* **(C)** H&E-stained section demonstrating a blood vessel with associated fibrin thrombi and surrounding necrosis (original magnification × 200). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05515.* **(D)** Warthin-Starry special stain showing the presence of numerous coiled spirochetes, some invading a blood vessel (original magnification × 400). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05516.*

diagnostic challenge because of its diverse clinical presentations. The diagnosis of secondary syphilis requires a high index of clinical suspicion because the primary stage may have gone undiagnosed.[17] Clinical symptoms are usually nonspecific, with patients complaining of headaches, low-grade fever, myalgia, generalized lymphadenopathy, and pharyngitis. A mucocutaneous maculopapular rash occurring predominantly on the trunk and extremities, often with both palmar and plantar involvement, is a consistent feature.[11]

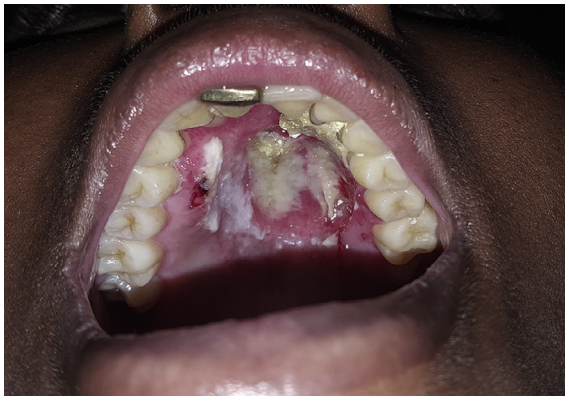

Fig. 4. Presentation at 2-week follow-up.

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 2 subtypes: (1) slightly elevated−type plaques that are occasionally ulcerated and covered with a gray or white pseudomembrane; and (2) multiple mucous patches that may coalesce to give rise to serpiginous lesions, described as "snail track ulcers." White plaques with a verrucous aspect, the so-called leukoplakia-like plaques, are also described as another frequent form of the disease.[18] Lesions can, however, be clinically and histopathologically nonspecific and may mimic other entities.[13] The current case highlights the fact that in some cases, the disease can manifest atypically and that the diagnosis may, therefore, 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 because of neurologic and cardiovascular complications. The characteristic syphilitic lesion during this stage is the *noninfective gumma*, a term that refers to an area of necrotizing granulomatous inflammation, with the occurrence in the oral cavity well documented. Gummatous foci involving the hard palate and tongue are typical. The palatal lesions often result in destruction of bone resulting in an oroantral communication. Tongue lesions tend to heal with pronounced scarring and muscular contracture.[11,19]

Patients with HIV coinfected with syphilis have been studied in past decades. The syphilis infection can present with the typical oral lesions or as painless mucous patches. However, HIV coinfection may dramatically alter the clinical appearance of lesions and is associated with a more aggressive disease course. Moreover, some cases pose difficulty in delineating the differential diagnosis.[12,19]

Histologically, syphilis often shows intense subepithelial plasma cell infiltration, which should be differentiated from idiopathic plasmacytosis, IgG4-related sclerosing disease, contact stomatitis, candidiasis, inflammatory pseudotumor, and plasmacytoma. Primary syphilis and secondary syphilis are characterized by plasma cell infiltration extending deeply beyond the lamina propria, surrounding capillaries, and nerve bundles. The plasma cells may be arranged, along with lymphocytes and macrophages, in a band-like pattern within the superficial lamina propria, with the appearance 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, are characteristic of tertiary oral syphilis. Obliterating endarteritis may be seen in all stages of the disease.[20]

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

Syphilis may also be diagnosed by using serology tests, which include nontreponemal and treponemal assays. Nontreponemal tests are cost effective and are useful for screening patients and for monitoring response to treatment by detecting antibodies that are not specifically directed against *T. pallidum*. Treponemal assay tests that are available include the Venereal Disease Research Laboratory test and the rapid plasma reagin test, with the results reported as titers reflecting both IgM and IgG antibodies. This test may be utilized after treatment to demonstrate 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 fluorescent treponemal antibody absorption test as well as *T. pallidum* particle agglutination tests and enzyme immunoassay. Once the patient tests positive with the treponemal test, the person remains positive for the duration of his or her lifetime. Patients diagnosed with syphilis with HIV coinfection should be treated in accordance with the recommendations of the Centers of Disease Control and Prevention, with the same regimen as that for HIV infection.

The preferred treatment for syphilis remains benzathine penicillin G (2.4 million units administered intramuscularly); 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 after 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.

Serologic tests are the mainstay in the diagnosis of syphilis. It must be emphasized that a high index of suspicion needs to be maintained by both clinicians and pathologists because clinical and histologic findings may be subtle, and mistaken for those of other, more common entities.

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