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Tertiary Treponematosis of the Nasal Cavity – Oral Medicine Case Book

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ABSTRACT

Both genital and non-genital treponematoses are overtly similar in pathogenesis, natural history and histologic features. In the head and neck, a relatively small percentage of untreated, infected patients may progress from latency to tertiary disease, with perforation or collapse of the palate and nasal septum. Due to the rarity of tertiary disease and the non-specific histomorphologic features, the disease may go undiagnosed, often with dire consequences. Clinicopathological correlation, a high index of suspicion and a judicious mix of histological and immunohistochemical stains may help the pathologist in arriving at the correct diagnosis. In this article, we report a unique case of nasal treponematosis in a young South African male, discussing the clinical findings, histological features and diagnostic methods of detection.

Keywords

Tertiary Syphilis, nasal cavity, Treponema pallidum, Immunohistochemistry, Granulomatous inflammation, Treponematosis, endemic syphilis, South Africa.

INTRODUCTION

The human treponematoses comprise sexually transmitted syphilis and endemic forms of the disease. The etiologic agents of human treponematoses are gram negative bacteria that belong to the genus Treponema. There are three subspecies of Treponema pallidum: T. pallidum pallidum that causes sexually transmitted syphilis, T. pallidum pertenue and T. pallidum endemicum that cause endemic non-sexually transmitted treponematoses; yaws and bejel (endemic syphilis) respectively.[1] Yaws generally occurs in tropical countries, such as Ghana and Indonesia. In contrast, endemic syphilis (bejel) occurs in warm, arid areas (Southern Africa, Kuwait and Saudi Arabia). Endemic treponematoses are usually seen in children and young adults, and are commonly transmitted through food utensils.[2-4]

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The clinical manifestations of sexually transmitted syphilis and endemic treponematoses are commonly divided into early stage (comprising primary and secondary manifestations) and late stage. Early-stage lesions are highly contagious and can persist for weeks to months, or even years.[1] When early lesions resolve spontaneously, patients enter a latency phase that, in many cases, lasts for a lifetime. In a relatively small percentage of untreated patients, however, the infection may progress from latency to tertiary disease, characterised by destructive lesions of skin, bone and cartilage.[1] The pathognomonic head and neck manifestation of tertiary disease is perforation/collapse of the palate and nasal septum, producing the characteristic saddle nose deformity.[5] If left untreated, tertiary syphilis has some of the most devastating clinical manifestations as it exerts its effects on the cardiovascular and nervous system (neurosyphilis).[6]

Proper diagnosis requires, first and foremost, that treponemal disease be part of the pathological differential diagnosis, especially if not clinically suspected.

We report a rare case of nasal treponematosis in a 17-year-old South African male patient and discuss the clinical spectrum of disease along with the diagnostic histopathology.

Clinical and radiological presentation

An African 17-year-old male patient presented at the Ear, Nose and Throat (ENT) outpatient clinic of Tygerberg Hospital (Cape Town, South Africa) with a unilateral left-sided nasal obstruction, which had been progressively worsening over the course of one month. Additionally, the patient reported intermittent left-sided epistaxis, with no accompanying hyposmia/anosmia, rhinorrhoea, pain, eye changes or neurological symptoms. The patient had no significant past medical history, including no prior surgical procedures in the region or trauma to the nose.

On clinical examination, an exophytic mucosa-surfaced mass was observed bulging into and nearly completely obstructing the left nasal cavity precluding optimal endoscopic evaluation. Flexible endoscopy of the right nasal cavity revealed no extension of the mass into the nasopharynx. The patient also presented with bilateral single, mobile and non-tender upper cervical lymph nodes.

A contrasted CT scan of the paranasal sinuses revealed a soft tissue mass centred in the left anterior nasal cavity, involving the left inferior turbinate and causing saucerisation of the frontal process of the maxilla, maxillary spine and perpendicular ethmoid plate. Importantly, there was no extension of the mass into the maxillary or ethmoid sinuses

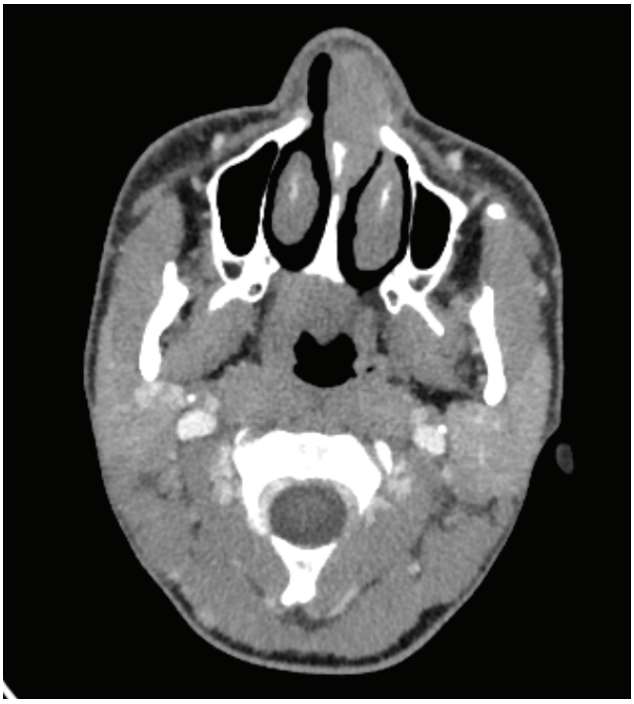

Figure 1. A contrasted CT scan of the paranasal sinuses demonstrating obliteration of the left nasal cavity by a polypoid lesion. Closer inspection of the CT reveals perforation of the nasal septum.

(Figure 1). The main clinical differential considerations included pyogenic granuloma, nasal polyp and juvenile angiofibroma.

Histologic features

An incisional biopsy of a representative area was performed under local anaesthesia and the specimen was submitted for histological evaluation. Gross examination revealed a 2.2 x 0.8 x 0.3cm polyp with surface ulceration. Microscopically, the polyp was surfaced by a metaplastic squamous epithelium. The subepithelial connective tissue exhibited a dense non-specific lymphoplasmacytic infiltrate with scattered vague granulomas, consisting of epithelioid histiocytes. Focally, a necrotic background was seen with occasional eosinophils (Figures 2 and 3). Special stains, PAS+D and Methanamine silver were negative for fungi, while Zheel Nielsen (ZN) and Fite were negative for mycobacteria. The plasma cells were strongly immunoreactive for CD138 (Syndecan-1) and PLA (VS38c). Kappa and Lambda in situ hybridisation showed a polycolonal population of plasma cells. CD 56 IHC and EBER in situ hybridisation were negative. Treponema pallidum IHC was positive for spirochetes. The spirochetes were predominantly intraepithelial (epitheliotrophic) with scattered stromal organisms (Figure 4). Based on the histological and immunohistochemical features, a diagnosis of nasal treponematosis was made. The differential diagnosis included sexually transmitted syphilis and endemic syphilis. Due to the relatively young age of the patient at presentation, the possibility of endemic syphilis was favoured. Serological tests, Venereal Disease Research Laboratory (VDRL) and HIV were recommended. However, the patient was subsequently lost to follow-up. Closer inspection of CT images revealed perforation of the nasal septum (Figure 1).

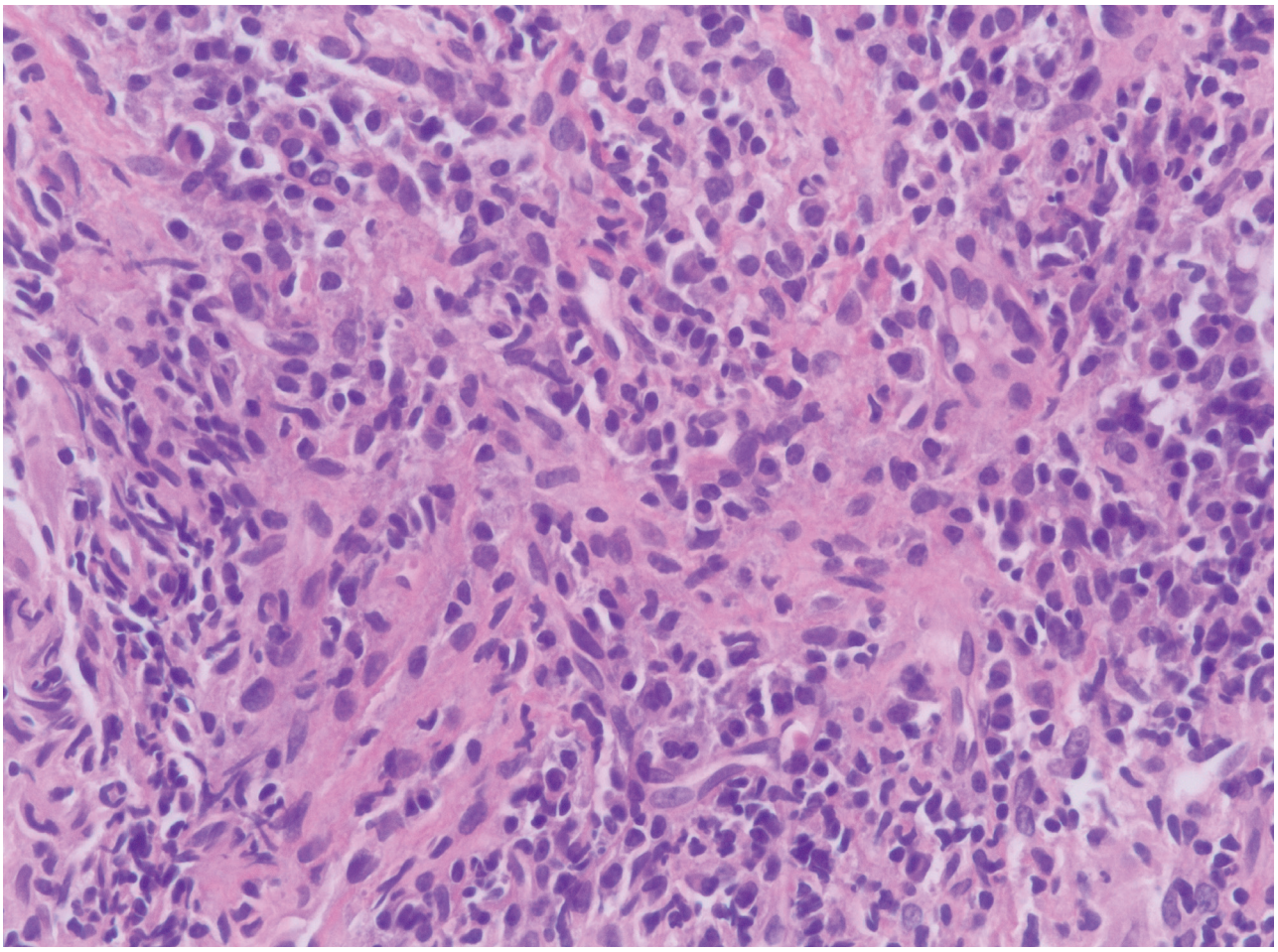

Figure 2. A vague granuloma is seen consisting of epithelioid histiocytes, surrounded by a dense plasmacytic infiltrate (H&E, x40)

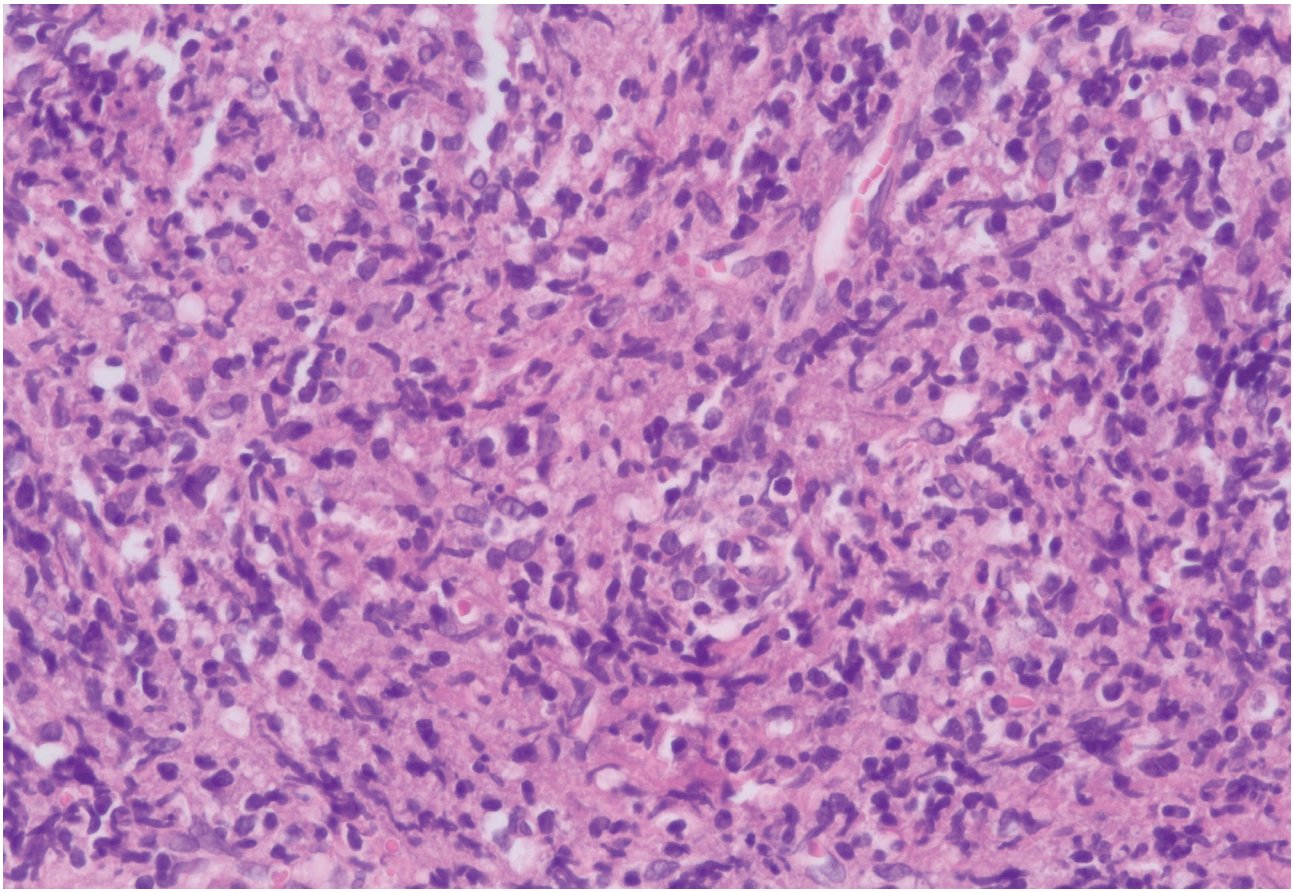

Figure 3. Vague granulomatous inflammation with necrotic background with an occasional eosinophil (H&E, x40)

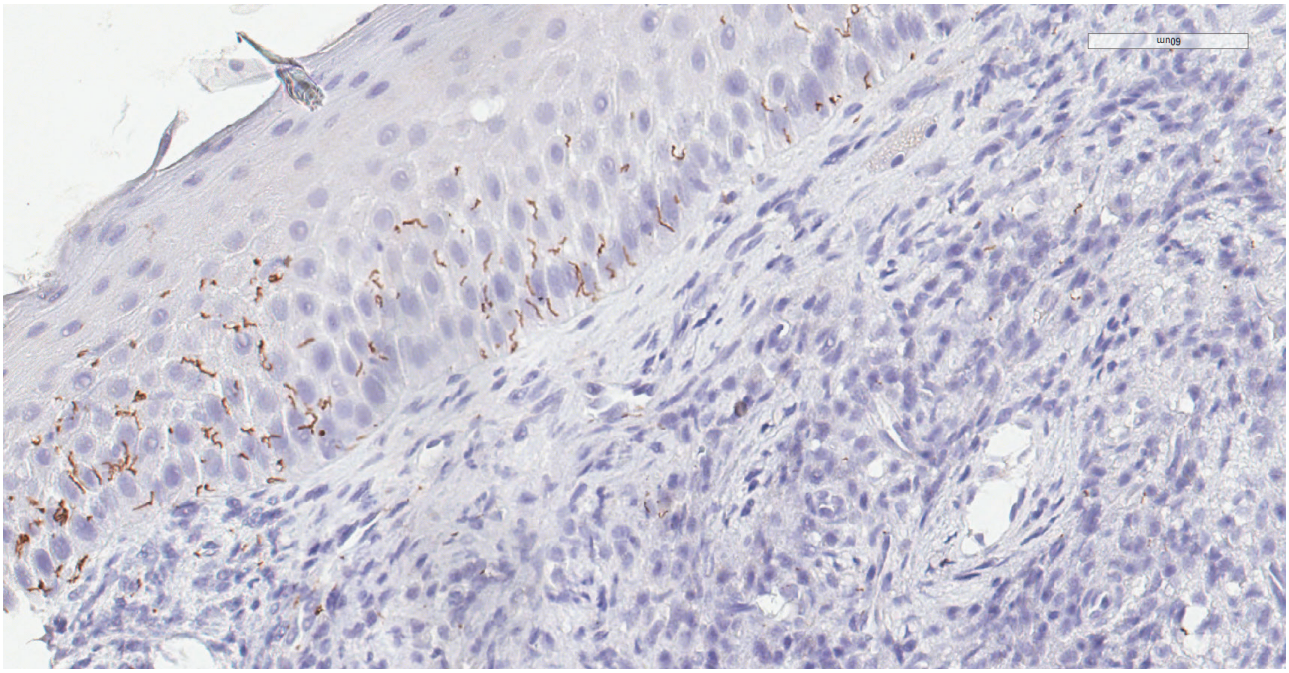

Figure 4. Treponema pallidum IHC shows numerous elongated coiled intraepithelial spirochetes. A few stromal spirochetes are also noted (IHC, x40)

DISCUSSION

In 1948, there were about 50 million cases of yaws, one million cases of endemic syphilis (bejel) and 20 million cases of sexually transmitted syphilis worldwide.[7,8] This prompted the World Health Organization (WHO) and the United Nations International Children's Fund (UNICEF) to lead a screening campaign in 46 developing countries, treating individuals with evidence of active and latent infection with penicillin.[9] By the end of the campaign, the worldwide burden of cases of endemic treponematoses was lowered to 2.5 million cases, a staggering 95% reduction.[9] Unfortunately, these impressive achievements encouraged the WHO to gradually halt the targeted control programmes with resurgence of the endemic treponematoses in many developing countries.[10]

According to the WHO, there were 7.1 million new cases of sexually transmitted syphilis in 2021.[11]

Sexually transmitted syphilis is prevalent in populations seemingly at high risk for contracting a variety of sexually transmitted infections. These populations include men who have sex with men, people who have sex with men who have sex with men, and those who may be immunocompromised for a number of reasons, including oncologic care, but in Africa, particularly prevalent in HIV-positive patients.[12] Transmission occurs vertically and by sexual contact, the latter accounting for 90% of the infections. Additionally, given the introduction of prophylaxis against HIV infection, particularly in developed nations, sexually transmitted infections other than HIV have shown marked increases.[13]

In Southern Africa, endemic syphilis appears to have been prevalent in Southern Zimbabwe, South-Eastern Botswana, Bloemfontein and Western Cape, Northern and Western Gauteng, extending into the Karoo and Northern Cape.[14,15] Endemic syphilis is primarily spread via saliva, especially by contaminated drinking/eating utensils. Direct lesion to skin contact is also important. Overcrowding and suboptimal community hygiene likely play a role. Childhood endemic syphilis provides immunity to sexually transmitted syphilis in adulthood.[14]

Intraoral chancres and mucous patches are characteristic primary and secondary manifestations of sexually transmitted and endemic treponematoses.[16] Chancres are painless ulcers with indurated, well-circumscribed borders and a purple base that appear 2-3 weeks following Treponema pallidum inoculation. Because they are painless, they often go unnoticed and untreated. Intraoral chancres commonly develop on the lips, dorsal surface of tongue and tonsils. The highly infectious chancre-ulcers typically persist for 3-7 weeks. Twelve weeks after the chancre's appearance, and if left untreated, the patient enters the secondary phase of the infection with fever and generalised lymphadenopathy. Head and neck manifestations of secondary disease are hyperplastic coalescing maculopapular lesions (condyloma lata) that develop along the nasolabial folds and "mucous patches".[16,17] Intraoral mucous patches are raised hyperplastic lesions with a grey membrane. Once early lesions resolve spontaneously, the patient enters a latency phase that, in many cases, lasts for a lifetime. In a relatively small percentage of untreated patients, however, the infection may progress from latency to tertiary disease, characterised by granulomatous destructive lesions of skin, bone and cartilage.[1] Destruction of the nasal bony framework and, ultimately, the contraction of fibrous tissue, results in the distinctive saddle nose deformity.[5]

Histologically, the treponematoses present with a non-specific lymphoplasmacytic infiltrate with perivascular cuffing of plasma cells and necrotising granulomatous inflammation. In some cases, the granulomas may be vague or obscured by the dense infiltrate of plasma cells (Figures 2 and 3). As the histological findings are non-specific, the major issue is considering syphilis in the differential diagnosis. A high index of suspicion and clinicopathological correlation are the key to correct histological diagnosis. First and foremost, it is crucial for the practicing histopathologist to be aware of the recent rise in the number of syphilis cases worldwide and the varied symptomatology of the disease in the head and neck region (ulcers, polyps, perforations, mucous patches, etc) to ensure proper diagnosis. If a diagnosis of syphilis is suspected, it is important to alert the clinician to the appropriate additional investigative techniques which will allow a sound diagnosis to be attained. Our study serves to emphasise the importance of clinicopathological correlation in the assessment of a polypoid intranasal mass with septal perforation to remind pathologists of tertiary syphilis as an aetiological factor in destructive midline lesions. The mimicry of several other conditions confounds the specificity of the changes. However, careful scrutiny of all the histopathological features may permit a relatively refined differential diagnosis to be established. The histological differential diagnosis usually includes bacterial (tuberculosis and leprosy) and fungal infections, sarcoidosis, plasma cell neoplasms (eg plasmacytoma) and NK/T-cell lymphoma.[18,19] Mycobacterial and fungal infections should be excluded by special histological stains, namely Zheel-Nielsen (ZN), Fite and silver stains. Sarcoidosis presents with non-necrotising granulomas and hilar lymphadenopathy. A plasma cell neoplasm can be excluded by demonstrating a polyclonal population of plasma cells with Kappa and Lambda IHC or in situ hybridisation (ISH). NK/T-cell lymphoma is a highly aggressive malignancy, endemic to some African and Asian countries, and should be strongly suspected in young African patients with destructive midline lesions. In addition, a vague granulomatous appearance may be seen in some cases of NK/T-cell lymphoma; however, careful microscopic examination shows the presence of highly atypical small irregular lymphoid cells with angiocentricity and angiodestruction, that are positive for EBER ISH and CD56 IHC. Immunohistochemistry with commercial polycolonal antibodies is more sensitive than the silver stain for direct detection of the spirochetes, especially in tertiary disease, where few spirochetes could be present (Figure 4).[20] However, Treponema pallidum IHC cannot discriminate between sexually transmitted and endemic treponematoses. It has been proposed that endemic syphilis is more epitheliotrophic (as seen in present case) than sexually transmitted syphilis (Figure 4). Serological tests such as the Venereal Disease Research Laboratory (VDRL) test are usually used as a screening test.[21] When a patient has a positive VDRL test result, specific treponemal testing should be done to confirm T. pallidum infection. Fluorescent treponemal antibody absorption (FTA-ABS) assay or T. pallidum particle agglutination (TPHA) tests are specific treponemal tests used to confirm the presence of T. Pallidum.[21] Just like Treponema pallidum IHC, serological testing cannot discriminate between sexually transmitted and endemic treponematoses. Clinicopathological correlation is essential. Nevertheless, in regions where sexually transmitted and endemic syphilis coexist, definitive and costly subtyping may not be essential, since both can be easily eradicated by penicillin.

HIV testing is essential in patients with suspected diagnosis of sexually transmitted syphilis. Co-infection is common and certainly a consideration, when unknown HIV status and nascent diagnosis of a suspected sexually transmitted syphilis subtype.[22] Being infected with syphilis enhances the susceptibility of acquiring HIV. The behaviour of syphilis in an HIV-positive individual is much more aggressive than in the HIV-negative patient.[23-24] The progression from primary to tertiary syphilis may occur over several years instead of the usual several decades in the case of HIV-negative individuals. Chancres may be more numerous, larger and deeper. In patients with advanced HIV, secondary syphilis may present as malignant secondary syphilis. This is

characterised by severe ulcerating lesions and gummatous infiltration of mouth, eye, subcutaneous tissue, bone, joints and cerebrospinal system. The likelihood of developing symptomatic neurosyphilis is also dramatically increased, especially uveitis.[26,27]

Antibiotic therapy with a single intramuscular Benzathine penicillin dose of 2.4 million units has remained the mainstay of treatment.[28] A longer duration of therapy is needed for late stage lesions. Local treatment of lesions is advised. Local treatment of the nasal lesions includes clearing the crusts and then regularly clearing the nasal passages with copious alkaline douches one to three times a day and local application of yellow mercury oxide.[5] Due to the destructive nature of the lesions, the patient may be left with a nasal deformity and atrophic rhinitis, necessitating reconstructive surgery once the patient has been cured.

CONCLUSION

Both sexually transmitted and endemic treponematoses share similar histologic features. The diagnosis of endemic tertiary treponematosis should be suspected in a young patient with histologically positive spirochetal infection as it takes many years or even decades for tertiary lesions of sexually transmitted syphilis to develop. To ensure a proper diagnosis, a cross-disciplinary approach with close collaboration with otorhinolaryngologists and radiologists is highly recommended. Paying particular attention to all histological details allows a relatively refined differential diagnosis to be made.

The histological differential diagnosis of tertiary nasal treponematosis includes a range of necrotising midline lesions, such as tuberculosis, leprosy, mucormycosis and aggressive lymphomas. Treponema IHC is an easy, inexpensive and highly sensitive test that in recent years has replaced dark field microscopy and Warthin-Starry silver staining. Treponema IHC is particularly valuable in the setting of spirochete-poor lesions of tertiary treponemtosis. Treponema-positive patients may require serological testing for other STDs, especially HIV, as co-infected individuals demonstrate an aggressive clinical course.

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CPD questionnaire on page 452

The Continuing Professional Development (CPD) section provides for twenty general questions and five ethics questions. The section provides members with a valuable source of CPD points whilst also achieving the objective of CPD, to assure continuing education. The importance of continuing professional development should not be underestimated, it is a career-long obligation for practicing professionals.