***NICOLAE TESTEMITANU* STATE UNIVERSITY OF MEDICINE AND PHARMACY OF THE REPUBLIC OF MOLDOVA**

DEPARTMENT OF ORO-MAXILLOFACIAL SURGERY AND ORAL IMPLANTOLOGY *ARSENIE GUTAN*

SOFIA LEHTMAN

SPECIFIC INFECTIOUS DISEASES IN THE MAXILLOFACIAL TERRITORY

Methodological guide for the 3rd year students
Faculty of Stomatology

CHISINAU
2023

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INTRODUCTION

While odontogenic infections are daily encountered in dental and oral and maxillofacial surgery practices, some practitioners may be unfamiliar with the wide range of other infections of diverse etiology, some of them relatively uncommon, or even rare. Patients so affected come to their attention either through referrals from primary care providers or due to patients' uncertainty about where to seek help for diseases manifesting themselves in the oro – maxillofacial territory.

In the OMF region a special group are inflammatory processes, caused by the specific pathogens, such as:

- ✓ actinomyces israelli;
- ✓ actinomyces odontoliticus;
- ✓ pallidum treponema;
- ✓ microbacteria of tuberculosis.

These pathologies are characterized by the presence of the specific pathogens that causes the disease and by the clinical features characteristic of each disease.

Knowing the clinical signs characteristic of these pathologies is very important because some of them may accompany the initial stages of the disease, so it is possible to determine the pathology in the onset phases and initiate specific treatment.

This r is recommended to third year students, Faculty of Stomatology with the role of increasing the quality of teaching and mastering the subject.

1. ACTINOMYCOSIS

The aim of the study

Evaluation of the characteristics and treatment of actinomycosis in the maxillofacial territory.

Duration and type of activity

The material is taught in 7 academic hours, of which: 2 hours of theoretical course, 5 hours of seminar and practical lessons.

Objectives

1. Elucidation of the etiological factors responsible for the occurrence of actinomycosis.
2. Revealing the importance of clinical and paraclinical examination (specific) in establishing the diagnosis of actinomycosis.
3. Knowledge of the pathognomonic characters and forms of actionmycosis in the maxillofacial region.

At the end of the practical lesson / seminar the student will be able to

During the seminar, students learn the etiology, pathogenesis, symptoms, diagnosis and treatment of actinomycosis the maxillofacial territory. During the practical lesson students will participate in the examination, diagnosis and treatment of patients and write down in the notebooks the performed procedures.

Methods and materials

The theoretical material of the topic is taught in a classical way, through lectures, seminars and practical lessons. Different semiotic systems are used to teach and learn the topic, such as scientific language, graphic and computer language. Teaching materials used: tables, diagrams, photographs, radiographs, video material, CBCT software, PowerPoint presentations.

Self-assessment questions

1. Cervicofacial actinomycosis: etiology, microbiology, pathological anatomy.
2. Classification according to clinical forms and location (cutaneous, subcutaneous, mucosal, submucosal form, actinomycetic

odontogenic granuloma, muscular subcutaneous form, actinomycosis of lymph nodes, actinomycosis of the periosteum, actionmycosis of bones, organs of the oral cavity).

3. Diagnosis (according to clinical data, onset and evolution, microbiological analyses, skin prick tests, immunodiagnosis, radiological and morpho pathological peculiarities).
4. Differential diagnosis and treatment (surgical, immunotherapy, anti-inflammatory, desensitization, radiotherapy, physiotherapy, etc.).

Comments of the topic

1.1. Background

Actinomycotic infections of the cervicofacial region are uncommon. Most major medical centers report approximately one case per year. Presenting clinical manifestations are confusing because they often mimic other disease processes. Diagnosis may be difficult due to a general lack of familiarity with the disease and the fastidious nature of the organism in culture. The cervicofacial manifestations of actionmycosis are varied, and a high index of suspicion is required to make an accurate and timely diagnosis.

Actinomyces are saprophytic, gram-positive anaerobic bacteria that are part of normal oral flora. The primary pathogen is *A. israelii*, although other species can also cause infection. *Actinomyces* colonize tonsillar crypts, dental plaque, and gingival sulci. The presentation may be acute or chronic, with the bacteria entering through a site of trauma (tooth extraction site), infected tonsil or soft tissue injury. In the acute suppurative phase, yellowish colonies of bacteria may be visible ("sulfur granules"), while the chronic form has extensive fibrosis, imparting a hard or "wooden" area of induration. A fistula may develop with extension to the surface, while periostitis and osteomyelitis may also develop.

1.2. Etiology

Actinomycetes are part of the saprophytic components of the oral flora. Sites of colonization in oral cavity include the tonsillar crypts,

dental plaque and calculus, carious dentin, bone sequestra, salivary calculi, gingival sulci, and periodontal pockets. In the studies of the specialized literature of documented actinomycosis, *Actinomyces israelii* is the causative organism in the majority, with *A. viscosus* being second. Less frequent causes of the infection are *A. naeslundii, A. odontolyticus, A. meyeri, A. pyogenes, A. viscosus,* and *A. bovis,* along with *Arachnia propionica* and *Bifidobacterium dentium*

1.3. Clinical Features

Actinomycosis may be an ***acute***, rapidly progressing infection or a ***chronic***, slowly spreading lesion that is associated with fibrosis. Approximately 50% of cases of actinomycosis are diagnosed in the cervicofacial region, with 30% occurring in the abdominal and pelvic region and 15% in the pulmonary system. The remaining 5% exhibits a variety of patterns, such as superficial skin infections, or infections of the genitourinary region.

- **Acute onset** is characterized by the presence of a fascial spaces or perioseous suppurative process, with predominantly nocturnal pain, with irradiation in hemicranium. Present swelling is sensitive to palpation, surrounded by an hard inflammatory infiltrate or an erythematous area. Perilesional may occur numerous microabscesses, which can spontaneously fistulize through a granular secretion.
- **Chronic onset** is nodular, with initially circumscribed lesions, painless on palpation, that progressively invades neighboring tissues after absceding. In the period of symptoms manifestation, the swelling extends, and there are lesions in different evolutionary stages like: nodes, abscess, fistula. Multiple lesions at different evolutionary stages induce the clinical appearance of skin „in splashes".

The suppurative reaction of the infection usually discharge large yellowish flecks that represent colonies of the bacteria called **sulfur granules.** Although, sulfur granules are not always present. In the cervicofacial region, the organism typically enters tissue through an area of prior trauma, such as a soft tissue injury, periodontal pocket, nonvital tooth,

extraction socket, or infected tonsil. The infection does not spread along the typical fascial planes and usually disregards the normal lymphatic and vascular vessel. Direct extension through soft tissue is seen, and lymph nodes become involved only if they are in the path of the process.

The classic description is of a „wooden" indurated area of fibrosis, which ultimately forms a central, softer area of abscess. The infection may extend to the surface, forming a sinus tract. Pain often is minimal. The soft tissues of the submandibular, submental, and cheek areas are common areas of involvement, with the area overlying the angle of the mandible being the most frequently affected site.

In the oral cavity, the tongue is the most frequently mentioned site, but any oral mucosal location is possible. Tonsillar hyperplasia thought to be secondary to actinomycotic infestation of the crypts does not appear responsive to antibiotics, probably because of the superficial location of the bacterial colonies. Tonsillectomy is generally the most effective treatment for this situation.

Actinomycotic osteomyelitis of the mandible and maxilla has been reported. Trauma, periodontal infections, nonvital teeth, and extraction sites have all provided access. **Forms:**

1. Dermal;
2. Subdermal;
3. Submucosal,
4. Mucosal,
5. Odontogenic actinomycosis granuloma.
6. Subdermal-muscle (deep).
7. Actinomycosis of maxilla periost.
8. Actinomycosis of lymph nodes.
9. Actinomycosis of maxilla bone.
10. Actinomycosis of mouth cavity organs – tongue, tonsils, salivary glands, supramaxillary cavity.

1. Dermal form of the actinomycosis occurs relative seldom. Disease appears in the result of odontogenic infection spread. Patients complain on the insignificant pains and induration on the small extends

of cheek skin, submandibular region or neck. Dental actinomycosis courses without temperature increasing. During the examination it is observed inflammatory infiltration of the skin, emerges one or several focuses, which grow outside.

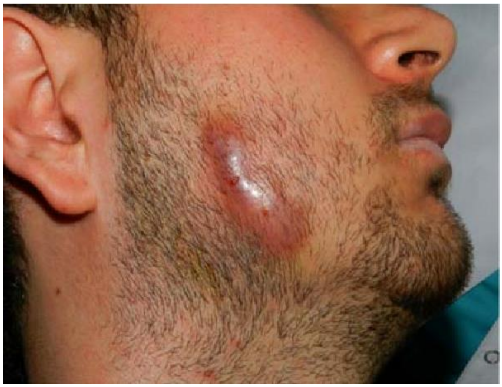

Fig. 1. Dermal form of actinomycosis

2. Subdermal form of actinomycosis is characterized by the developpment of the pathological process in the subdermal layer, as a rule, directly near odontogenic focus. Patients complain on pain and induration in the buccal or other regions: submandibular, parotid-masticatory, retromandibular regions, neck. The infliltration is diffuse, during the palpation in the subdermal layer is defined roundish infiltrate. Initially, the infiltrate is hard and painfull, but forward during fusion of granulomas, soft and painless.

3. Submucosal form of the actinomycosis occurs relatively seldom. It courses without temperature rise or its insignificant rise until the subfebrile value, with moderate painful sensation in the focus center. Pains increase during the movement – mouth opening, deglutition, speech. During the palpation a solid infiltrate of roundish form is observed. Submucosal actinomycosis focuses in peritonsillar region is characterized by significant solid tissues, which together with hypertrophic amygdale remind the clinical feature of malignant tumor. Focus opening

allows the presence of clearly restricted region, filled by serous – purulent exudate and granulations.

4. Actinomycosis of the mouth cavity mucous membrane occurs seldom. Pathogens penetrates through damaged and inflamed mouth mucosa membrane. Favorite place of affection is mucosa membrane of the lower lip and cheek, sublingual region, lower and lateral side of tongue. The mucosa membrane in the place of affection has red, sometimes cyanotic color.

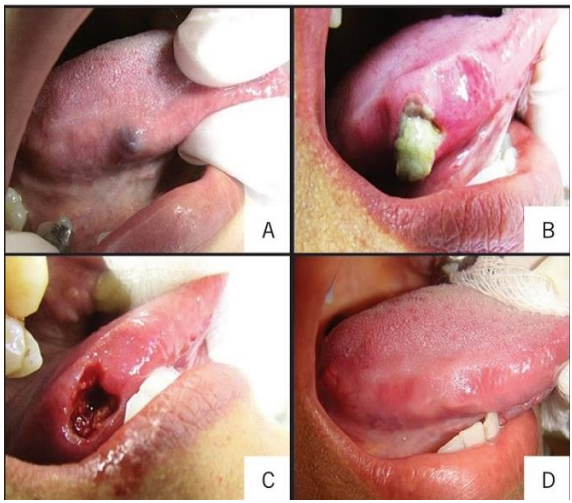

Fig. 2. Actinomycosis of the mouth cavity mucous membrane

5. Odontogenic actinomycotic granuloma. Appearance of the primary actinomycetic granuloma in the periodontal tissues happens more often then other forms. During the localization of the actinomycetic odontogenic granuloma in the dermal and in the subdermal layer, a band along the transitory fold, coming from tooth to the focus in soft tissues is observed.

6. Subdermal – muscle (deep) form of the actinomycosis develops in the subdermal, intermuscular, interfascial layer. It is localized in the submandibular, buccal or parotid-masticatory regions, and also affects tissues of temporal, suborbital, zygomatic, subtemporal fossa, spaces

from lateral part of the neck. During the acute phase it is observed cyanosis of the skin over the infiltrate. The separate appearance of inflammatory focuses, reminds the clinic of microabscesses.

7. Actinomycosis of lymph nodes. During the actinomycosis of lymph nodes the process is localized in buccal and cervical lymph nodes. Patients complain on the limited induration corresponding to one of the lymph nodes group. From the anamnesis it is apparent, that affection of the lymph nodes develops slowly, nodes increased slowly and around them a tissues infiltration grows.

8. Actinomycosis of bone periosteum. Predominantly the periosteum from the vestibular part of the mandibular bone is affected, more often it is marginal process on the level of first lower molar. Clinically, a solid infiltrate, more often along the transitory fold, its flatness is observed, mucosa membrane over it is red, sometimes bluish color.

9. Bone actinomycosis presents two anatomical-clinical forms: peripheral and central. Central bone actinomycosis (pseudotumoral) is characterized by the presence of bone cavities, which gradually deform the bone contour, without affecting, however, the underlying soft tissues. Peripheral bone actinomycosis has as a starting point actinomycosis of soft tissues, which progressively invade the bone, with diffuse, progressive demineralization. According to X-ray picture, the bone actionmycosis is characterized by the presence of one or several cavities of roundish form, but always clearly circumscribed.

10. Actinomycosis of the mouth cavity organs – actinomycosis of the tongue, tonsils, salivary glands, maxillary cavity – occur comparatively rare and represent significant difficulties for diagnostics. Clinical, in lingual parenchyma is palpated a wellbounded nodule that increases dimensionally, having a pseudotumoral appearance, producing functionnal disorders (mastication, phonation). The clinical course is slow accompanied by mucosal damage and granular secretions.

11. Actinomycosis of the maxillary sinus occurs rarely. Infection penetrates by rhinogenic and rarely by odontogenic way. Clinically is present a difficult nasal breathing, sometimes purulent discharge from the

nose is observed. The frontal side of the maxilla is thickened; the mucosa membrane of the transitory fold is thickened by the periosteum. According to X-ray examination actinomycosis of the maxillary sinus is characterized by homogeneous blackening with the well-marked cavity walls.

1.4. Differential diagnosis

- With cervicofacial nonspecific infections by the clinical features characteristic of nonspecific infections
- With other specific infections such as syphilis, tuberculosis
- With benign or malignant oro-maxillofacial tumors by the signs characteristic of neoplastic formations
- Scleroderma-facies acquire the appearance of "Byzantine icon".

1.5. Diagnosis

The diagnosis of actinomycosis is achieved ideally by culture, but less than 50% of cases are positive because of the overgrowth of associated bacteria, prior antibiotic therapy, or improper anaerobic media conditions. A strong presumptive diagnosis can be obtained through a demonstration of the typical colonies in lesional biopsy material. The material for culture and histopathologic examination typically is obtained during surgical exploration, with fine-needle aspiration in many cases. **Sulfur granules** in infections other than actinomycosis are so rare that their demonstration strongly supports the diagnosis.

To summarize, the diagnosis is based on the clinical examination of the patient with the presence of actinomycosis specific clinical feature and paraclinical explorations, that can be:

Examination by biopsy will identify actinomycotic node, which has three areas: central, mononuclear cell area and peripheral areal. The Central Zone is formed by purulent secretion with granular appearance. Mononuclear cell area plasma epithelioid type contains numerous giant cells resulting from phagocytic the parasite. The peripheral zone contains numerous mononuclear cells, being responsible for fibrosclerosis processes.

Cytological exanimations of the colored smear allows to find out the process character, to establish the presence of mycelium actinomycetis.

Microbiological and histopathological examinations need to be repeated, as they are described false positives and false negatives.

Radiological examination in bone actinomycosis does not show characteristic images, may occur diffuse bone radiotransparent homogeneous areas in the peripheral form and pictures of radiotransparency similar to cystic images in central form.

1.6. Treatment

The treatment of the actinomycosis should be complex and composed of administration of antibiotics, immunotherapy (actinolysate-therapy and vaccine-therapy) and surgical treatment.

The treatment of choice for actinomycosis in chronic fibrosing cases is prolonged high doses of ***antibiotics*** in association with abscess drainage and excision of the sinus tracts. A high antibiotic concentration is required to penetrate larger areas of suppuration and fibrosis. Although penicillin remains the standard of care with no documented *in vivo* resistance, some clinicians believe amoxicillin represents a better first-choice antibiotic. Other investigators have demonstrated *in vitro* resistance to penicillin and recommend tetracycline, which is as effective as penicillin and is the drug of choice for patients with a known allergy to penicillin. Early cervicofacial actinomycosis typically responds to a 5- to 6-week course of penicillin; patients with deep-seated infections may require up to 12 months.

Immunotherapy involves the use of medicines capable of acting on the immune system in the fight against the pathogen.

- **Actinolysat** – is a medication, which represents the product of aerobic cultures of pathogenic actinomycetis, detached from the pathological material during the people's actinomycosis.
- **Actinomycetic polyvalent vaccine (APV)** – is a new medication, offered for actinomycosis treatment

The surgical treatment of the actinomycosis consists of:

- **Extraction** of teeth, which were portal of entry of actinomycetic infection.
- **Incision and drainage** of suppurate collection are practiced, widening of fistulous trajectories and removal of the formed granulation tissue.
- Mandatory intraoperative secretion is collected for antibiogram and tissue fragments for histopathological examination. After removal of pathological tissues, the wound is processed with solution of silver proteinate (Protargol) and irrigate with antiseptic solutions of the type of Betadine. The toilet of the wound is carried out two to three times per day.

Prognosis. Prognosis during the actinomycosis in OMF region in many cases is productive (advantageous).

2. TUBERCULOSIS

The aim of the study

Evaluation of the characteristics and treatment of tuberculosis in the maxillofacial territory.

Duration and type of activity

The material is taught in 7 academic hours, of which: 2 hours of theoretical course, 5 hours of seminar and practical lessons.

Objectives

1. Elucidation of the etiological factors responsible for the occurrence of tuberculosis.
2. Revealing the importance of clinical and paraclinical examination (specific) in establishing the diagnosis of tuberculosis.
3. 3.Knowledge of the pathognomonic characters and forms of tuberculosis in the maxillofacial region.

At the end of the practical lesson / seminar the student will be able to

During the seminar, students learn the etiology, pathogenesis, symptoms, diagnosis and treatment of tuberculosis in the maxillofacial terri-

tory. During the practical lesson students will participate in the examination, diagnosis and treatment of patients and write down in the notebooks the performed procedures.

Methods and materials

The theoretical material of the topic is taught in a classical way, through lectures, seminars and practical lessons. Different semiotic systems are used to teach and learn the topic, such as scientific language, graphic and computer language. Teaching materials used: tables, diagrams, photographs, radiographs, video material, CBCT software, PowerPoint presentations.

Self-assessment questions:

1. Microbiology, etiology, pathological anatomy, classification of tuberculosis.
2. Primary tuberculosis, clinical forms, symptomatology, diagnosis, treatment.
3. Secondary tuberculosis (ulceration, TB gumma, TB lupus), symptoms, diagnosis, treatment.

Comments of the topic

2.1. Background

Tuberculosis is a chronic bacterial infection caused by Mycobacterium tuberculi, characterized by formation of granulomas in infected tissue by cell mediated hypersensitivity. It may affect the soft tissue and the bones, as a primary, secondary lesion or as a lesion of the maxillary bones. It can occur in the mouth involving the tongue with very unusual features and forms. So oral lesions, although rare, are very important for early diagnosis and interception of primary tuberculosis.

Worldwide, it is estimated that 2 billion people (one-third of the population) are infected. Each year approximately 8 million additional individuals become infected, with 2 to 3 million deaths annually attributed to TB. Worldwide, the prevalence of the infection declined with the introduction of effective antimicrobials, but in recent years it has

demonstrated an increased frequency that appears to be associated with emergence of AIDS and drug-resistant strains.

2.2. Epidemiology

1/3of the world's population is infected with M. tuberculosis, with 8.7 million new cases reported each year. Conditions that predispose to the disease include crowded urban living, drug abuse, poor health and hygiene, poverty. Viral infections like HIV with or without the development of AIDS, cause immunosuppression which has lately emerged as a very significant risk factor for development. Almost all infections are due to inhalation of droplet nuclei, rarely by ingestion, inoculation or transplacental route. There are 2 key determinants of infection- closeness of contact and infectiousness of the source, but the strongest risk factor for disease progression is AIDS. The biggest issue in TB treatment is the drug resistance, in some cases patients present multi-drug resistance (to isoniazid and rifampin) or extensively drug-resistance (isoniazid, rifampin, fluorquinolone and second-line injectable drug).

2.3. Pathogenesis

Tuberculosis is caused by 3 main strains of microorganisms- Myc. Tuberculli, Myc. Bovis, Myc. Avium intercellular. The bacteria are rod shaped, non sporing anaerobes, aerobic, acid fast- due to high content of mycolic acids.

Infection requires a cellular immune response, as the airborne droplet nuclei reach the terminal alveola, being ingested by the pulmonary macrophages and transported to the regional lymph nodes. Visible growth takes 3 to 8 weeks, producing incomplete necrosis with a cheesy, acellular material, contained in pulmonary cavities- caseous necrosis.

Tuberculosis oral lesions have a relatively rare occurrence. The incidence has been reported as less than 0.5-1% amongst all the Tuberculosis patients, according to various studies.

Saliva is considered to have a significant role which explains the paucity of oral lesions, despite the large numbers of bacilli present in

sputum contacting the oral mucosa in a typical case of pulmonary tuberculosis. Other attributing factors to relative resistance of oral cavity for TB are presence of saprophytes, resistance of striated muscles to bacterial invasion, and thickness of protective epithelial covering. It is believed that the organisms enter the mucosa through small breaches in the surface epithelium which makes it a favorite site for colonization of bacteria. Local factor that may facilitate the invasion of oral mucosa includes poor oral hygiene, leukoplakia, local trauma, and irritation by clove chewing, etc. Self-inoculation by the patient usually results from infected sputum or by hematogenous or lymphatic dissemination.

2.4. Histopathologic Features

The cell-mediated hypersensitivity reaction is responsible for the classic histopathologic presentation of TB. Areas of infection demonstrate the formation of granulomas, which are circumscribed collections of epithelioid histiocytes, lymphocytes, and multinucleated giant cells, often with central caseous necrosis (Fig. 5-22). The nuclei of the giant cells frequently are arranged along the periphery of the cell in a horseshoe or ring shape (Langhans giant cells). In a person with TB, one of these granulomas is called a tubercle. Special stains, such as the Ziehl-Neelsen or other acid-fast stains, are utilized to demonstrate the mycobacteria (Fig. 5-23). A newer technique, fluorescence microscopy of auramine-rhodamine stains, is employed by many institutions in an attempt to increase the ease of finding the organisms. Because of the relative scarcity of the organisms within tissue, the special stains successfully demonstrate the organism in only 27% to 60% of cases. Therefore, a negative result does not completely rule out the possibility of TB.

2.5. Clinical features

a. Primary tuberculosis – is the infection of an individual who has not been previously infected or immunized. Any area of chronic preexisting trauma may favor the localization of the Koch bacillus. The tongue is the most commonly affected, followed by other sites of the oral cavity- palate, lips, buccal mucosa gingiva, palatine tonsils and the floor

of the mouth. Primary tuberculosis can be presented in a variety of forms, such as: ulcers, nodules, tuberculomas and periapical granulomas, associated with the enlargement of the regional lymph nodes, with no caseation of dependent lymph nodes.

When oral tuberculosis occurs as a primary lesion, the most common manifestation is an ulcer on the lateral margins of the tongue. Deep tubercular ulcers of the tongue are typical in appearance with a thick mucous material at the base. These tongue lesions are characterized by severe unremitting and progressive pain that profoundly interferes with proper nutrition and rest. Classically, tubercular ulcers of the tongue may involve the tip, lateral margins, dorsum, the midline, and base of the tongue. They are irregular, pale, and indolent with inverted margins and granulations on the floor with sloughing tissue. The lesions are characterized by severe unremitting and progressive pain, which interferes with nutrition.

Primary gingival involvement is more common in children and adolescents, it usually presents as a single painless indolent ulcer, which progressively extends from the gingival margin to the depths of the adjacent vestibule and is often associated with enlarged cervical lymph nodes. They may be single or multiple, painful or painless, and usually appear as irregular, well-circumscribed ulcer with surrounding erythema, without induration and satellite lesions.

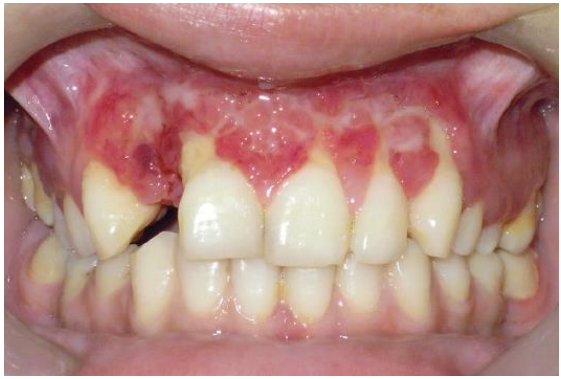

Fig. 3. Primary tuberculosis (ulcerated gingiva)

b. Secondary tuberculosis - the lesions rather are secondary to a pulmonary disease. It appears most likely that the organisms are carried in the sputum and enter the mucosal tissue through a break in the surface. It is also possible that they are carried through the hematogenous route, deposited in the submucosa, and subsequently to proliferate and ulcerate the overlying mucosa. In the oral cavity, it can be found in 3 aspects: ***ulcerations, gumma and tuberculous lupus***. Ulcerations can appear anywhere in the oral cavity, but more frequently they affect the tongue and the vestibular mucosa. It's painful at palpation or during the functional movements. The clinical aspects are similar to the primary tuberculosis ulcerations, but the surface is granulated, covered with yellowish membranes and surrounded by yellow spots- Trelat granulations.

Fig. 4. Secondary tuberculosis (tuberculous lupus)

2.6. Treatment

The treatment of oral tuberculosis lesions is the same as the systemic tuberculosis. Currently, the most effective regimens require a combination of four drugs (isoniazid, rifampicin, pyrazynamide, and ethambutol) administered daily for the first two months, followed by an additional

four months with only two drugs (isoniazid and rifampicin). The complexity of this regimen prompted the World Health Organization (WHO) to launch a new global strategy for TB control known as „directly observed therapy, short course" (DOTS) in 1997. The central component of this strategy is direct observation, by trained personnel, which both ensures patient compliance with the drug regimen and reduces the likelihood of drug resistance. However, this strategy also increases the cost of treatment and makes TB therapy more inconvenient.

Control of Tuberculosis is difficult because of two primary factors: persistence and resistance. Inspite of the fact that, antibiotics are available, *M. tuberculosis* is highly persistent, possibly because the bacterium induces chronic inflammation that sequesters it within the tissues, protecting it against drug exposure. Thus, drug treatment must be extended to fully destroy the bacterium and prevent relapse.

Drug resistance is the result of genetic mutations that cause a heritable loss of drug susceptibility. Although resistance to a single drug does not render therapy ineffective, multidrug-resistant strains make TB much more costly and difficult to treat. For this reason, the need for newer and more effective drugs that achieve multiple goals in improving TB control is imperative.

There are two types of resistance usually observed in the context of TB; MDR (multidrug resistant TB), XDR (Extensively drug resistant)

MDR-TB is defined as *Mycobacterium tuberculosis* (M. tuberculosis) resistant to the most potent first-line anti-TB medications, isoniazid and rifampicin, while XDR-TB has additional multi-drug resistance to the most active second-line agents, injectable drugs (aminoglycosides and/or cyclic polypeptides-capreomycin, kanamycin and amikacin) and fluoroquinolones.

Clearly, the need of the hour is to expand the range of the treatment by either enhancing the application of existing agents or introducing new drugs.

3. SYPHILIS (LUES)

The aim of the study:

Evaluation of the characteristics and treatment of syphilis in the maxillofacial territory.

Duration and type of activity:

The material is taught in 7 academic hours, of which: 2 hours of theoretical course, 5 hours of seminar and practical lessons. Ambulatory.

Objectives:

1. Elucidation of the etiological factors responsible for the occurrence of syphilis.
2. Revealing the importance of clinical and paraclinical examination (specific) in establishing the diagnosis of syphilis.
3. Knowledge of the pathognomonic characters and forms of syphilis in the maxillofacial region.

At the end of the practical lesson / seminar the student will be able to:

During the seminar, students learn the etiology, pathogenesis, symptoms, diagnosis and treatment of syphilis in the maxillofacial territory. During the practical lesson students will participate in the examination, diagnosis and treatment of patients and write down in the notebooks the performed procedures.

Methods and materials

The theoretical material of the topic is taught in a classical way, through lectures, seminars and practical lessons. Different semiotic systems are used to teach and learn the topic, such as scientific language, graphic and computer language. Teaching materials used: tables, diagrams, photographs, radiographs, video material, CBCT software, PowerPoint presentations.

Self-assessment questions:

1. Microbiology, etiology, pathogenesis.
2. Primary, secondary and tertiary stages.
3. Clinical picture, diagnosis and differential diagnosis.

Comments of the topic

3.1. Background

Syphilis is a sexually transmitted disease caused by infection with Treponema pallidum, a Gram-negative bacterium, which is an obligate internal parasite of spiral shape. Natural infection with T. pallidum is limited to the human host and is usually transmitted by sexual contact; the infectious lesion is on the skin or mucous membrane. Treponema pallidum rapidly penetrates intact mucous membranes or microscopic dermal abrasions and, within a few hours, enters the lymphatics and blood to produce systemic infection. The disease progresses in a series of overlapping stages: primary, secondary, latent, and tertiary. Disease transmission between mother and child in utero results in congenital syphilis.

3.2. Clinical features

3.2.1 Primary syphilis.

Incubation time from exposure to development of primary lesions at the site of inoculation averages 3 weeks but can range from 10-90 days, but it may occur also on the lip, gingiva, tongue, tonsils. A papule develops at the site of infection and breaks down to form an ulcer – chancre. The ulcerous-erosive, uninflammatory lesion is usually singular, painless, with base infiltration and hardened high margins. After the appearance of the chancre, regional lymphadenopathy occurs.

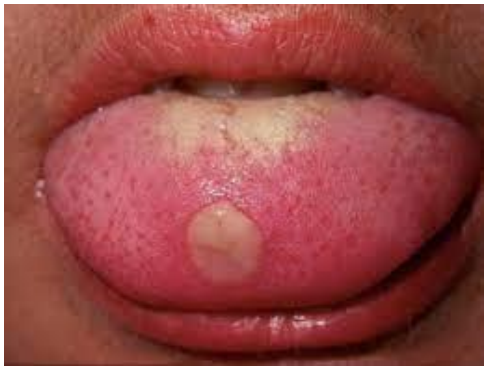

Fig. 5. Syphilitic chancre in primary syphilis

3.2.2 Secondary syphilis

The next stage is known as secondary (disseminated) syphilis and is discovered clinically 4 to 10 weeks after the initial infection. The lesions of secondary syphilis may arise before the primary lesion has resolved completely. During secondary syphilis, systemic symptoms often arise. The most common are painless lymphadenopathy, sore throat, malaise, headache, weight loss, fever, and musculoskeletal pain. A consistent sign is a diffuse, painless, maculopapular cutaneous rash, which is widespread and can even affect the palmar and plantar areas. The rash also may involve the oral cavity and appear as red, maculopapular areas. Although the skin rash may result in areas of scarring and hyperpigmentation or hypopigmentation, it heals without scarring in the vast majority of patients. In addition, roughly 30% of patients have focal areas of intense exocytosis and spongiosis of the oral mucosa, leading to zones of sensitive whitish mucosa known as *mucous patches*. Occasionally, several adjacent patches can fuse and form a serpentine or snail-track pattern. Subsequently, superficial epithelial necrosis may occur, leading to sloughing and exposure of the under-lying raw connective tissue. These may appear on any mucosal surface but are found commonly on the tongue, lip, buccal mucosa, and palate. Elevated mucous patches also may be centered over the crease of the oral commissure and have been termed split papules. Occasionally, papillary lesions that may resemble viral papilloma arise during this time and are known as condyloma lata. Although these lesions typically occur in the genital or anal regions, rare oral examples occur. In contrast to the isolated chancre noted in the primary stage, multiple lesions are typical of secondary syphilis. Spontaneous resolution usually occurs within 3 to 12 weeks; however, relapses may occur during the next year.

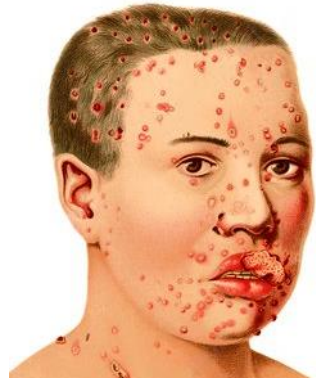

Fig. 6. Secondary syphilis

3.2.3 Tertiary syphilis

It develops 4-8 years later with progressive multi-organ involvement, known as latent syphilis. This period of latency may last from 1 to 30 years; then the third stage known as tertiary syphilis develops in approximately 30% of affected individuals. This stage includes the most serious of all complications. The vascular system can be affected significantly through the effects of the earlier arteritis. Aneurysm of the ascending aorta, left ventricular hypertrophy, aortic regurgitation, and congestive heart failure may occur. Involvement of the central nervous system (CNS) may result in tabes dorsalis, general paralysis, psychosis, dementia, paresis, and death. Ocular lesions such as iritis, chorioretinitis, and Argyll Robertson pupil may occur. Argyll Robertson pupils constrict upon focusing, but they fail to respond to bright light (nicknamed „prostitute's pupil" because they accommodate but do not react).

Less significant, but more characteristic, are scattered foci of granulomatous inflammation, which may affect the skin, mucosa, soft tissue, bones, and internal organs. This active site of granulomatous inflammation, known as a gumma, appears as an indurated, nodular, or ulcerated lesion that may produce extensive tissue destruction. Intraoral lesions usually affect the palate or tongue (sclerosing glossitis). When the palate is involved, the ulceration frequently perforates through to the nasal cavity. The

tongue may be involved diffusely with gumma and appear large, lobulated, and irregularly shaped. This lobulated pattern is termed interstitial glossitis and is thought to be the result of contracture of the lingual musculature after healing of gumma. Diffuse atrophy and loss of the dorsal tongue papillae produce a condition called luetic glossitis. In the past, this form of atrophic glossitis was thought to be precancerous, but several more recent publications dispute this concept.

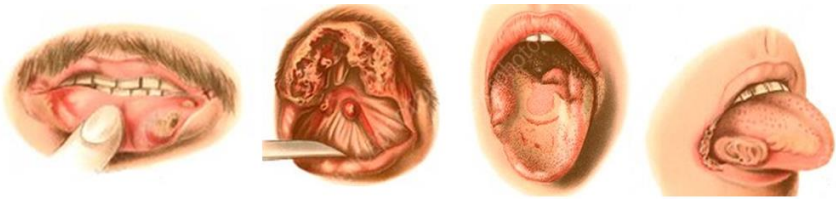

Fig. 7. Tertiary syphilis with an oral gumma

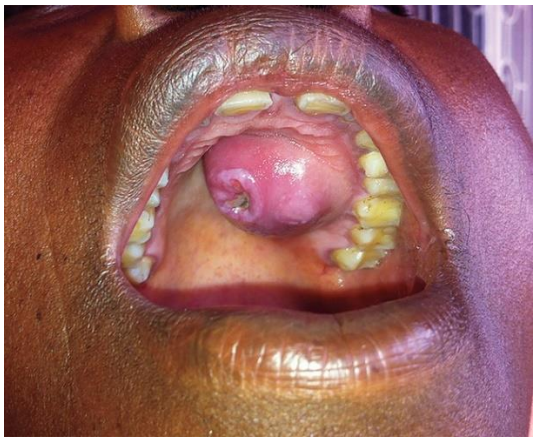

Fig. 8. Tertiary syphilis with an oral gumma

The upper jaw, and more particularly the hard palate, is more frequently involved than the lower one. It may be destroyed by gummas of the floor of the nose or of the mouth, extending from the submucosa and periosteum (nasocranial osteitis of Fournier). The middle of the hard palate is more often attacked, while the sides or the alveolar processes

are less frequently involved. There may be rapid destruction with ulceration, perforation and casting off of sequestrums. The roentgen observations are a loss of bony substance in the turbinate, vomer and hard palate and of the bony markings of the ethmoid and sphenoid sinuses, the degree of loss depending on the location, extent and severity of the process. The lesions may vary from minute changes to destruction of the turbinates, vomer and nasal bones; the entire body of the sphenoid may be destroyed, with death ensuing from extension of infection into the meninges. in the skin. Such manifestations occur in the form of gummatous nodular serpiginous syphilis which spread over large surfaces and which, in healing, leave soft scars with pigmentation and hyperpigmentation. Lesions of long duration, especially on the face, may lead to fearful destruction, the nose often being lost. The lips, eyelids and eyes may suffer, and there may remain for the mouth only scars with a small opening through which nourishment may be taken with difficulty.

3.2.4 Congenital Syphilis

In 1858, Sir Jonathan Hutchinson described the changes found in congenital syphilis and defined the following three pathognomonic diagnostic features, known as Hutchinson triad:

- Hutchinson teeth
- Ocular interstitial keratitis
- Eighth nerve deafness

Like many diagnostic triads, few patients exhibit all three features. In addition to Hutchinson triad, a number of other alterations may be seen, such as saddle-nose deformity, high-arched palate, frontal bossing, hydrocephalus, intellectual disability, gumma and neurosyphilis. Infants infected with syphilis can display signs within 2 to 3 weeks of birth. These early findings include growth impairment, fever, jaundice, anemia, hepatosplenomegaly, rhinitis, rhagades (circumoral radial skin fissures), and desquamative maculopapular, ulcerative, or vesiculobullous skin eruptions. Untreated infants who survive often develop tertiary syphilis with damage to the bones, teeth, eyes, ears and brain. It is these findings that were described well by Hutchinson.

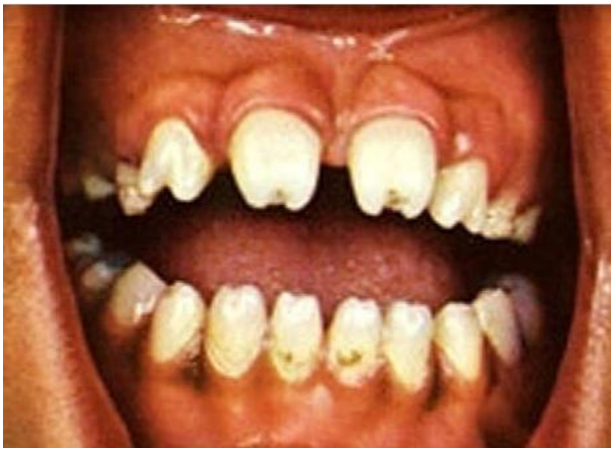

Fig. 9. Hutchinson incisors

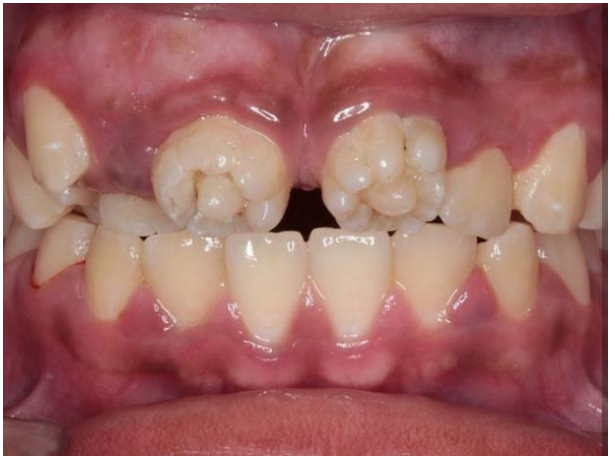

Fig. 10. Mulberry molars

The infection alters the formation of both the anterior teeth (Hutchinson incisors) and the posterior dentition (mulberry molars, Fournier molars, Moon molars). Hutchinson incisors exhibit their greatest mesiodistal width in the middle third of the crown. The incisal third tapers to the incisal edge, and the resulting tooth resembles a straight edge screwd-

river. The incisal edge often exhibits a central hypoplastic notch. Mulberry molars taper toward the occlusal surface with a constricted grinding surface. The occlusal anatomy is abnormal, with numerous disorganized globular projections that resemble the surface of a mulberry.

Worldwide, the prevalence of congenital syphilis has increased fourfold to fivefold over the last 10 years. The World Health Organization (WHO) has stated that the number of congenital syphilis cases worldwide now equals the prevalence of neonatal AIDS, but this problem has received very little attention globally

3.3. Diagnosis

Regardless of the stage of disease and location of lesions, histopathologic hallmarks of syphilis include endarteritis and a plasma cell rich infiltrate. However, lesional histopathology is not diagnostic. Definitive diagnostic methods are dark field examination and direct immunofluorescent tests of lesional exudates that detect presence of Treponema, but are applicable only in presence of primary or secondary lesions. Diagnosis is commonly made by serologic testing; however, no one test is sufficient in itself. The most commonly used screening tests are the Rapid Plasma Reagin (RPR) and the Venereal Disease Research Laboratory (VDRL). These are non-specific, non-treponemal tests that use reagin, cardiolipin-lecithin-cholesterol antigens to test for antibodies against T. pallidum. The most specific serologic tests for syphilis are the fluorescent treponemal antibody absorbed assay (FTA.Abs) and the microhemagglutination assay for antibody to T. pallidum (MHA-TP). These detect antibodies that are produced against treponemal antigens.

3.4. Treatment

Parenteral penicillin G is the drug of choice is for all stages of syphilis. Selection of the ap- propriate penicillin preparation is important, because T. pallidum can reside in sequestered sites like CNS and aqueous humor that are poorly accessed by some forms of penicillin. Penicillin desensitization may be used in patients with known penicillin allergies if necessary. The Jarisch-Herxheimer reaction is an acute febrile reaction

frequently accompanied by headache, myalgia, fever, and other symptoms that usually occur within the first 24 hours after the initiation of any therapy for syphilis. Patients should be informed about this possible adverse reaction. Studies on the efficacy of ceftriaxone and azithromycin as an alternative for the treatment of syphilis in penicillin allergic patients are presently inconclusive, and Center for Disease Control (CDC) guidelines neither support nor refute its use.

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