REVIEW ARTICLE

The Role of Immunopathologic Mechanisms in the Pathogenesis of the Odontogenic Abscesses and the Flegmon of the Maxillofacial Area and the Collum

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Abstract

Pyoinflammatory diseases of maxillofacial area (MFA) are one of the most serious problems of maxillofacial surgery. The high medical and social significance of these diseases are due to their frequent occurrence in persons of working age and the risk of life-threatening complications: Bleeding from the great vessel, brain abscess, the spread of infection into the deep cellular spatium of the collum. In more than 1/3 of all patients, pyogenic lesions of MFA develop on the background of secondary immunodeficiency, accompanied by impaired regulation of the secretion of pro-inflammatory cytokines, and predisposing to prolonged smoldering flow or, on the contrary, rapid spread of inflammation with extensive tissue damage. This fact determines the importance of developing integrated approaches to diagnostics and treatment. The aim of the study is to generalize modern ideas about causative agents and their effect on the features of the inflammatory diseases of the MFA. We systematized and analyzed contemporary works of Russian and foreign authors on the study of the effects of causative agents of bacterial and viral nature and characteristic changes in the immune status. The modern data on the role of microbial factors in the development and maintenance of local and systemic immunological status disorders in case of inflammatory disease of MFA are presented, the impact on the development of bacterial and viral microflora diseases is given, with special attention paid to immunomodulatory effects of causative agents. The factors of pathogens influence most frequently associated with inflammatory diseases of theMFA and collum, as well as the relationship of individual microorganisms with the clinical manifestations of this pathology type and the detection of the pathogenetic role of immune disorders, allow to conduct studies on the formation of optimal correction schemes for each patient (personified) depending on the features of the course of the disease.

Key words: *Aggregatibacter actinomycetemcomitans*, *Campylobacter rectus*, Epstein-Barr virus, herpesviruses, odontogenic abscesses and phlegmon of the maxillofacial area and collum, *Porphiromonas gingivalis*, *Prevotella intermedia*, *Treponema denticola, Tannerella forsythia*

INTRODUCTION

Odontogenic abscesses and phlegmon of the maxillofacial area and collum (MFA and collum) are one of the most serious complications in maxillofacial surgery.

In recent years, the incidence of atypical and complicated course of these diseases has been increasing in Russia. There is a steady increase in their prevalence among people who suffer from drug addiction, HIV infection, and secondary

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immunodeficiencies of another etiology.[1,2] Patients with this pathology are considered to be serious ones since in the first case the process proceeds long and difficult, and in the second they are characterized by an increased probability of developing systemic complications and chronicity. The high medical and social significance of these diseases are due to their frequent occurrence in persons of working age and the risk of life-threatening complications: Spreading to adjacent cellular spatiums, mediastinitis, meningitis, sepsis, bleeding, and brain abscess.[3]

More than half of patients have odontogenic lesions of MFA and collum develop against a background of secondary immunodeficiency accompanied by impaired regulation of the secretion of pro-inflammatory cytokines and predisposing to smoldering slow flow of the disease or, on the contrary, rapid spread of inflammation with extensive damage to tissues.[4,5]

A frequent cause of odontogenic abscesses and phlegmon of the MFA and collum is unqualified dentist actions in the treatment of periodontitis. As a result, complications develop: Periostitis, phlegmons, and osteomyelitis.[6]

One of the main reasons for odontogenic abscesses and phlegmon of the MFA and collum is the late seeking of patients for medical care (3–5 or more days after the onset of inflammation, because under these conditions there is a significant activation of aerobic and anaerobic microflora). This is especially relevant in those regions where a large area has one or two specialized dental facilities, and patients are delivered, to assist, with a significant delay. Kabardino-Balkaria belongs to this region.[6]

The immunological status suffers insignificantly with odontogenic abscesses and phlegmons that capture one cell spatium. However, with major phlegmon or putrefactive necrotic phlegmon, immunological reactivity decreases significantly.[7]

The peculiarities of etiologically significant microbial agents and patient-specific changes in immune status are the topics of most of the works in recent years devoted to the pathogenesis of odontogenic abscesses and phlegmon of the MFA and collum.

The pathogenesis of odontogenic abscesses and phlegmon of the MFA and collum can be objectively considered only taking into account the characteristics of infectious factors and the immune status of the host organism.

The high prevalence and social significance of odontogenic abscesses and phlegmon of the MFA and collum show the importance of searching and developing complex approaches that allow us to understand the logic of the pathological process and to approach the model of personalized medicine.

In this article, we want to make an overview of modern ideas about the significance of abnormalities of local and systemic immune status in the pathogenesis of odontogenic abscesses and phlegmon of the MFA and collum and the role of microbial factors in the development and maintenance of the abovementioned disorders.

According to the available data, in the pathogenesis of odontogenic abscesses and phlegmon of the MFA and collum, in addition to bacteria, a certain role is played by viruses that have a pathogenic effect in the composition of viral-bacterial associations, which enhance local destructive appearance manifestations of inflammation and hinder reparative processes [Figure 1].

Therefore, we have also tried to evaluate the contribution to the development of diseases of both bacterial and viral microflora.

THE ROLE OF BACTERIA IN THE PATHOGENESIS OF ODONTOGENIC ABSCESSES AND PHLEGMON OF THE MFA AND COLLUM

We would like to draw the attention to two important features before consideration the bacteria role in the pathogenesis of odontogenic abscesses and phlegmon of the MFA and collum.

First of all, 96% of cases in dentistry, the cause of odontogenic abscesses and phlegmon of the MFA and collum are affected teeth.[6]

Second, the features of the anatomic conditions of this placement area, the high level of blood supply and innervation, the proximity of vital organs, the presence of fatty tissue, lymph nodes, cell spaces that have a broad connection between themselves and similar mediastinal space formations.[6]

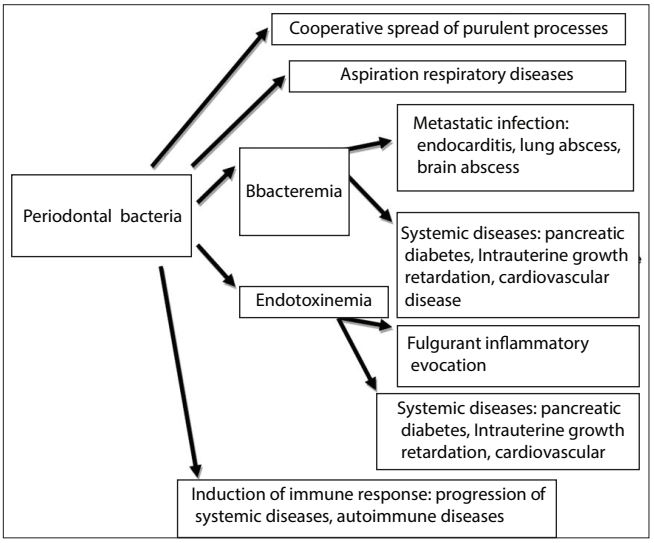

Figure 1: Mechanisms of pathogenic action of periodontal bacteria

The leading aerobic pathogens are alpha-hemolytic streptococci while odontogenic abscesses and phlegmon of the MFA and collum. Among the anaerobic pathogens, the analysis of microflora shows the presence of 90% non-spore-forming microbes in pus.[8] *Peptostreptococcus* spp., *Klebsiella pneumoniae,* and *Prevotella* spp.[8-11]

The presence of anaerobic pathogens in the pus of patients with odontogenic abscesses and phlegmon of the MFA and collum significantly aggravates the course of the inflammatory process and the aspect of a disease. These microorganisms are distinguished by high virulence, toxicity, resistance to the majority of antimicrobial agents. The microbe anaerobe is in the blood, organs, and tissues, when the natural balance of the body is abnormal, causing serious inflammation. Anaerobic sepsis does not have reliable clinical signs.[10]

The important role in the inflammatory processes development of the MFA and collum is played by *Bacteroides*. These are Gram-negative rods that have a polysaccharide capsule, which is one of the important factors of virulence. *Bacteroides* - one of the main representatives of the constant human microflora, from the normal ratio of anaerobic and aerobic bacteria (10:1) in the oral cavity, *Bacteroides*, especially the melaningenicus group, constitute a significant part [11].

According to the reports of Bozhanova *et al.* it is noted that with odontogenic abscesses and phlegmon bacteria, the amount of fusobacteria and campylobacteria is about 60–75%. Aerobes are found more often than anaerobes (aerobic etiology is noted in approximately 60% of cases).[11,12] The etiology of odontogenic abscesses and phlegmon of the MFA and collum has peculiarities in cases when patients have diabetes mellitus (DM). In patients of this group, the most frequent pathogens in this pathology are *K. pneumonia*,[10,12] *Staphylococcus epidermidis*, and *Candida albicans*.[12]

There are at least 12 species of microbes, which are associated cerebral palsy (CP) and its complications as odontogenic abscesses and phlegmon, but none is sufficient for the obligatory development of the disease. There is some uncertainty about which microorganisms are considered significant for pathogenesis.[11,13]

This is due to factors such as:

1. Complex composition of microbiome of subgingival tissues (more than 300 species)
2. Difficulties associated with the standardization of sampling
3. Complexity of cultivation of many pathogenetically significant microorganisms
4. Clinical heterogeneity of CP and its complications.

Thus, odontogenic abscesses and phlegmons of the maxillofacial region and neck are the results of chronic inflammation associated with prolonged infection of the jaw surrounding by soft tissue with bacteria from the heart of CP.[14]

According to the abovementioned, we will consider some of the most important microorganisms involved in the pathogenesis of chronic periodontitis. Normally, in periodontal pockets, bacteria exist in the biofilm, the structure of which protects them from the immune response and limits their proliferation. The most bacteria of a healthy person are Gram-positive. The composition of the local microbiocenosis changes and the dominant role is acquired by Gram-negative bacteria and anaerobes, while chronic periodontitis, as the severity of inflammation increases.

In addition to bacterial pathogens, the important role in the development of chronic periodontitis plays a pathogenic fungus of the genus *Candida*, especially in cases when patients have DM.[15-17]

And so, the most important microorganisms involved in the pathogenesis of chronic periodontitis are *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans (Actinobacillus actinomycetemcomitans), Tannerella forsythia, Prevotella intermedia, Campylobacter rectus,* and *Treponema denticola.*

P. gingivalis

P. gingivalis - Gram-negative anaerobic fixed rod, belongs to the genus *Bacteroides*. It is assumed that *P. gingivalis* has the most pronounced association with chronic periodontitis in comparison with other microorganisms. It is found only in 10% of healthy individuals and in 40–100% of adults with periodontitis.[18-20] The microbe often inhabits deep, less shallow periodontal pockets, and is 4 times more often found in foci of progressive than non-progressive periodontitis.

A. actinomycetemcomitans

A. actinomycetemcomitans - small fixed Gram-negative rods. Phylogenetically, the bacterium is close to *Haemophilus influenzae*. The main factors of its pathogenicity include lipopolysaccharide (LPS) and toxic for fibroblasts thermolabile toxin.[21] There are six serotypes of *A. actinomycetemcomitans* (a, b, c, d, e, and f) having different pathogenetic significance for humans. Thus, association with aggressive periodontitis is characteristic of serotype b. In the case of chronic periodontitis, serotypes c, b, and e are most common. An important factor in the pathogenicity of *A. actinomycetemcomitans* is LPS, which causes local activation of innate immunity due to mechanisms mediated by the transcription factor nuclear factor-κB (NF-κB). LPS interacts with the toll-like receptor 4, which leads to activation of the MyD88 signal protein (the primary response protein of myeloid differentiation 88).[22] According to the data, in addition to innate immunity, the role of adaptive immune mechanisms also plays a role in the pathogenic action of *A. actinomycetemcomitans*.

Thus, after inoculation of *A. actinomycetemcomitans* and specific to antigens of this microorganism of B-cells in rats,

an increase in B-cell secretion of the receptor activator NF-κB ligand and the development of the CP pattern[23] occur.

T. forsythia

In 1979, *T. forsythia*, a microorganism of the *Bacteroides* family, was described. The association of *T. forsythia* with CP is noted, and the causative agent tends to colonize periodontitis in the early stages of CP, is associated with an intensive course of the disease and with refractory to the treatment.

The frequency of sowing of the microbe increases with the transition from mild form to moderate form of the CP. *T. forsythia* is quite demanding on the conditions of cultivation, which is associated with certain difficulties in its study. Pathogenicity factors include LPS, surface O-glycans, and bacterial surface protein A. *T. forsythia* shows a direct damaging effect of the sub-cellular matrix due to the secretion of proteases specific for its components.[20] *T. forsythia* has effective mechanisms of immune evasion. Thus, the terminal carbohydrate motifs of surface O-glycans expressed by *T. forsythia* inhibit bacterial phagocytosis by dendritic cells and inhibit the initiation of a Th17-mediated immune response.[24] It should also be noted that LPS *T. forsythia* is a potent inflammatory agent, stimulates the synthesis of pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor b (TNFb) by gingival fibroblasts.[25] Both TNFb and IL-6 can contribute to tissue damage and osteolysis in purulent diseases of MFA.

P. intermedia

P. intermedia - a Gram-negative fixed anaerobic rod that forms colonies of black color. *P. intermedia* often can be detected with CP, as well as with other periodontal diseases: Aggressive periodontitis, destructive periodontitis, and juvenile gingivitis.[20] The studies show that the outcome of the treatment of chronic periodontitis was worse for foci, where *T. forsythia* and *P. intermedia* could be sown before therapy. In patients with aggressive periodontitis, the microbial load of *P. intermedia* correlates with the loss of the level of clinical attachment.[26] *In vitro* demonstrated that *P. intermedia* LPS causes expression of pro-inflammatory cytokines by gingival epitheliocytes of a gum and human periodontal ligament cells.[27]

C. rectus

The *C. rectus* is associated with chronic and aggressive periodontitis of pregnant and diabetic patients - Gram-negative microaerophilic mobile bacillus.[28-30] The components of *C. rectus* induce the synthesis of pro-inflammatory mediators: Thus, LPS of a cell wall stimulates the synthesis of prostaglandin E2 gingival fibroblasts, the pro-inflammatory cytokines IL-1c and IL-6, and the rectum culture supernatant *C. rectus* induces the synthesis of IL-1b, IL-6, and IL-8 in the culture of human macrophages.[31] In addition, GroEL, a heat shock protein that is part of *C. rectus*, induces secretion by IL-6 gingival fibroblasts.[32]

T. denticola

Among other microorganisms involved in the pathogenesis of chronic periodontitis include *T. denticola*.[33-37] The virulence factors of this bacterium include proteases, in particular, chymotrypsin-like protease, capable of destroying the components of the intercellular matrix of man. The substrates lysed by *T. denticola* include hyaluronic acid, chondroitin sulfate, fibronectin, laminin, and fibrinogen.[38,39] Bacterial proteolytic activity contributes to damage of connective tissue and can create favorable conditions for the further invasion of microorganisms. *T. denticola* is more common in the mild course of the disease, and in severe forms, its presentation decreases.[15]

In Table 1, the main pathogenicity factors of the pathogens are considered. It should be noted that for all pathogens, with the exception of *T. denticola*, the main pathogenetic mechanisms are associated with the effect on the immune system. This is not surprising, given that the main component of the pathogenesis of CP - a violation of the balance of osteolytic and osteoprotective mechanisms - appears to have a largely immune-mediated character.

THE ROLE OF HERPESVIRUS IN THE PATHOGENESIS OF ODONTOGENIC ABSCESSES AND PHLEGMON OF THE MFA AND COLLUM

The leading role in the pathogenesis of odontogenic abscesses and phlegmon of the MFA and collum belongs to bacteria.

However, some evidence emerged that point to the role of viral pathogens in the development of purulent-inflammatory diseases of MFA.[40-44]

The oral cavity and mucous membrane are the main places of the persistence of some human viruses. In particular, many herpesviruses are capable of active replication and persistence in the cells of the epithelium of the oral cavity. Hence, the primary reservoir of the Epstein-Barr virus (EBV of herpesvirus type 4) is the epithelial cells of the salivary glands. The frequency of excretion of EBV with saliva increases with immunodeficiency.

Cytomegalovirus (CMV) - a virus tropic to epitheliocytes of the salivary glands, with localized forms of infection is detected only in the salivary glands. In systemic forms, CMV realizes its lymphotropism, and can persist in organs rich in lymphoid tissue, mainly found in mononuclear phagocytes

Table 1: Factors of pathogenicity of causative agents involved in the pathogenesis of chronic periodontitis

Name of the microorganism	Pathogenicity factors
P. gingivalis	1. Proteolytic cleavage c5ar, cd14, cd4, cd8, icam-1, pecam-1[2,3] 2. Induction of osteoclastogenesis due to cleavage of osteoprotegerin[30,49]
C. rectus	LPS: Stimulation of synthesis by gingival prostaglandin fibroblasts e2, il-1 and il-6[32] Groel: Induces secretion by gingival cells il-6 and il-8[38,45]
T. denticola	Chymotrypsin-like protease: Lysis of the components of the intercellular matrix (hyaluronic acid, chondroitin sulfate, fibronectin, laminin, fibrinogen)[16,17]
A. actinomycetocomitans	1. Activation TLR-4 and myd88: Stimulation of differentiation of blood monocytes into osteoclasts[22] 2. Stimulation of RANKL B-lymphocyte synthesis and activation of osteoclasts[50]
T. forthisia	o-glycans: Inhibition of t1 response[24] LPS: Induction of il-6 synthesis, tnfb by gingival fibroblasts BspA: Induction of the th2 response associated with bone resorption[25] 1. Proteases: Degradation of the intercellular matrix[40]
P. intermedia	LPS: Induction of the synthesis of pro-inflammatory cytokines by gingival epitheliocytes and periodontal ligament cells[30] 1. Enhanced expression of metalloproteinases mmp-2 and mmp-9 with osteoblasts[41]

P. gingivalis: Porphiromonas gingivalis, C. rectus: Campylobacter rectus, T. denticola: Treponema denticola, A. actinomycetemcomitans: Aggregatibacter actinomycetemcomitans, T. forsythia: Tannerella forsythia, P. intermedia: Prevotella intermedia, LPS: Lipopolysaccharide, BspA: Bacterial surface protein A, TLR4: Toll-like receptor 4, RANKL: Receptor activator NF-κB ligand, NF-κB: Nuclear factor-κB

and B-lymphocytes. Most often, both EBV and CMV infection occurs when they contact saliva.[44]

Viral infection in itself does not cause any pathology from the side of the MFA, but local replication of viruses can serve as a provocative or aggravating factor in their development. In recent years, there have been data indicating a possible association of odontogenic inflammatory diseases of the MFA and collum with the reactivation of latent herpesvirus infection. Thus, CMV and EBV DNA are found in the periapical tissue in the areas of periapical periodontitis but is not found in healthy areas.

In one study, of 34 periodontal tissue samples with acute periapical periodontitis, 20 had EBV and CMV, 7 had only CMV, 1 had only EBV, and 6 had none of the viruses. However, more recent studies have shown that in cases of chronic periodontitis the probability of detecting CMV and EBV in the periodontal tissue is lower and is about 50%.[45,46]

The probability of detection in the CMV periodontitis foci is higher in HIV-infected patients[47,48] than in those, who have not HIV infection. More often EBV and CMV are found more often in large pathological foci in comparison with small ones, and more often with chronic granulating periodontitis than with chronic fibrous periodontitis.

There was also a high incidence of detection of HSV-1 in the chronic periodontal foci of the herpes simplex virus (HSV-1), and in two of them, the detection of the virus correlated with the depth of the gingival pockets and the violation of the dentogingival joints.[49,50] However, in other studies, the association of HSV-1 with chronic periodontitis was not noted.

It is important to mention that a significant correlation is found between the level of EBV and CMV in periodontal tissue and saliva of patients with chronic periodontitis.[51] At the same time for CMV foci of chronic periodontitis, apparently, are the main source of virus entry into saliva, since the virus is not detected in the saliva of relatively healthy persons who do not suffer from periodontitis: Patients with gingivitis and in carriers of dentures.

It should be pointed out that after the removal of inflammation in periodontium, there is a significant reduction in the expression of viral DNA in the periodontal tissue and its quantity in the saliva. At the same time, there was no association between the presence of herpesvirus in saliva and the results of endodontic treatment of chronic periodontitis.[52]

CONCLUSIONS

Odontogenic inflammatory diseases of the MFA and neck are widespread in Russia and have a significant socio and economic significance. These diseases are accompanied by marked changes in the microflora of the oral cavity. The best known is connection between odontogenic inflammatory diseases of the MFA and neck with opportunistic bacteria (*P. gingivalis, A. actinomycetemcomitans, T. forsythensis, P. intermedia, C. bacterfectus,* and *T. denticola*), whose action is related to both own damaging mechanisms and to the induction of immune mechanisms that cause tissue damage.

Over the past years, there have been reports of involvement in the pathogenesis of odontogenic inflammatory diseases of

the MFA and the neck of viruses: The HSV, the EBV, etc. Viruses can form associations with representatives of the opportunistic microflora and enhance the immune response in patients.

To improve the diagnostics and to increase the effectiveness of patients treatment of with odontogenic inflammatory processes of the MFA and neck, in particular, odontogenic abscesses and phlegmon, it is of a great interest further to study the relations between changes in the microflora of the oral cavity in chronic periodontitis and immune status disorders in inflammatory diseases of the MFA.

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