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Review

Rheumatoid arthritis and periodontal disease

Jean-Marie Berthelot*, Benoît Le Goff

Service de rhumatologie, Hôtel-Dieu, CHU de Nantes, place Alexis-Ricordeau, 44093 Nantes cedex 01, France

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ABSTRACT

The prevalence of periodontal disease has increased two-fold among patients with rheumatoid arthritis (RA) compared to the general population. This increased prevalence is unrelated to secondary Sjögren's syndrome but instead reflects shared pathogenic mechanisms, including an increased prevalence of the shared epitope HLA-DRB1-04; exacerbated T-cell responsiveness with high tissue levels of IL-17; exaggerated B-cell responses, with plasma cells being the predominant cell type found within gingival tissue affected with periodontitis and B cells being twice as numerous as T cells; RANK overexpression; and an increase in the ratio of RANK-L over osteoprotegerin with a high level of RANK-L expression on gingival B cells, most notably those capable of recognizing *Porphyromonas gingivalis*. Other factors conducive to periodontitis include smoking and infection with the Epstein-Barr virus or cytomegalovirus, which act by promoting the growth of organisms such as *P. gingivalis*, whose DNA is often found in synovial tissue from RA patients. *P. gingivalis* produces the enzyme peptidylarginine deiminase that induces citrullination of various autoantigens, and levels of anti-CCP antibodies are considerably higher in RA patients with than without periodontal disease, suggesting that periodontitis may contribute to the pathogenesis of RA. Further support for this hypothesis comes from evidence that other antigens involved in RA, such as HC-gp39, are also present in gingival tissue. TNFα antagonists slow alveolar resorption but may perpetuate infection of periodontal pockets. Therefore, rheumatology patients, including those taking biotherapies, are likely to benefit from increased referral to dental care (e.g., scaling, root planing and, if needed, dental surgery), particularly as periodontitis is also associated with an increased risk of premature atheroma.

1. Rheumatologists should pay closer attention to the gums of their patients with rheumatoid arthritis

Rheumatologists rarely examine the oral cavity of patients with rheumatoid arthritis (RA). Nevertheless, RA patients are at increased risk for periodontal disease, which develops earlier and is more severe than in the general population [1]. In addition, the last few years have brought disturbing evidence of pathogenic similarities between RA and periodontal disease. Thus, organisms such as *Porphyromonas gingivalis* may play a role in both conditions [2], and similar bone resorption mechanisms may underlie the joint erosions seen in RA and the tooth loss characteristic of periodontitis.

Some degree of periodontitis is found in 75% of adults. Furthermore, evidence of periodontitis is detectable in two-thirds of adolescents, a population characterized by heavy consumption of soft drinks, which promote the growth of the 200 or so bacterial species involved in dental plaque formation. These data indicate a need for frequently referring rheumatology patients to dental care to ensure that appropriate interventions are carried out (scaling, root planing and, if needed, dental surgery).

2. Natural history of periodontitis

The periodontium is composed of the specialized tissues that maintain the tooth in the socket, namely the gingiva, periodontal ligament, and cementum (to which the ligament attaches). Chronic gingival inflammation gradually destroys the periodontium, leading to tooth loss. The first sign is bleeding, which may occur only when a probe is used to measure the depth of the periodontal pockets. A pocket depth of 5 mm or more (stage II) indicates separation of the gingiva from the tooth, which allows penetration into the pocket of dental plaque, scale, food and, more importantly, oral bacteria, all of which exacerbate the inflammation (Fig. 1). The gums swell, recede from the teeth, and bleed readily upon contact. Exposure of the root surface leads to pain in response to heat or cold, as the dentine at the neck of the tooth is highly sensitive. The alveolar bone begins to undergo resorption. Stage III periodontal disease is defined as pocket depth greater than 6 mm. At this stage, bone resorption often leads to detachment of the periodontal ligament followed by abnormal tooth mobility and, eventually, tooth loss.

* Corresponding author. Tel.: +33 240 084 822/801/825.
E-mail address: jean-marie.berthelot@chu-nantes.fr (J.-M. Berthelot).

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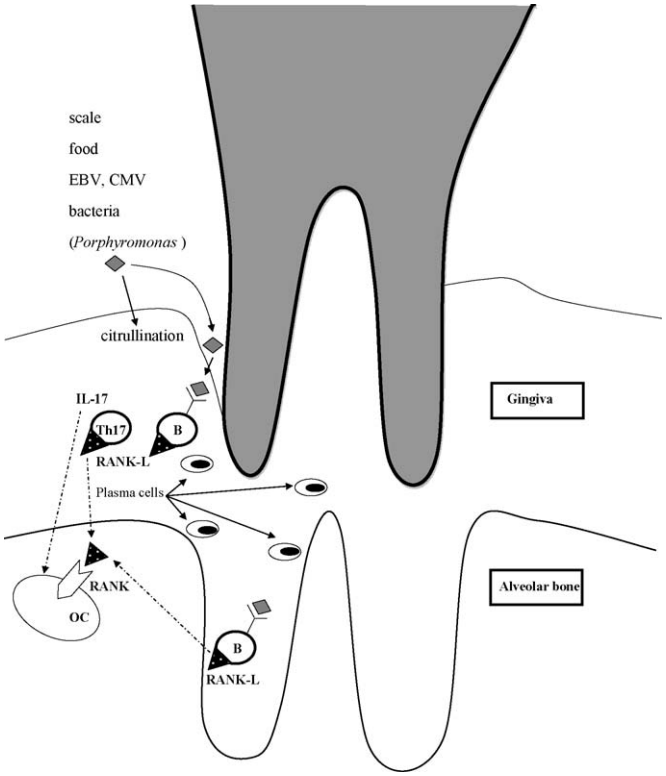

Fig. 1. Food and scale deposit on the neck of the tooth, initiating an inflammatory response. Then, smoking and infection with the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) promote the growth of bacteria such as *Porphyromonas gingivalis*, which can penetrate within the gingival mucosa, leading to the following events: (a) citrullination of some proteins, which may promote loss of tolerance to citrullinated self-antigens in predisposed individuals, most notably during RA; and (b) an immune response, with marked involvement of B cells, which are twice as numerous as T cells (including Th-17 cells that produce IL-17, thereby promoting osteoclastogenesis). B cells specific of some organisms such as *P. gingivalis* probably make a larger contribution than T cells to osteoclast proliferation, most notably via the release of RANK-L. The result is gradual resorption of alveolar bone and eventually loss of teeth via a mechanism similar to that responsible for subchondral bone erosions in RA.

Box 1: Links between periodontitis and rheumatoid arthritis.

-Periodontitis is twice as common and twice as severe in patients with than without RA, and RA patients are twice as likely to become edentulous [6].

-The clinical and radiological severity of periodontitis correlate with those of RA [7,8].

-Risk factors for both conditions are HLA-DRB1-04 [8,9], smoking [40], and infections with the Epstein-Barr virus and cytomegalovirus [41,42].

-Excessive amounts of DNA from oral bacteria such as *Porphyromonas gingivalis* are present in the gingiva of patients with periodontitis [12] and in the synovial membrane from patients with RA [49,50] and may promote citrullination of various self-antigens [51].

-Strong correlation (2.6-fold risk increase) between presence of anti-CCP antibodies and presence of periodontitis in patients with RA [53].

-Presence of Gp-39 (cartilage antigen targeted by the autoimmune response in rheumatoid synovitis) in gingival tissue [54].

-Key role for B cells and plasma cells in chronic inflammation of gingival and synovial tissues.

-Mechanism underlying alveolar resorption similar to the mechanism involved in joint erosions.

3. Increased prevalence and severity of periodontal disease in rheumatoid arthritis, independently from the presence of sicca syndrome

Studies consistently showed that the prevalence of periodontal disease was increased (about two-fold on average) in patients with RA [1,3,4]. Furthermore, disease severity was greater in RA patients [5]. The largest study evaluated 4461 individuals aged 60 years or older, among whom 103 had RA [6]. After adjusting on age, sex, and smoking status, patients in the RA group had about two-fold increases in edentulism (odds ratio [OR], 2.27; 95% confidence interval [95%CI], 1.56–3.31) and periodontitis (OR, 1.82; 95%CI, 1.04–3.20), and the risks of these events were highest in the RA patients with rheumatoid factors [6]. Another study showed that the periodontitis score in RA patients correlated with the erythrocyte sedimentation rate, C-reactive protein level, swollen joint count, and Health Assessment Questionnaire score [7]. Periodontitis is associated with HLA-DRB1-04 in patients with [8] and without [9] RA. In RA patients, joint destruction at the wrists is associated with alveolar resorption ($P < 0.001$), and bone destruction at both sites is associated with the shared epitope (OR, 2.5) [8] (box).

Patients with sicca syndrome exhibit increased cavity formation and high rates of oral lactobacilli and yeast carriage. However, neither the increased prevalence nor the increased severity of periodontal disease in RA is ascribable to secondary Sjögren syndrome, and neither does primary Sjögren syndrome increase the prevalence of periodontitis [3,10,11]. The similar prevalence of periodontal disease in patients with and without sicca syndrome may be ascribable in part to the lack of an association between oral dryness and presence of organisms associated with periodontal disease *(P. gingivalis, Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum, Prevotella intermedia, Treponema denticola, Eikenella corrodens, Campylobacter rectus, Bacteroides forsythus,* and *Streptococcus oralis)* [11]. The similar severity of periodontal disease in patients with and without sicca syndrome suggests that the pathogenesis of periodontal bone resorption may share similarities with that of bone erosions in rheumatoid joints. Further support for this possibility comes from the absence of joint erosions in patients with arthritis related to Sjögren syndrome.

4. Pathogenic factors shared by rheumatoid arthritis and periodontal disease: the immune response, including B-cell overactivity

The gingival tissue affected with periodontitis exhibits increased angiogenesis, which is also a feature in the rheumatoid synovium. Neutrophils are the predominant cell type in both joint fluid and crevicular fluid. However, neutrophils contribute less than 5% of cells in the gingival tissue [12], where other cell types involved in innate and adaptive immunity play a far greater role in perpetuating the inflammatory process and subsequent alveolar resorption. Macrophages [13] release numerous cytokines, thereby promoting vessel hyperplasia (gingival bleeding) and an influx of other cell types involved in immune responses. Then, dendritic cells, most notably those stimulated by *P. gingivalis* [14], promote lymphocyte activation, perpetuating B-cell overactivity [13]. Thus, gingival tissue affected with periodontitis contains a larger proportion of B cells than of T cells [12]. Some of the T cells exhibit a regulatory phenotype (Treg), and the percentage of $CD4^{+}CD25^{+high}$ Treg cells increases with lesion severity and with the proportion of B cells relative to T cells [15]. Despite the presence of Treg cells, the levels of regulatory cytokines such as IL-4 and IL-10 in crevicular fluid from RA patients are usually low, and the lowest levels are found in patients with severe periodontitis.