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Rheumatoid Arthritis and Otolaryngological Findings: Highlights

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Commentary

Ear-nose-throat (ENT) manifestations of connective tissue disorders can be the first manifestation of these disorders and represent a diagnostic challenge for clinicians as they often constitute the initial sign of an otherwise asymptomatic autoimmune disease. Rheumatic diseases have high taxes spread worldwide and the otolaryngological manifestations (auditory, nasal, laryngeal) of this represent a great challenge not only to the generalist physician but also to the ENT doctor and rheumatologist [1,2].

The irreversible destruction of the cartilage, tendon, and bone that comprise synovial joints is the hallmark of both rheumatoid arthritis (RA), affecting approximately 1% of human population, and osteoarthritis (OA) [3]. The effector mechanism, which initially attacks small joints, is T-cell driven. As a result, an aggressive synovial pannus develops, which destroys articular cartilage and bone, leading to massive ankylosis and deformities of peripheral joints [4]. While cartilage is made up of proteoglycans and type II collagen, tendon and bone are composed primarily of type I collagen. RA is a progressive and autoimmune disease afflicting numerous joints throughout the body. The inflammatory cytokines such as interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha) stimulate the production of matrix metalloproteinases (MMPs), enzymes that can degrade all components of the extracellular matrix. The collagenases, MMP-1 (produced primarily by the synovial cells) and MMP-13 (a product of the chondrocytes), play predominant role in RA. In addition to collagen, MMP-13 also degrades the proteoglycan molecule, aggrecan, giving it a dual role in matrix destruction. Expression of other MMPs such as MMP-2, MMP-3 and MMP-9, is also elevated in arthritis and these enzymes degrade non-collagen matrix components of the joints [3,4]. There are numerous rodent models that simulate some or many of the clinical, immunological, or histopathological features of the disease. Recently, it has become a strong working hypothesis that MHC and non-MHC genetic components share loci that are common in various autoimmune diseases, and in corresponding animal models. The most relevant animal models of rheumatoid arthritis appear to be those induced by cartilage matrix components such as type II collagen or proteoglycan aggrecan [4].

A review studied the evidence that rheumatoid arthritis (RA) depends on autoimmunity to articular collagen, and mechanisms whereby autoantibodies to type II collagen (CII). Three major autoantigenic reactants have been identified in RA; the corresponding autoantibodies are rheumatoid factor (RF), antibodies to citrullinated peptide antigens (ACPA), citrullinated peptides (anti-CCP), and anti-type II collagen (anti-CII). Both RF and ACPA are well-validated and predictive markers of severe erosive RA, but cannot be linked to pathogenesis itself. The close resemblances between human RA and collagen-induced arthritis in animals suggest that autoimmunity, and particularly autoantibodies to CII, are important for both the initiation and perpetuation of RA in a dual manner: as contributors to the inflammation associated with immune complex deposition, and as agents with direct degradative effects on cartilage integrity and its repair [5,6].

Another review was concerned of the role of interleukin-17, a proinflammatory cytokine, produced by activated memory $CD4^+$ T cells, in pathogenesis of rheumatoid arthritis. As interleukin-17 shares properties with IL-1 and TNF-alpha, it may induce joint inflammation and bone and cartilage destruction. This cytokine is found in synovial fluids of patients with rheumatoid arthritis. It increases IL-6 production, induces collagen degradation and decreases collagen synthesis by synovium and cartilage and proteoglycan synthesis in cartilage. Interleukin-17 is also able to increase bone destruction and reduce its formation [7].

To date, numerous genetic risk factors leading to RA have been identified including a group of MHC class II alleles, such as HLA-DR4, -DR1 and -DR10 [5]. Shared Epitopes (SEs) which share variants of the Q/R-K/R-R-A-A amino acid motif present in the third hypervariable region of the DRβ1 chain. This component constitutes of the peptide binding groove. Another genetic risk factor for RA patients with ACPA positive is the susceptibility allele 620 W of PTPN22; a gene encodes a tyrosine phosphatase and a gene in the TNF receptor-associated factor 1-C5 (TRAF1-C5) region [8].

Given the global growth of rheumatic diseases, driven by population ageing and exposure to a larger number of inducers of autoimmune changes, the identification of ENT symptoms in these patients can become an important tool of such diseases. Mahdi et al. have discovered that a SE, PTPN22 and smoking showed the strongest association with the anti-citrullinated α-enolase-positive subset and concluded that citrullinated alpha-enolase links smoking to genetic risk factors in the development of RA [8]. It seems that smoking and a SE interaction enhances immunity to various different citrullinated epitopes resulting in the autoimmune response associated with RA. While the molecular mechanisms responsible for the influence of smoking in RA are not fully elucidated yet, some studies have shown an association between RA and toxic compounds found in cigarette smoke, such as 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), nicotine and reactive oxygen species. The correct evaluation of rheumatic conditions, helps the physician to identify signs of disease activity, which directly affects the patients' quality of life and their prognosis [2,8].

A study carried out on 25 patients with classical RA and 16 controls observed the effect of the disease on auditory function by producing conductive hearing loss, abnormal otoadmittance and sensorineural hearing loss [9]. Multi-frequency tympanometry provides more accurate and detailed information about the middle ear dynamics than standard tympanometry. Otosclerosis and rheumatoid arthritis

characteristically increase the resonant frequency (RF) of the middle ear. Ossicular chain discontinuity, atelectatic tympanic membrane, and otitis media with effusion typically decrease the RF of the middle ear. Multifrequency tympanometry can also assess the stage of rheumatoid arthritis in the presence of middle ear involvement [10].

Nose and paranasal sinuses are variably affected during the course of Wegener's granulomatosis, Churg-Strauss syndrome, relapsing polychondritis and sarcoidosis. The cricoarytenoid joint can be involved during the course of rheumatoid arthritis, ankylosing spondylitis and gout; osteoarthritic changes have also been described. A systematic literature review in Medline showed that laryngeal involvement mostly occurs in rheumatoid arthritis (13-75% of patients). It is not uncommon in active and progressive clinical course, though can also occur in silent or inactive connective tissue disorders (CDTs). The cricoarytenoid joint is the most commonly affected site. Common symptoms include throat pain, dyphonia and hoarseness. Careful clinical assessment of the larynx by flexible naso-endoscopy, video-stroboscopy, or direct laryngoscopy, and appropriate imaging are required for pertinent patient management. Stridor is a sign of a life-threatening condition, and may require prompt surgical intervention. However, mild symptomatology may mislead clinicians, and the related diagnosis may be significantly delayed. The current evidence as identified in the present study suggest that laryngeal manifestations of CDTs are often underdiagnosed, due to a range of non-specific symptoms. A multidisciplinary team approach with ENT input is necessary to improve the overall patient management [11].

Temporomandibular joint (TMJ) involvement in rheumatoid arthritis (RA) is not uncommon. In a study with a questionnaire, clinical assessment, and high resolution computerized tomography (HRCT) that were used in 15 patients with rheumatoid arthritis to evaluate the diagnostic criteria of TMJ involvement. The symptoms due to TMJ involvement were present in 33.3% of the patients. Frequency of involvement was 40.0% on clinical assessment but 86.6% with HRCT assessment. All patients with positive clinical findings also had positive HRCT findings [12]. Another study with 43 patients, based on the 1987 criteria of the American College of Rheumatology found that temporomandibular joint involvement was clinically observed in 65.1% of patients, and radiologically in 76.7% of them. The most frequent physical examination finding, a "click" in the joint upon opening of the mouth, was found in almost 50% of the patients. The most frequently observed radiological finding was synovial proliferation seen in 51.1%. A statistically significant correlation was observed between erythrocyte sedimentation rate and the findings on magnetic resonance imaging; between the rheumatoid factor results and physical examination findings; and between the findings of the physical examination and magnetic resonance imaging [13].

It is important to remember that the early identification of these symptoms is critical to the early implementation of an immunosuppressive treatment, reducing the morbidity and mortality of these conditions.

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