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REVIEW ARTICLE

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Laryngeal involvement in rheumatoid arthritis

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Abstract Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting the synovial membrane, which causes joint damage and bone destruction. Extra-articular manifestations are numerous, involving multiple organ systems. Rheumatoid nodules are common extra-articular findings occurring in 20% RA patients. They develop most commonly in pressure areas (elbows and finger joints) and may occasionally affect internal organs including pleura, lungs, meninges, larynx, and others. Furthermore, RA affects the ear, nose, and throat, causing various otorhinolaryngological symptoms. In this report we describe two patients with RA and laryngeal involvement, mostly rheumatoid nodule formation, with a review of the literature.

Keywords Rheumatoid arthritis · Laryngeal involvement · Rheumatoid nodule · Cricoarytenoid joint

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects the synovial membrane, leading to bone damage and joint destruction. It is a progressive and disabling disease causing substantial disability. RA is a systemic disorder with numerous extra-articular manifestations (EAM). They are common, sometimes serious, and most of them are due to serositis, nodule formation or vasculitis [1]. RA also affects the larynx, the ear, and the nose, causing various otorhinolaryngological symptoms. Although the ear and nose involvement in RA is relatively benign and uncommon, laryngeal RA manifestations are much more serious.

The prevalence of laryngeal involvement in RA ranges from 13 to 75% in different series and between 45 and 88% in postmortem studies [2–17]. Laryngeal manifestations of RA involve the cricoarytenoid joint (CJ), the presence of rheumatoid nodules of the vocal cords, amyloidosis and secondary Sjogren's syndrome (SS) affecting the larynx [8]. We describe two cases of RA patients with laryngeal involvement due to CJ arthritis and formation of rheumatoid nodules, with a review of the literature.

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Case 1

A 68-year-old woman with a 19-year history of seropositive RA presented to our outpatient rheumatology clinic in December 2002 because of dysphagia, odynophagia, and hoarseness. Her past medical history included hypertension treated with nifedipine and osteoporosis. The patient was refractory or she did not tolerate at least four disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX), hydroxychloroquine, parental gold salts and D-penicillamine. The current treatment consisted of cyclosporine A (CsA) (200 mg/day) and prednisone (7.5 mg/day). Physical examination showed deforming arthritis involving the wrists, metacarpophalangeal (MCP), proximal interphalangeal (PIP), and metatarsophalangeal (MTP) joints bilaterally. The presence of rheumatoid nodules was noted over the extensor surface of the forearms and olecranon area bilaterally. She was admitted to the hospital, where chest radiograph and computed tomography (CT) scans of the chest were normal. Direct laryngoscopy showed that the CJs were

inflamed and their movements were restricted. The patient was treated with prednisone (60 mg/day) without improvement. Four days later, she developed acute and severe dyspnea and an urgent tracheostomy was performed. Immobilization of the vocal cords due to CJ ankylosis was diagnosed and a rheumatoid nodule of the left arytenoid cartilage was recognized on laryngoscopy. A biopsy of the nodule was performed, which confirmed the diagnosis (Fig.1). The patient was treated with intravenous doses of methylprednisolone (1 g for three consecutive days) with substantial clinical improvement. Her condition gradually improved and when she was last seen in September 2003, she was taking 10 mg/day of prednisone and CsA (200 mg/day) plus leflunomide (20 mg/day).

Case 2

The second patient was a 72-year-old woman with an 18-year history of seropositive RA who presented to our outpatient rheumatology clinic in April 2003 because of hoarseness and cough. Past medical history included brucellosis 40 years earlier and hypertension treated with converting enzyme inhibitors. The patient was refractory to or did not tolerate various DMARDs, including parental gold salts, D-penicillamine and hydroxychloroquine. The current treatment consisted of MTX (17.5 mg/week) and prednisone (5 mg/day). Physical examination revealed a chronic symmetric deforming arthritis involving wrists, MCPs, PIPs, MTPs, knees and the presence of rheumatoid nodules over the extensor surfaces of the hands bilaterally. A chest radiograph as well as a CT scan of the chest revealed no abnormalities. Fiberoptic laryngoscopy showed swelling over the arytenoids and a small rheumatoid nodule of the left vocal cord while the CJs maintained their movements. The patient was treated with oral steroids (prednisone 60 mg/day) with substantial clinical improvement. One month later, her voice was normal and the dose of prednisone was tapered. Two months later a second laryngoscopic examination showed that the rheumatoid nodule had disappeared. The patient was last seen in January 2004, when she was receiving MTX (20 mg/week) and prednisone (10 mg/day).

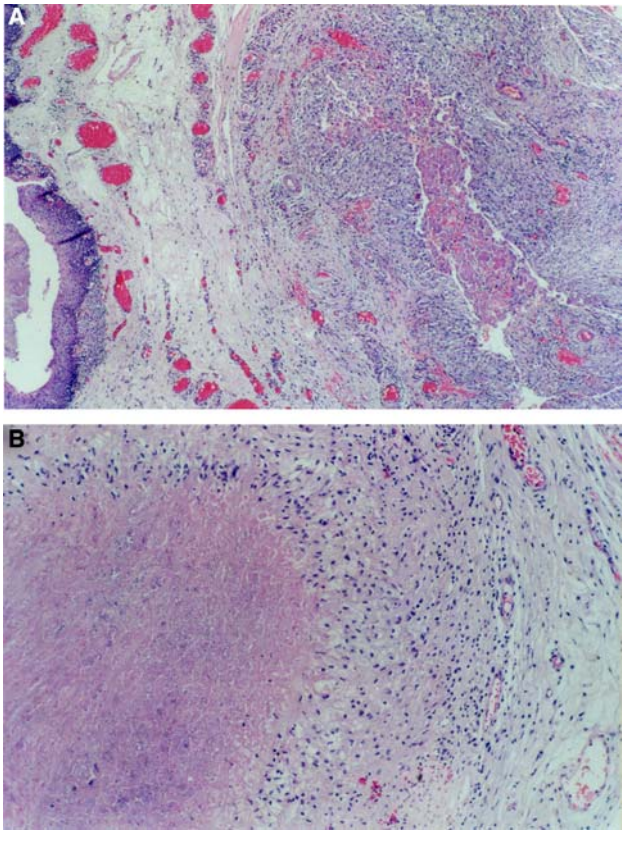

Fig. 1 Laryngeal biopsy specimen. **A** There is formation of a rheumatoid nodule in the lamina propria composed of a central necrotic area surrounded by palisaded histiocytes (H&E×180). **B** The same rheumatoid nodule with extensive necrosis at higher magnification (H&E×320)

Discussion

RA is a chronic inflammatory disease affecting the diarthrodial joints, and it has numerous EAM which augment morbidity and mortality. The prevalence of laryngeal involvement in RA is variable depending on the population studied and the sensitivity of the diagnostic tests used [9]. Laryngeal manifestations of RA were mentioned as early as 1880 by Mackenzie M. [18] and later in 1894 by Mackenzie G.H. [19] although fixation of CJs was recognized before these reports by other investigators. Interest in rheumatoid manifestations of the larynx was newly generated in the early 1950s when Montgomery et al [10] reported the effects of RA in the CJs and Hart and Mackenzie [20] presented a case of bilateral palsy requiring permanent tracheostomy. Subsequent publications included figures of postmortem specimens of the CJ demonstrating the villous synovial proliferation characteristic of rheumatoid synovitis [4, 11, 14]. The first studies began in 1960 with randomly selected patients who underwent clinical and laryngoscopic assessment [4, 14]. Approximately 31% of these patients had symptoms referable to the larynx during the disease course, while 26% had some abnormalities detected by indirect laryngoscopy. Another study published later showed that 43% of the 88 randomly selected patients had some prior symptoms of laryngeal involvement, while 40% had at least one abnormality recognized by laryngoscopy [7]. Using CT to evaluate laryngeal involvement of 45 RA patients, 54% had abnormalities on CT while 32% had other findings confirmed by indirect laryngoscopy [9]. The detection of laryngeal RA manifestations by CT was higher (72%) in another study [21]. However, the true

incidence of laryngeal involvement in RA is unknown. The prevalence ranges from 13 to 75% in various clinical studies and between 45 and 88% in postmortem studies [2–17]. These findings indicate that laryngeal manifestations of RA are common. Furthermore, clinical suspicion and progression in the understanding of the disease are necessary to recognize them. Although the incidence of laryngeal symptoms does not seem to correlate with disease duration, it appears that they are more common in RA patients with severe systemic involvement [4, 10, 22].

Laryngeal manifestations of RA involve CJ arthritis, rheumatoid nodules, and rarely amyloidosis as well as secondary SS affecting the larynx. The CJs consist of the articular surfaces between the cricoid and arytenoid cartilages in the back wall of the larynx held in position by a ligamentous capsule lined by a synovial layer. The CJs are rotated by vibrations from the vocal cords, thus changing the tone of voice. They are diarthrodial articulations and are affected in 17–70% of RA patients [21, 23, 24]. Histological examination of CJs in RA showed synovitis as the earliest change, leading to synovial proliferation, fibrin deposits, formation of pannus on the joint surfaces, erosion of joint cartilage and finally obliteration and ankylosis of the joints. Neural atrophy of the laryngeal muscles and degenerative changes in laryngeal nerves secondary to vasculitis may accompany CJ involvement [8].

The first symptoms of CJ arthritis in the acute stage are often fullness in the throat or a feeling of tension. In addition, hoarseness, odynophagia, or dysphagia (as in case 1) may be present, as well as pain or tension made worse by speaking. Coughing and pain radiating to the ears as well as dyspnea and tenderness are also described [8]. Furthermore, stridor may be the presenting symptom [25, 26]. In addition, stridor and dyspnoea occurring in respiratory infections may cause upper airway obstruction [28–34]. Cricoarytenoid arthritis may cause acute upper airway obstruction in RA as well as in juvenile RA [28–36]. Chronic disease of the CJs may present with recurrent acute symptoms. Husky voice and stridor, which occurs on exertion, with infection or during sleep, are the main symptoms. Patients with CJ ankylosis may develop breathing difficulties after general anesthesia. Laryngeal ankylosis may cause pulmonary and cardiac infection and fatal complications have been reported [37]. Acute and/or chronic disease may be asymptomatic, but signs may be evident on examination.

The clinical diagnosis of CJ arthritis is sometimes difficult and does not always correlate with disease activity [7]. Laryngoscopy, low voltage radiographs and CT are used for the diagnosis of CJ involvement and to exclude other infectious, inflammatory or granulomatous lesions [38]. In the acute phase laryngoscopy reveals bright red swelling over the arytenoids. The vocal cords may appear normal, slightly edematous. Findings in the chronic phase include thickened mucosa over the arytenoids, a narrowed glottic chink, bowing of the vocal cords during phonation and a variable degree of arytenoid fixation [8]. Although radiographs may demonstrate erosive CJ arthritis, CT is considered the method of choice [39]. The main findings include CJ thickening or erosions, arytenoid subluxation and asymmetry of the glottis or aryepiglottic folds. Magnetic resonance imaging (MRI) may also be useful for laryngeal RA assessment. The most difficult differential diagnosis of CJ ankylosis is bilateral paresis of the recurrent laryngeal nerves. A normal electromyogram of the vocal muscles and fixation of CJs on laryngoscopy confirm the diagnosis of ankylosis.

The treatment of CJ arthritis involves parenteral or high per os doses of steroids, or even steroids injected into the joint. Tracheostomy (as in case 1) is performed in chronic cases with severe dyspnea [40–44] and surgery is the radical therapy when indicated [40, 45].

Laryngeal involvement in RA also includes rheumatoid nodules of variable size. They are found mainly in seropositive RA, as are cases 1 and 2. Methotrexate, which is widely used in the treatment of RA, may increase the development of rheumatoid nodules [46]. The patient in case 2 was treated for many years with MTX. Repeated microtrauma may also predispose to rheumatoid nodules. Mostly, rheumatoid nodules are found subcutaneously and their localization in the larynx has been described in a few case reports [4, 47–50]. Hoarseness, coughing, and dysphonia are the main clinical symptoms of laryngeal rheumatoid nodules. The diagnosis depends on a high index of suspicion when the above-mentioned clinical symptoms are present in RA patients, as well as a careful histological examination. Treatment with steroids improves symptoms, while colchicine has been used successfully in some cases [47]. Large rheumatoid nodules may be removed by laryngoscopy.

Amyloidosis secondary to RA is a rare cause of laryngeal manifestation [8]. In addition, secondary SS causes mucosal dryness and may affect the larynx, leading to hoarseness. The patient in case 2 also had secondary SS, which may have contributed to the hoarseness.

Our patients had a long-standing seropositive disease refractory to many DMARDs, and skin rheumatoid nodules. They presented laryngeal involvement consisting of CJ arthritis and rheumatoid nodules, successfully treated with corticosteroids. Indeed, laryngeal involvement of RA occurs mostly in seropositive disease and is associated with EAM; mainly skin rheumatoid nodules, rheumatoid lung and others [4, 22, 28, 40, 47].

In conclusion, laryngeal involvement in RA is rather benign, although sometimes it may be a life-threatening condition. CJ arthritis and rheumatoid nodules are the main laryngeal manifestations. The diagnosis needs a high degree of suspicion. CT, MRI and laryngoscopy are useful tools to achieve an early diagnosis in order to avoid life-threatening consequences. Further prospective, community-based studies concerning the prevalence of ear, nose, and throat involvement in RA are needed.

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