Ear – nose – throat manifestations of autoimmune rheumatic diseases

E.D. Papadimitraki¹, D.E. Kyrmizakis², I. Kritikos¹, D.T. Boumpas¹,³

ABSTRACT

Ear-nose-throat (ENT) manifestations of connective tissue disorders represent a diagnostic challenge for clinicians as they often constitute the initial sign of an otherwise asymptomatic autoimmune disease. Moreover, in patients with known autoimmune rheumatic diseases, ENT manifestations can be overlooked.

Hearing disturbances may be seen in patients with systemic lupus erythematosus, Wegener’s granulomatosis, relapsing polychondritis, polyarteritis nodosa, Cogan’s syndrome, Sjögren’s syndrome, and less frequently in Churg-Strauss syndrome and Adamiadis-Behçet’s disease. Nose and paranasal sinuses are variably affected during the course of Wegener’s granulomatosis, Churg-Strauss syndrome, relapsing polychondritis and sarcoidosis. Recurrent mucosal ulcerations are common in systemic lupus erythematosus and Adamiadis-Behçet’s disease. Nose and paranasal sinuses are variably affected during the course of Wegener’s granulomatosis, Churg-Strauss syndrome, relapsing polychondritis and sarcoidosis. Xerostomia is a common feature of primary and secondary Sjögren’s syndrome; salivary gland enlargement may be also seen in these patients, as well as in patients with sarcoidosis.

The cricoarytenoid joint can be involved during the course of rheumatoid arthritis, ankylosing spondylitis and gout; osteoarthritic changes have also been described. Motility disorders of the upper and/or the lower portions of the esophagus have been reported in patients with dermatomyositis/polymyositis, systemic sclerosis and systemic lupus erythematosus. Trigeminal nerve dysfunction may occur in patients with Sjögren’s syndrome, systemic sclerosis, systemic lupus erythematosus and mixed connective tissue disease. Peripheral facial nerve palsy has been described to complicate the course of Sjögren’s syndrome and sarcoidosis.

Introduction

Ear-nose-throat (ENT) manifestations of rheumatologic disorders represent a diagnostic challenge for the rheumatologist, the otolaryngologist, and the general practitioner. Not uncommonly ENT symptoms represent the initial sign of an otherwise asymptomatic or even undiagnosed autoimmune disorder which often calls for prompt and aggressive immunosuppressive treatment. Moreover, ENT symptoms may be overlooked by the patient or the internist who are usually preoccupied with the main manifestations of the disease. Herein we review the most frequent ENT manifestations of connective tissue disorders with emphasis on what we consider to be helpful diagnostic clues that could facilitate early diagnosis and treatment.

Hearing-audiovestibular disturbances

Immune-mediated inner ear disease (IMIED)

Ear damage has been occasionally reported to complicate the course of various rheumatologic disorders. Immune mediated inner ear disease (IMIED) produces immune mediated sensorineural hearing loss while other manifestations such as vertigo, tinnitus and an occasional sense of auricular fullness complete the clinical spectrum of the disorder. Patients may complain of diminished hearing acuity or decreased sound discrimination. IMIED typically evolves subacutely or with a time course that ranges from a few days to several months. This helps the clinician to distinguish between IMIED and Meniere’s syndrome, which usually follows a more prolonged time course. In addition, IMIED is at least to some extent bilateral (although the two sides can be affected asymmetrically or even asynchronously with the interval be-
between involvement of the two sides reaching one year in rare cases), which is a useful diagnostic tool for the distinction between IMIED and acoustic neuroma. An MRI investigation, however, is usually essential to rule out the diagnosis of cerebellopontine angle lesion – usually a vestibular schwannoma – particularly in the initial stages where no signs of bilateral involvement are clinically evident. Fluctuating symptom patterns over a period of several months have also been described. A subset of patients with disease limited to the inner ear have serum antibodies against a 68 KD inner ear antigen (1). Both unilateral and bilateral sensorineural hearing loss (SNHL) predominantly affecting the middle and high frequencies have been reported in patients with SLE and there is enough evidence to support a strong association between SNHL and the presence of high titers of antecardiolipin antibodies. Subclinical SNHL has been described in more than 22% of patients with SLE by some investigators. Acute audiovestibular failure has also been described in primary antiphospholipid syndrome (APS). There are scarce bibliographic evidence that suggest a potential association between SNHL and acute aortic insufficiency, a rare manifestation of SLE. No correlation between the disease status or the presence of ANA antibodies and the appearance of SNHL has been confirmed. On the other hand, administration of NSAIDs and antimalarial drugs, a common clinical practice in SLE patients, may represent a confounding factor since both categories of medication have been associated with SNHL (2-5). SNHL of the middle and high frequencies and the clinical finding of a patulous eustachian tube have been described in patients with systemic sclerosis (SSc).

Mixed type hearing loss has been reported much less frequently (6). SNHL in the course of Sjögren’s syndrome (SS) is partially attributed to the presence of high titers of antecardi-olipin antibodies (7). Myeloperoxidase (MPO) associated vasculitis has been implicated in the pathogenesis of hearing loss in patients with polyarteritis nodosa (PN) and microscopic polyangiitis (MP). Not uncommonly progressive ear disease – either sensorineural or mixed hearing loss – represents the first manifestation of disease. In these cases the presence of high titres of anti-MPO-ANCA antibody is an extremely useful diagnostic tool (8, 9). Sudden or gradual hearing impairment has been estimated to occur in nearly 50% of all patients with relapsing polychondritis (RP) at some point in their disease. It may take the form of conductive hearing loss (attributed to the expansion of the inflammatory procedure to the middle ear and eustachian tube), sensorineural hearing loss (when vasculitis of the auricular artery or its cochlear branch occurs), or mixed hearing impairment (10).

The most frequent otologic deficit in patients with Wegener granulomatosis (WG) is conductive hearing loss resulting from granulomatous nasopharyngeal involvement, secondary eustachian tube dysfunction and serous otitis media. Serous otitis media results from inflammation and irritation from nasal secretions of the orifice of the eustachian tube. It manifests with conductive hearing loss without pain or signs of acute inflammation, although it is often complicated by recurrent episodes of acute otitis media. Clinical signs include the presence of a concave, lus- tress drum with or without superficial radial vessels and a colourless, yellow or mubby appearance. Some patients also suffer from purulent otitis media with pain, fever, a sensation of pressure in the ear, hearing loss, tympanic hyperperaemia and bulging – in the acute phase – or discharge, and painless hearing loss and central perforations of the tympanic membrane in the chronic forms. SNHL is much less frequent and when it occurs it is typically accompanied by tinnitus without vertigo. Mixed patterns are often seen and the toxic action of inflammatory products from the middle ear or direct granulomatous involvement of the inner ear are considered to be predisposing factors (1). Churg Strauss syndrome (CSS) and Adamantiades-Bechet’s disease (ABD) have been rarely associated with audiovestibular deficits (11, 12).

Cogan’s syndrome is characterized by ocular inflammation – usually intersisstial keratitis – and profound SNHL which results from recurrent episodes of inner ear disease that manifest with Meniere-like attacks and prominent vestibular symptoms such as vertigo, nausea, sensorineural hearing disturbances and ataxia. Various combinations of systemic vasculitic symptoms may coexist. Cardiac valve – particularly aortic valve – involvement is a potentially life-threatening acute complication of Cogan’s syndrome which warrants high clinical suspicion and early intervention (13).

Early detection of IMIED is of critical importance since the timely institution of aggressive corticosteroid therapy is essential for non-reversible hearing loss to be avoided. Meniere’s disease, barotrauma, noise exposure, presbyacousis, viral cocheilitis, ototoxic agents such as aminoglycosides and loop diuretics, meningitis and cerebrovascular ischemia represent other causes of SNHL. Acute or chronic otitis media, tumors of the middle ear, tympanic membrane perforation and lesions of the external ear such as osteomas, squamous cell carcinomas or other tumors, psoriasis and accumulation of cerumen have been accused of causing conduction hearing loss.

The Weber and Rinne tests examine the relative adequacy of air and bone conduction of sound. SNHL is to be suspected if the vibratory sound is louder on the “good” side and conductive hearing loss is to be suspected if the vibratory sound is louder on the “bad” side during the Weber test. A positive Rinne test is normal and a negative Rinne test – occurring when sound is at least equally loud or louder when the fork is placed on bone as compared to when it is held next to the ear – is consistent with conductive loss, particularly if the Weber test lateralizes to the same side (Fig. 1). A tympanogram and an MRI investigation should be used to confirm clinical findings and exclude other diagnoses.

When aggressive treatment is adminis-tered in time, auditory function can be preserved or recovered. A three-month regimen of prednisone which can be progressively tapered by the end of the
The fourth week usually controls disease. If significant improvement has not occurred by the end of the second week or if a relapse occurs during the tapering of corticosteroids, cyclophosphamide may be added to the steroid treatment. If auditory function has not been restored by the end of the 12th week, auditory damage is considered irreversible and treatment stops. Methotrexate has been proposed as an alternative, although less effective, therapeutic agent, preferably when the diagnosis of IMIED has not been securely established and other diagnoses such as Meniere’s syndrome have not been ruled out (1). However, a recent randomized trial including 67 patients with rapidly progressive bilateral SNHL has shown that methotrexate is of no benefit in maintaining the hearing improvement achieved with prednisone therapy (14).

Nose and paranasal sinuses

**Churg-Strauss vasculitis**

Allergic rhinitis is frequently present in patients with Churg-Strauss (CSS) vasculitis. Typical symptoms include seasonal or perennial itching nose, sneezing, and obstructed airflow, which are accompanied by a thin and colorless discharge and in more severe cases by facial pressure, pain, periorbital edema and cyanosis (15). Nasal examination reveals a pale bluish mucosa with turbinate edema; nasal polyposis and subsequent smell disturbances may further complicate the disease. Recurrent sinusitis is a common finding but neither rhinitis nor sinusitis seem to share the destructive pattern seen in WG and RP. Nasal eosinophilia together with a positive history for asthma — usually prominent during the initial phase and present in all patients with fully developed disease — support the diagnosis. Intra-nasal or extra-vascular granulomas and inflammatory lesions rich in eosinophils are the main histopathological features of nasal mucosa in CSS. Peripheral eosinophilia, eosinophilic infiltration of other tissues such as the gastrointestinal tract and lungs, and systemic vasculitic symptoms (malaise, fever, anorexia), pulmonary infiltrates, skin, heart, nervous system and renal disease are all late manifestations of the disease. Anti-neutrophil cytoplasmic antibodies (ANCA), eosinophilia and hypergammaglobulinaemia are helpful diagnostic tools for the clinician to distinguish between a simple atopic predisposition and the presence of active vasculitis (Fig. 2c) (16, 17).

**Wegener’s granulomatosis**

Nasal obstruction caused by diffuse crusting and abundant purulent secretions and bloody nasal discharge or epistaxis suggest active WG. On the other hand, necrosis of the septal cartilage anteceded by vessel destruction of the anterior portion of nasal septum (locus Kiessebachii) may lead to septal perforation, which together with saddle nose deformity caused by massive destruction of the nasal tissue characterize late, although not necessarily active disease. Smell disturbances may occur due to extensive mucosal involvement, while chronic carriage of *Staphylococcus aureus* partially responsive to antibiotics is typical of Wegener disease (18).

Paranasal sin involvement is of major importance in WG. During the acute phase — where a biphasic course of relapsing symptoms of rhinitis together with extreme malaise, high fevers, abundant purulent secretions, headaches and sensitive paranasal sinuses follow an initial subsidal of acute rhinitis — one cannot distinguish between ordinary infection and active vasculitis, not even by CT or MRI investigations. Post-nasal secretion, chronic cough, nasal congestion and concentration disturbances are all suggestive of chronic sinusitis. A friable nasal mucosa with nasal polyps and/or diffuse submucosal nodularity are the most frequent clinical signs.

Persistent, recurrent or worsening...
symptoms usually lead the clinician to a more extensive evaluation. By that time granulomatous lesions and/or diffuse mucosal thickening together with erosion and bony destruction of the septum and turbinates, erosion of the ethmoid sinuses and even complete bony obliteration of the maxillary, frontal and sphenoid sinuses may be apparent in CT scans (Fig. 2a, b) (19). The mastoids are also commonly involved. Granulomas can be detected as low signal intensity lesions on T1 and T2 weighted sequences in MRI scan-nings of the nasal cavity or paranasal sinuses. Intraorbital WG involvement is usually accompanied by paranasal sinus disease and a hypointense signal on a T2 weighted MRI image is helpful in suggesting the diagnosis (20, 21). Nasolacrimal duct obstruction and enlargement of the lacrimal gland can also occur. Histology reveals necrotising granulomatous vasculitis with varying degrees of chronic inflammatory cells (22).

Upper airway abnormalities are frequently present at initial presentation with up to 92-99% of patients developing such symptoms during the disease course (23). Not uncommonly, patients do not have renal or pulmonary involvement in the very initial stage despite the fact that 70%-80% of them will finally present with pulmonary and/or renal disease. Pulmonary nodules and infiltrates may be asymptomatic and renal disease may progress to advanced uremia without overt clinical manifestations. ANCA may be negative in a significant percentage of cases, particularly in the absence of severe disease (23). When atypical/recurrent/persistent episodes of sinusitis occur, a more extensive evaluation including a chest X-ray, serum creatinine and ANCA measurement, urinalysis and finally a biopsy of an involved site should be considered.

CD30, soluble CD26 and soluble CD23 are preferentially expressed in generalized, active disease. A shift of the T cell response from a Th1 pattern in localized disease towards a Th0/Th2 pattern in generalized-vasculitic disease has been reported to occur and may explain the different clinical presentations observed in the same patient or among different individuals (24,25). Localized Wegener’s granulomatosis (LWG) without pulmonary or renal involvement but ANCA-positive and with a compatible histology has been recog-
Various manifestations of disease (26). This further highlights the predisposition of WG for the head and neck region, denoting the frequent referral of such patients to an ENT department and the crucial role of heightened clinical suspicion and serologic confirmation for early diagnosis and treatment.

Relapsing polychondritis
Nasal stiffness with rhinorrhea, crusting and epistaxis can also be seen in patients with relapsing polychondritis. Later, when sustained or recurrent cartilage inflammation has developed, septal perforation and/or saddle nose deformity may occur. As in WG, olfaction can also be compromised. Nasal chondritis is present in 29% of patients with RP at the onset while 53% of them will eventually develop such a lesion (27). Auricular chondritis, non-erosive, asymmetric, migratory polyarthritis, ocular inflammation, respiratory tract chondritis with hoarseness and subsequent infections, cochlear or vestibular dysfunction, and cardiac manifestations often coexist. It is of note that upper and lower airway involvement is sometimes asymptomatic and unrecognized until recurrent secondary infection has occurred.

The most common presenting symptom is auricular chondritis, which is characterized by the sudden onset of pain and swelling, redness and warmth involving the cartilaginous portion of the external ear with sparing of the lobule (Fig.3). Severe relapsing polychondritis with laryngo-tracheal involvement has been associated with ear-piercing; it has been speculated that the commercially used steel studs may become immunogenic after conjugation with protein carriers during the period that they are left in the wounded cartilage (28). Repeated attacks give rise to a soft and floppy appearance of the external ear. The levels of anti-type II collagen (anti-CII) antibodies and urinary type II collagen neoepitope (uTIINE) seem to parallel the severity of the disease and uTIINE has been shown to reflect an enhanced TH1 immune response which is associated with uncontrolled disease (29).

A CT scan to evaluate laryngotracheal involvement is of extreme importance and a thorough cardiologic evaluation to detect valvular lesions and aortic aneurysms is also considered necessary.

Other diseases
Nasal obstruction, rhinorrhea, crusting, necrotising sinus and palatal destruction have been reported to occur in patients with sarcoidosis, sometimes prior to other manifestations such bilateral hilar lymphadenopathy, pulmonary, hepatic, skin and nervous system involvement (30). Nasal septal perforation manifesting with obstruction, epistaxis, post-nasal discharge, whistling and crusting may be seen in patients with SLE or primary antiphospholipid syndrome and is attributed to local ischaemia or inflammation (31). Granulomatous and non-granulomatous infections such as tuberculous and fungal rhinosinusitis respectively, and T-cell lymphomas (Stewart’s granulomas), leprosy, viral warts, carcinoma and sarcoma, have to be included in the differential diagnosis of chronic paranasal sinus disease.

Oral, pharyngeal, laryngeal and esophageal diseases
Oral ulcers
In systemic lupus erythematosus, usually but not invariably painless oral ulcers, characteristically localized on the soft and hard palate (in rare cases these may be found anywhere on the buccal mucosa or the tongue), which occasionally develop a central depression, expand and perforate, represent a common clinical finding. Nasal and genital mucosa may also be involved (31).

Recurrent painful oral ulceration (more than 3 attacks annually) represents an important early manifestation of ABD. Typically extensive and multiple, they are surrounded by erythema and range in size from a few millimeters to 2 centimeters (minor form <1 cm, major form >1 cm). The cheek, tongue, palate and oropharynx are commonly involved sites. Aphthous ulcers of ABD are remarkably persistent and their existence indicates active disease. As they often appear prior to other manifestations of ABD (genital ulceration, uveitis, skin lesions, arthritis, and large vessel involvement such as deep venous thrombosis and arterial aneurysms), the differential diagnosis from simple aphthous stomatitis, herpes simplex virus infection, inflammatory bowel disease, HIV infection and hematologic disorders that cause similar lesions could be difficult and a biopsy is then required. However, six or more ulcers of variable size, surrounding erythema and a predilection for the non-keratinized mucosa of the soft palate and oropharynx should raise the suspicion of ABD (Table I) (32, 33).

Deep, painful mucosal ulcers of the tongue, cheeks, palate and gingiva together with “strawberry gingival hyperplasia” have been described in rare cases to complicate WG (17). Relapsing polychondritis, reactive arthritis and mixed connective tissue disease (MCTD) can also manifest with oral ulcerations (27,34). Topical or systemic corticosteroids, colchicine and even biologic agents such as etanercept have been proposed for the management of severe recurrent aphthous ulcers (35-37).

Xerostomia
Xerostomia is an invariable characteristic of sicca syndrome, which is common in patients with primary or sec-

**Fig. 3.** Chondritis affecting the cartilaginous portion of the right ear of a 48-year-old patient who presented with an earache, asymmetric polyarthritis, tracheitis and an aortic aneurysm. The inflammatory process spares the lobule, a characteristic feature helping in distinguishing between relapsing chondritis and cellulitis of the ear.
Salivary gland enlargement

Salivary gland enlargement is another common manifestation of SS. The parotids and/or submandibular glands are unilaterally or more often bilaterally affected. Glands are firm, non-tender and usually diffusely enlarged on physical examination (lymphoepithelial sialadenitis) (38, 40). Patients with SS have an increased risk of developing salivary gland or extra-salivary lymphoma, and more often marginal zone/MALT lymphoma. Persistent enlargement of the parotid glands, low C4 levels and palpable purpura suggest the potential evolution to lymphoma and should be taken into consideration during the evaluation of parotid gland enlargement (41, 42). In the analysis of unilateral salivary gland enlargement, a neoplasm such pleomorphic adenoma, adenocarcinoma or other primary salivary gland tumor should also be ruled out. Other potential causes of bilateral salivary gland enlargement include viral infections, amyloidosis, lymphoepithelial cysts (HIV-related or not), tuberculosis, leprosy, alcoholism or cirrhosis, hyperlipidaemia and the coexistence of other clinical parameters should be estimated before attributing salivary gland enlargement to SS. Heerfordt syndrome is defined as a combination of bilateral parotid enlargement, anterior uveitis, fever and facial palsy, and is found in patients with sarcoidosis. However, isolated painless, usually unilateral salivary gland enlargement has also been described as a common clinical finding in these patients (43).

Sore throat (pharyngitis)

Sore throat and recurrent episodes of pharyngitis that prove remarkably resistant to ordinary therapeutic regimens have been reported as an important early clinical manifestation of adult onset Still’s disease (ASD). Sore throat was present in approximately 92% of patients who fulfilled the diagnostic criteria for ASD in a large study (44). In a review of 369 cases of ASD in the English literature, 69% of patients presented with persistent sore throat as one of the initial clinical manifestations (45). Arthralgias or arthritis, salmon rash, high fevers and palpable lymphadenopathy may or may not coexist in those early stages but should be anticipated to appear within the next few months in patients with ASD.

Trachitis

Persistent mucosal dryness and defective secretions account for the subacute inflammation that affects the pharynx, trachea and bronchi, thus producing an irritating dry cough in patients with SS. Gastroesophageal reflux disease, asthma, chronic post-nasal drip, chronic bronchitis, bronchectasis and the administration of ACE-inhibitors have to be considered in the evaluation of chronic cough.

Cricoarytenoid arthritis and subglottic stenosis

The cricoarytenoid joint can be potentially affected during the course of various inflammatory arthropathies. Rheumatoid arthritis (RA) is complicated by cricoarytenoid arthritis in 30% of cases. Sore throat, hoarseness and inspiratory stridor are the most common clinical manifestations. Airway obstruction requiring immediate tracheostomy has been described (46). Laryngoscopy reveals redness and oedema, reduced vocal cord motility, unilateral or bilateral vocal adduction, incomplete closure of the posterior commissure (which favors aspiration) and arytenoid cartilage asymmetry. Occasionally a significantly narrowed glottic fissure may also be noticed. Erosion-luxation of the cricoarytenoid joint and surrounding soft tissue swelling can be demonstrated on high resolution (HR) CT scan (47).

Upper airway obstruction due to laryngeal involvement is a rare but well documented complication of SLE, which usually occurs in association with other symptoms and signs that indicate active disease. Bilateral cord immobility can be noticed. Interestingly, SLE cricoarytenoid arthritis is highly responsive to steroid treatment which is usually inadequate for the cricoarytenoid arthritis of RA (48). Ankylosing spondylarthritis (AS) can also affect the cricoarytenoid joint.
Unilateral and very rarely bilateral vocal cord fixation with maintenance of the adducted cord position appear to be late manifestations of uncontrolled disease (49).

Gouty laryngeal arthritis presenting with hoarseness, dysphonia and dysphagia can accompany multiple joint involvement or appear as a single gout manifestation (50). Tophi of the laryngeal soft tissue or vocal cords causing similar symptoms have rarely been reported (51).

Degenerative ulcerations in the cricoarytenoid joint resembling osteoarthritis (OA) may also occur. These structural changes are comparable to OA of the limbs and may lead to impaired arytenoid cartilage movements (and thus impaired vocal quality and reduced vocal activity). In one study 50% of the laryngeal joints in patients over 40 years of age exhibited such degenerative changes (52).

Acute laryngitis, gastroesophageal reflux disease, chronic post-nasal drip, smoking, alcohol use and chronic vocal strain (all potential causes of chronic laryngitis), spasmodic dysphonia, hypothyroidism, vocal cord polyps and nodules, laryngeal palsy (post-thyroidectomy or due to other causes), laryngeal conversion disorders and laryngeal cancer represent some of the etiologic factors of hoarseness and dysphonia that have to be excluded. Severe subglottic stenosis (SGS) causing severe acute dyspnea and requiring tracheostomy has been described in patients with WG. In this set of patients SGS often occurs independently of the disease activity and the type of therapy and seems to be unresponsive to systemic immunosuppressive treatment (53).

**Oropharyngeal dysphagia**

In patients with dermatomyositis (DM) or polymyositis (PM), cricopharyngeal achalasia due to impaired cricopharyngeal muscle activity may cause oropharyngeal dysphagia manifesting as difficulty in swallowing liquids more than solids, dysarthria and dysphonia. The posterior cricoarytenoid muscle is the only muscle keeping the vocal cords in adduction so that when impaired, the vocal cords come together. Thus if the posterior cricoarytenoid muscle is involved, airway obstruction can occur. Oropharyngeal dysphagia may be further complicated by aspiration of the esophageal contents into the airways (54).

Narrowing of the oral aperture, rigidity and thinning of the soft palate, larynx and oral mucosa are responsible for oropharyngeal dysphagia in systemic sclerosis (SSc) (55). Videoesophagography is the most useful diagnostic tool for the evaluation of oropharyngeal dysphagia.

Primary Sjögren’s syndrome has been described to affect the contractility of the upper third of the esophagus (as evidenced by manometric studies), thus inducing symptoms of esophagolaryngeal reflux and dysphagia (Table II) (56).

**Esophageal dysphagia**

Connective tissue disorders can also affect the distal third or the entire esophagus, causing secondary gastro-pharyngeal-esophageal reflux disease (GPERD) or other esophageal motility disorders. GPERD has been implicated as an important causative factor of many serious ENT and other manifestations such as chronic throat clearing, dry cough, sore throat, asthma, globus pharyngeus, dysphagia, cricoarytenoid arthritis, subglottic stenosis following mechanical ventilation, contact ulcers and granulomas or even cancer of the larynx (57). Other commonly described manifestations of GPERD include heartburn, regurgitations and hypersalivation. Interestingly, ENT complaints may be present in the absence of heartburn – the hallmark of GPERD – in up to 60% of cases. Laryngoscopic evaluation reveals diffuse erythema and edema of the posterior portion of the larynx, granulomas and/or ulcerations of the vocal cords and histologically demonstrable esophagitis may or may be not be present.

Involvement of both the upper and lower portion of the esophagus occurs equally in the diffuse and limited subtypes of SSc but is rare in patients with localized scleroderma. Raynaud’s phenomenon affecting the vessels of the esophagus concurrently with Raynaud’s hands, latent neurogenic dysfunction resulting in muscle atrophy and, less importantly, infiltration/replacement of smooth muscle fibers with collagen have all been implicated in the pathogenesis of esophageal dysmotility (58, 59). Esophageal dysphagia of SSc typically takes the form of intermittent,

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**Table II.** Esophageal involvement and secondary ENT manifestations in autoimmune disorders*

<table>
<thead>
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<th>Esophageal disorder</th>
<th>Symptoms</th>
<th>Evaluation</th>
<th>Commonly associated disorders</th>
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<td>Oropharyngeal dysphagia</td>
<td>Prominent difficulty swallowing liquids, dysarthria, dysphonia, aspiration</td>
<td>Videoesophagscopy</td>
<td>DM, PM, SS, SSc</td>
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<tr>
<td>Esophageal dysphagia</td>
<td>Equal difficulty swallowing liquids and solids</td>
<td>Barium swallow, endoscopy, manometric studies</td>
<td>SSc, SLE</td>
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<tr>
<td>GPERD</td>
<td>± heartburn, hypersalivation, regurgitations, dry cough, sore throat, chronic throat clearing, secondary cervical dysphagia</td>
<td>24 hr ph-metry, endoscopy for complications</td>
<td>SSc, DM, PM, SLE</td>
</tr>
</tbody>
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non-progressive dysphagia involving equally solids and liquids and being characteristically accompanied by heartburn. Reflux esophagitis, diffuse esophageal spasm (manifesting with non-cardiac chest pain and intermittent dysphagia), stricture formation, progressive dysphagia concerning predominantly solid foods, and an impressive subsidence of reflux symptoms can all alter the typical initial presentation. Classic manometric findings include an incompetent lower esophageal sphincter, low amplitude contractions of the distal smooth muscle portion of the esophagus and diminished peristalsis of the upper muscle in more severe cases. 24-hour-pH-metry is suggested for both symptomatic and asymptomatic GPERD patients with SSc due to the high prevalence of asymptomatic disease in this population (60). Dermatomyositis (DM) and polymyositis (PM) sometimes cause clinically significant malfunctioning of the smooth muscle of the upper gastrointestinal tract, resulting in profoundly delayed gastric and esophageal emptying, concerning both patients symptomatic for GPERD and asymptomatic patients. Esophageal muscle dysmotility in the course of DM and PM correlates well with peripheral skeletal muscle disease activity (61).

Hypoperistalsis or aperistalsis due to an inflammatory reaction localized to the esophageal muscles (predominantly those of the lower esophagus) or to ischemic vasculitic damage of the Auerbach plexus may or may not be accompanied by esophagitis in patients with SLE, and subclinical or asymptomatic disease has been described in up to 72% of patients in some series (Table II) (62).

**Temporomandibular joint**

Temporomandibular joint syndrome (TMJS) manifests with pain which is usually localized around the ear or the pre-auricular area, may radiate to the ear, jaw, dentures or cervical region and is exacerbated by protracted chewing. Headaches and rarely tinnitus are typical symptoms and crepitus during joint maneuvers, restricted or “guarded” jaw motion, and painful joint swelling can be noticed during physical examination. Although internal derangement due to micro- or macro-traumatic loading represents the most frequent cause of TMJS, the clinician should bear in mind that the temporomandibular joint can be affected during the course of inflammatory arthropathies such as RA, SS, seronegative spondyloarthropathies [ankylosing spondyloarthritis (AS), psoriatic arthritis (PA) and reactive arthritis], and OA(63, 64).

Psychogenic nocturnal bruxism or jaw clenching and malocclusion, dental abnormalities and manipulations, anatomical abnormalities of the temporomandibular joint and even lymphoproliferative disorders, carotidynia, stylohyoid (Eagle’s) syndrome, trigeminal or glossopharyngeal neuralgia and parotid gland disorders, should all be considered during the evaluation of TMJ symptomatology.

Prolonged chewing or talking leads to jaw claudication in patients with cranial giant cell arteritis (GCA). Scalp tenderness, headaches, amaurosis fugax or ischemic optic neuropathy and symptoms of polymyalgia rheumatica such as stiffness and pain in the shoulders and pelvic girdle muscles represent common accompanying manifestations. Physical examination showing thickened, tender, nodular and tender temporal artery with diminished pulses in a 64-year-old patient who presented with dull headaches and scalp tenderness. Histologic analysis showed the presence of arteritis.

**Facial disease**

**Trigeminal nerve**

Trigeminal neuropathy that spares the ophthalmic division of the nerve (thus preserving corneal reflex) and presents with bilateral sensory loss in the face or muscle weakness of the mandibular muscles has been described in patients with SS (69).

Trigeminal neuropathy has also been demonstrated in patients with SSc and MCTD (a multi-systemic disorder with...
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overlapping features of SLE, SSc, and PM). It can be differentiated from them by the presence of high titers of anti-U1-ribonucleoprotein antibodies, representing the most common central nervous system (CNS) manifestation of these disorders (70).

Trigeminal neuralgia (tic douloureux) is a different clinical entity which includes recurrent episodes of unilateral, paroxysmal, brief, lancinating pain that may last from several seconds to hours and radiate to the lips, gingiva, cheeks and jaw. Involuntary contraction of facial muscles – hence the name “tic” – may coexist. Usually there are no abnormal neurological findings. Trigeminal neuralgia has been associated with SLE, SSc and MCTD (71, 72).

Facial nerve

Facial nerve palsy has been shown to complicate the course of many connective tissue disorders. SS and sarcoidosis are the rheumatologic diseases that have been most commonly associated with facial nerve palsy, which accompanies other manifestations of active disease in the majority of cases. In patients with sarcoidosis, peripheral facial nerve palsy can be unilateral or bilateral (simultaneously or sequentially) and recurrent (73). Some other causes of acute facial nerve palsy include Bell’s palsy [possibly due to herpes simplex virus (HSV)] Varicella-Zoster infection (Ramsay-Hunt syndrome) Guillain-Barré syndrome, Lyme disease, acute or chronic otitis media and cholesteatoma of the middle ear. Caution should be exercised in the evaluation of recurrent or permanent facial nerve palsy, which may be the presenting symptom of neoplasms such as parotid and temporal bone malignancy, middle ear paragangliomas, cholesteatomas or other neoplastic lesions affecting the facial nerve.

Acknowledgements

We thank Dr D. Drigiamnakis for the figures illustrating ANCA and Dr A. Voloudaki for the interpretation of the CT scans.

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