# ENT Manifestations in Systemic and Inflammatory Diseases

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## 54.1 Introduction

**Systemic and Inflammatory Diseases** can affect the head and neck regions in a variety of manners. These manifestations may be the initial indications of the systemic disease, or sequela of the established diagnosis. The ENT symptoms and findings may mimic a variety of local illnesses, thus making this distinction an important part of the evaluative process. An awareness of the possible head and neck manifestations of underlying systemic disease is important in a proper diagnosis of the illness with consequent proper management.

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## 54.2 Hereditary Hemorrhagic Telangiectasia HHT (Formerly Osler Weber Rendu)

- It's an autosomal dominant disease.
- Present with multiple telangiectasias of the skin and mucosa.
- **Diagnosis**: Using the Curacao criteria: The HHT diagnosis is Definite if 3 criteria are present, Possible or suspected if 2 criteria are present, and Unlikely if fewer than 2 criteria are present.
  - Epistaxis which is spontaneous and recurrent.
  - Mucosal telangiectasia, multiple, at characteristic sites including lips, oral cavity, fingers, and nose.
  - Visceral lesions such as gastrointestinal telangiectasia (with or w/o bleeding), pulmonary AVM, hepatic AVM, cerebral AVMs, spinal AVM.
  - Family history with a first degree relative with HHT [1].
- **Treatment options showing in** Table 54.1:

## 54.3 Kawasaki Disease

- Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome. It is an acute febrile disease of childhood and is


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**Table 54.1** Treatment options for hereditary hemorrhagic telangiectasia (HHT)

| Medical management | Surgical management |
|---|---|
| Topical moisturizers (mupirocin and saline gel) | Cauterization using laser, bipolar, or radiofrequency |
| Topical or oral estrogen agents | Septodermoplasty |
| Topical timolol | Young's procedure |
| Oral tranexamic acid | |
| Topical or IV bevacizumab (Avastin) | |

characterized by medium-sized arteries' vasculitis with predilection for the coronary arteries. This gives a potential for the development of coronary artery aneurysms and sudden death.

- It is the leading cause of acquired heart disease in developed nations [2, 3].
- **Clinical symptoms**:
  - Fever >5 days and have 4–5 of following symptoms:
  - Acute unilateral non purulent cervical lymphadenopathy with size >1.5 cm.
  - Erythematous desquamative rash of palms and soles.
  - Polymorphus rash.
  - Bilateral painless bulbar conjunctivitis.
  - Erythema of tongue (strawberry tongue—protuberance of papillae), lips, oral cavity.
- **Workup**: KD is a clinical diagnosis.
- Labs: could show elevated CRP and ESR, thrombocytopenia.
- Echocardiography to look for CAAs, 7–20% of the patients will develop coronary artery aneurysms.
- Myocardial infarction within 2–12 weeks of disease onset.

**Treatment**: The main objective is to prevent coronary artery disease. Early administration of IVIG and aspirin within 10 days after the onset of symptoms is the mainstay of treatment to prevent the development of cardiac sequelae [2, 3].

## 54.4 Giant Cell Arteritis GCA Also Known as (Temporal Arteritis)

- It is a vasculitis of unknown etiology. It is the most common vasculitis in adults and it usually affects the older persons and manifest in a wide variety of systemic, neurologic, and ophthalmologic symptoms.
- Classified as a large-vessel vasculitis but typically also involves medium and small arteries, particularly the superficial temporal arteries hence the term temporal arteritis.
- It most commonly affects the ophthalmic, occipital, vertebral, posterior ciliary, and proximal vertebral arteries.
- More common in females, presents >50 years of age.
- Common signs and symptoms include visual disorder, headache, jaw claudication, cervical pain, and scalp tenderness.

**Diagnosis**: Temporal artery biopsy remains the criterion standard for diagnosis of this granulomatous vasculitis.

**Treatment**: Corticosteroids are the mainstay of therapy.

- In steroid-resistant cases, drugs such as tocilizumab, cyclosporine, azathioprine, or methotrexate may be used as steroid-sparing agents.

## 54.5 Cogan's Syndrome

- **Pathophysiology**: unknown, autoimmune etiology, produce Hydrops similar to Meniere's disease.
- **Symptoms**:
- Non-syphilitic interstitial keratitis (blurriness, rapidly progresses to blindness and labyrinthitis (causing SNHL, vertigo, and tinnitus).
- Most patients have typical syndrome of ocular and sudden true vertigo.

- Hearing loss: initial unilateral, high-frequency loss, followed by bilateral and progressive, can become profound.
- If untreated, may lead to profound sensorineural hearing loss and loss of vestibular function.

**Treatment:** corticosteroids, cyclophosphamide, Azathioprine.

## 54.6 Granulomatosis with Polyangiitis (Wegener Granulomatosis)

- Is a rare multisystem autoimmune disease of unknown etiology. Its main features include necrotizing granulomatous inflammation and pauci-immune vasculitis in small- and medium-sized blood vessels.
- Most common granulomatous disease to affect the upper respiratory system.
- Triad of upper/lower airway necrotizing granulomas, systemic vasculitis, glomerulonephritis.
- **ENT manifestations**:
- Chronic sinusitis is the most common initial manifestation; failure to respond to conventional treatment is suggestive for the diagnosis, rhinitis 22%, epistaxis 11%, saddle-nose deformity, serous otitis media and hearing loss and strawberry gingival hyperplasia.
- Stridor, potentially leading to respiratory compromise, from tracheal or subglottic granulomatous masses.
- **Diagnosis**: c-ANCA positive (specificity 90% in systemic vasculitis stage, 65% in granulomatous phase, 30% in remission), and nasal biopsy after thorough removal of nasal crusting.
- **Treatment**:
  - Prednisone 1 mg/kg/day × 4 weeks then taper.
  - Cyclophosphamide 2 mg/kg/day for 6–12 months.
  - IVIG in non-responders.
  - Azathioprine (2 mg/kg/day) for maintenance of remission.

## 54.7 Sarcoidosis

- Is a systemic noncaseating granulomatous condition of unknown etiology which may affect any part of the body.
- Most frequently involves the lungs and intrathoracic lymph nodes, in over 90% of cases.
- It is 10–20 times more common in African-Americans than Caucasians.
- Is a condition of young adults with a peak onset between the third and fourth decades.
- It is more frequent in women than men.
- **Pathophysiology**: There are abnormalities of both the cell-mediated and humoral immune systems. Macrophages and T-cell activation lead to the release of cytokines, including tumor necrosis factor (TNF), with resultant granuloma formation.
- **ENT manifestation**:
- Sinonasal sarcoid is reported in 1–4%.
- Nasal manifestations are almost always part of chronic multisystem sarcoid.
- Nasal symptoms commonly include obstruction, crusting, bleeding, or facial pain.
- The nasal mucosa: a characteristic granular appearance, ‘strawberry skin’.
- The anterior nasal septum is most often affected and may perforate, particularly if traumatized by surgery.
- Patients may present with a soft-tissue mass or expansion of the nasal bridge. This may be associated with thickening and purplish discoloration of the overlying skin known as lupus pernio.
- Salivary gland enlargement is seen in 5–10%.
- Heerfordt’s syndrome (enlarged parotid glands, facial nerve palsy, uveitis and fever).
- The larynx is involved in 1–5% of cases, most commonly the supraglottis (85%), with symptoms of cough, hoarseness, dysphagia, and more rarely stridor.
- Unilateral/bilateral facial paralysis.
- Recurrent bilateral parotid swelling.
- **Diagnosis**: Biopsy with the classic histological appearance: noncaseating granuloma with central epithelioid cells surrounded by lymphocytes and fibroblasts.

- Serum angiotensin-converting enzyme (ACE) is elevated in up to 85% during active disease.
- Serum and urinary calcium levels are elevated in approximately 15% of cases.
- Bi-hilar lymphadenopathy on chest X-ray.

**Treatment**: Include oral corticosteroids, immunosuppressive agents (cyclophosphamide and methotrexate), topical saline rinses and steroids for symptomatic relief and FESS in controlled inflammatory disease.

## 54.8 Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

- It's a small to medium vessel vasculitis, which leads to necrosis, with unknown etiology.
- *American College of Rheumatology criteria for diagnosis*:
  - Asthma.
  - Eosinophilia of more than 10% in peripheral blood.
  - Paranasal sinusitis.
  - Pulmonary infiltrates.
  - Histological proof of vasculitis with extravascular eosinophils.
  - Mononeuritis multiplex or polyneurography.
- *Three clinical phases of disease*:
  - Prodromal Phase with (Asthma and upper respiratory involvement).
  - Peripheral Eosinophilic infiltrative phase with (Pulmonary and GI involvement with eosinophilic tissue infiltration leading to pneumonia/gastroenteritis).
  - Disseminated phase with systemic necrotizing vasculitis affecting (lung, CNS, GI and skin).
- **Diagnosis**: (1) Tissue Biopsy. (2) Labs: p-ANCA positive in 70%.
- **Treatment**: Oral corticosteroids and immunosuppressive agents (such as cyclophosphamide in life-threatening cases or poor prognosis).

## 54.9 Amyloidosis

- Amyloidosis is an idiopathic clinical disorder caused by extracellular and/or intracellular deposition of insoluble abnormal amyloid fibrils that alter the normal function of tissues.
  - Classification of amyloidosis: historical classification systems for amyloidosis were clinically based.
  - Modern classification systems are biochemically based (Table 54.2).

**Table 54.2** Modern classification systems of amyloidosis

| | |
|---|---|
| 1. Based on the cause into: | – Primary: unknown cause; the deposition is in the disease site itself<br>– Secondary: with underlying known disease |
| 2. Based on extent of amyloid deposition: | – Systemic involving multiple organs<br>– Localized amyloidosis involving one or two organs or sites |
| 3. Based on clinical location: | – Pattern I: involves tongue, heart, intestines, skeletal and smooth muscle, skin and nerves<br>– Pattern II: involves liver, spleen, kidney and adrenals<br>– Mixed pattern: involves sites of both pattern I and II |
| 4. Based on tissues in which amyloid is deposited: | – Mesenchymal: organs derived from mesoderm<br>– Parenchymal: organs derived from ectoderm and endoderm |
| 5. Based on the histological basis: | – Peri collagenous: corresponding in distribution to primary amyloidosis<br>– Peri reticulin: corresponding in distribution to secondary amyloidosis |
| 6. Based on precursor biochemical proteins, into a specific type of serum amyloid proteins: | – AL = amyloid light chain<br>– AA = amyloid-associated protein<br>– Aβ2M = amyloid β2-macroglobulin<br>– ATTR = amyloid transthyretin |

**Biopsy**: Using immunocytochemical studies, amyloidosis is diagnosed when Congo red (apple-green birefringence)–binding material is demonstrated in a biopsy specimen.

- **ENT manifestations**:
  - Primary: tongue most commonly involved.
  - localized: larynx most common site of deposition in respiratory tract followed by trachea, can present as subglottic stenosis.

**Treatment**: Immunotherapy and autologous stem-cell transplantation .

## 54.10 Relapsing Polychondritis

- Is an episodic and progressive severe inflammatory condition that involves cartilaginous structures, predominantly those of the ears, nose, and laryngotracheobronchial tree. It may also affect the eyes, cardiovascular system, middle and inner ear, and central nervous system.
- **Head and neck manifestation**:
  - Auricular chondritis: 85–95% of the patients develop auricular chondritis, which presents with unilateral or bilateral auricular pain, swelling, and redness develop suddenly but spare the lobules.
  - Nasal chondritis: it is acute and painful and occurs in almost half of patients with relapsing polychondritis. Mild epistaxis may be present. A saddle-nose may develop in longstanding disease.
  - Respiratory tract chondritis: affects 40–56% of patients, weakens the tracheal cartilage rings, resulting in wheezing, dyspnea, cough, and hoarseness.
  - Inflammation and swelling of the laryngeal tissues may require tracheostomy.
  - Audiovestibular derangements are experienced by 46–50% of patients, usually those with concomitant auricular chondritis. Sudden hearing loss is usually permanent, while tinnitus, and vertigo may subside. In some patients, hearing loss is attributed to vasculitic damage to the eighth cranial nerve.
- **Treatment**: the mainstay of treatment is systemic corticosteroid therapy.

## 54.11 Systemic Lupus Erythematosis

- Is an autoimmune disorder characterized by antibodies to nuclear and cytoplasmic antigens, multisystem inflammation involving (skin, joints, kidneys, blood vessels, nervous system, heart), protean clinical manifestations, and a relapsing and remitting course. More than 90% of cases of SLE occur in women, frequently starting at childbearing age.
- **Head and neck manifestations**:
  - Malar rash (50%)
  - Painful oral mucosal ulcers (25%)
  - Cranial neuropathy (15%)
  - Acute parotid enlargement (10%)
  - Septal ulceration/perforation (3–5)%
  - Telangiectasia
  - Laryngeal/tracheal: vocal cord thickening/paralysis, cricoarytenoid arthritis and subglottic stenosis
  - Chronic xerostomia

## 54.12 Medications Used to Treat SLE Manifestations Include the Following in Table 54.3

**Table 54.3** Medications used to treat systemic lupus erythematosis

| Drug class | Examples |
|---|---|
| Nonsteroidal anti-inflammatory drugs (NSAIDS) | Ibuprofen, naproxen, diclofenac |
| Corticosteroids | Methylprednisolone, prednisone |
| Nonbiologic DMARDS (disease-modifying antirheumatic drugs) | Cyclophosphamide, methotrexate, azathioprine, mycophenolate, cyclosporine |
| Biologic DMARDs (disease-modifying antirheumatic drugs) | Belimumab, rituximab, and/or IV immune globulin |
| Antimalarials | Hydroxychloroquine sulfate |

## 54.13 Rheumatoid Arthritis (RA)

- Rheumatoid arthritis is a chronic systemic inflammatory disease of unknown cause. An external trigger (e.g., cigarette smoking, infection, or trauma) that triggers an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals.
- HLA DR1 and HLA DR 4 most common serotypes associated with RA.
- HLA-linked RA susceptibility locus accounts for <20% RA in the general population.
- **Head and neck manifestations shown in** Fig. 54.1:
- **Treatment:** analgesics and NSAIDs; antirheumatic drugs such as methotrexate.

## 54.14 Behcet's Syndrome

– Behçet disease is a rare vasculitis disorder with the ability to affect small, medium, and large vessels; it is characterized by a triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis.

### 54.14.1 Treatment

– For oral and genital ulcerations, topical steroids or sucralfate solution is the first-line therapy.
– For ocular disease, azathioprine is widely accepted as the initial agent [4].

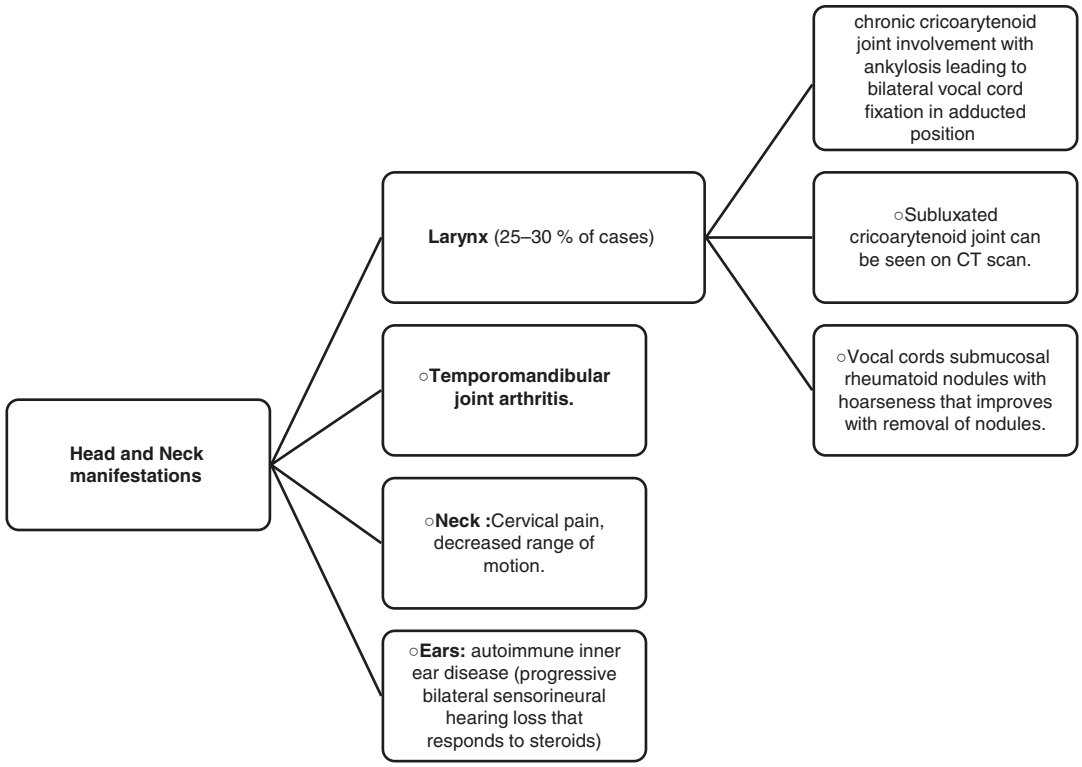


**Fig. 54.1** Manifestation of rheumatoid arthritis in head and neck

## 54.15 Sjogren's Syndrome

– Is the second most common chronic autoimmune connective tissue disorder characterized by xerostomia and xerophthalmia due to profound lymphocytic infiltration into the salivary and lacrimal glands.

### 54.15.1 Classification

– Primary disease in which there are only symptoms and signs affecting the eye and mouth.
– Secondary Sjogren's syndrome in which there is xerostomia, xerophthalmia and associated connective tissue disorder most frequently rheumatoid arthritis or systemic lupus erythematosus.

### 54.15.2 ENT Manifestations

– The xerostomia of Sjogren's syndrome can be profound, giving rise to dysarthria and dysphagia. The oral dryness leads to retention of food on the teeth, mucosa, and gingiva and thus increases the frequency of caries and acute gingivitis.
– Affected patients may have intermittent swelling of the major salivary glands—notably the parotid glands, this often reflects nonspecific inflammatory change within the glands.
– There is an increased risk of non-Hodgkin's lymphoma of the major salivary gland, mainly MALT tumors.

### 54.15.3 Diagnosis

1. Biopsy of minor salivary glands (lips, septum, hard palate).
2. Blood tests:
   - Primary: SS-A/Ro (60%), SS-B/La (30%), HLA-DW3, HLA-B8.
   - Secondary: HLA-DW4.
   - Other positive findings: RF, ANA.

### 54.15.4 Treatment:

1. Local agents, such as salivary substitutes and chewing gum.
2. Systemic agents: as pilocarpine, cevimeline, bethanechol, interferon alpha.
3. Electrostimulation, acupuncture, and dietary supplements.

## 54.16 Myasthenia Gravis MG

- **Pathophysiology**: is a relatively rare acquired, autoimmune disorder caused by an antibody-mediated blockade of neuromuscular transmission, resulting in skeletal muscle weakness. The autoimmune attack occurs when autoantibodies form against the nicotinic acetylcholine postsynaptic receptors at the neuromuscular junction of skeletal muscles.
- Myasthenic weakness typically affects the extraocular, bulbar, or proximal limb muscles. Droopy eyelids or double vision is the most common symptom at initial presentation of MG, with more than 75% of patients.

**ENT Symptoms**: Up to 20% of patients with MG may have prominent oropharyngeal symptoms early in the disease course, including dysarthria, dysphagia, and difficulty chewing.

– Slurred Speech (from weakness of the tongue); it worsens with prolonged talking.
– Swallowing may become difficult, and aspiration may occur with fluids which leads to coughing or choking while drinking. Liquids are more difficult to swallow than the solid food. Because of palatal muscle weakness, patients often complain of nasal regurgitation of liquids.

### 54.16.1 Diagnosis

**Following maneuvers are helpful for diagnosis of MG**:

- Sustained up gaze (1–3 min); results in fatigable ptosis in one or both eyes.

- Counting loud (from 1 to 50): Enhances dysarthria (nasal, lingual, or labial) and results in dyspnea. Patient may sound relatively clear on speaking initially but will become increasingly dysarthric to the point of becoming unintelligible.
- Weakness of the laryngeal muscles results in dysphonia. This can be evoked by asking the patient to say ("eeee") sound for a several seconds.
- Blood test:
  - The anti–acetylcholine receptor (AChR) antibody (Ab) test is highly specific (about 85%)
- **Electrodiagnostic studies** such as repetitive stimulation of a muscle at 2–3 Hz, also known as repetitive nerve stimulation (RNS) and single-fiber electromyography (SFEMG)
- Treatment:
  - **Medial**: Anticholinesterase (AchE) inhibitors such as (pyridostigmine and neostigmine), intravenous immune globulin (IVIg), plasmapheresis and long-term immunosuppression
  - **Surgical**: Thymectomy

## 54.17 Pemphigus Vulgaris

- Pemphigus vulgaris is an autoimmune, intraepithelial, blistering disease affecting the skin and mucous membranes. It is mediated by circulating autoantibodies directed against keratinocyte cell surfaces. A potentially life-threatening disease; it has a mortality rate of approximately 5–15%.

### 54.17.1 ENT Symptoms

- Mucous membranes of the oral cavity are involved in almost all patients (ill-defined, irregularly shaped, gingival, buccal, or palatine erosions, which are painful and slow to heal).
- Erosions may be seen on any part of the oral cavity, and they may spread to involve the larynx, with subsequent hoarseness.

### 54.17.2 Diagnosis

- Histopathology from the edge of a blister.
- Direct immunofluorescence (DIF) demonstrates in vivo deposits of antibodies and other immunoreactants, such as complement. DIF usually shows immunoglobulin G (IgG) deposited on the surface of the keratinocytes in and around lesions.

### 54.17.3 Treatment

- Corticosteroids and immunosuppressants to reduce the inflammatory response and autoantibody production.

### 54.17.4 Scleroderma

- Is a disease characterized by progressive skin hardening and induration.
- Scleroderma is an aspect of systemic sclerosis, which is a systemic autoimmune connective tissue disease that also involves subcutaneous tissue, muscles, and internal organs.
- The risk of systemic sclerosis is much higher in women than in men.
- The peak onset occurs in individuals aged 30–50 years.
- Can be associated with Sjogren's syndrome or **CREST**, which is a limited form of the disease with (calcinosis, Raynaud's phenomenon, esophageal stenosis, sclerodactyly and telangiectasias).
- **Head and neck manifestations**:
  - Difficulty opening mouth secondary to fibrosis of masticatory muscles
  - Nasal cavity telangiectasias leading to epistaxis
  - Esophagus: aperistalsis of lower two-third and esophageal dilation; absent lower esophageal sphincter contraction allowing reflux

**Treatment**: Symptomatic treatment, immunosuppressants (methotrexate, cyclophosphamide) and phototherapy using ultraviolet A (UVA) light.

**Take Home Messages**

- ENT symptoms may represent an early sign of an undiagnosed systemic disorder that often requires immediate and aggressive treatment.
- An otolaryngologist should maintain a high index of suspicion to identify the underlying disease as these may be the only manifestations of the systemic disease in early stages.
- Early and accurate diagnosis with prompt treatment or referral to specialists may prevent morbidity and mortality related to these diseases.

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