Oral Complications of Multiorgan Disorders

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KEYWORDS

• Multiorgan • Systemic disease • Immunosuppresants

KEY POINTS

- Oral manifestations of multiorgan disorders may be the first clinical signs of systemic disease or may signify a new sign of established, recurrent, or refractory disease.
- Stigmata of some of these disorders, such as the "strawberry gingivitis" of granulomatosis with polyangiitis, are pathognomonic, allowing for early detection and intervention. Other disorders, such as IgG4-related disease, require a comprehensive evaluation to establish a definitive diagnosis.
- Clinical manifestations of these diseases are diverse, ranging from isolated mucosal nodules to salivary gland masses. Histopathologic examination, serologic analyses, and other investigations may be necessary to rule out the differential diagnoses.
- Treatment of many of these disorders involves immunosuppressive therapy and the use of biologic agents or adjuvants, many of which have oral side effects.

Amyloidosis

Brief description

Amyloidosis represents a group of acquired or hereditary diseases involving a systemic or localized accumulation of insoluble fibrillar proteins. Modern classification uses an abbreviation of the protein that composes most deposits, prefixed by the letter "A." AL amyloidosis, for example, the most common form of the disease, is caused by deposition of protein derived from immunoglobulin light chain fragments.

AL amyloidosis can occur alone or in association with multiple myeloma, Waldenström macroglobulinemia, or non-Hodgkin lymphoma. AA (serum amyloid A protein) amyloidosis may complicate chronic diseases, such as rheumatoid arthritis or inflammatory bowel disease. Dialysis-related amyloidosis ($A\beta_2$-microglobulin) may be seen in those on long-term dialysis. Transthyretin-related amyloidosis (ATTR) is a hereditary form. Alzheimer disease and orofacial amyloidosis are examples of localized amyloidoses.

Amyloid involvement of the tongue, appearing as macroglossia, is almost universally secondary to systemic disease.[1] In contrast, most cases of amyloidosis affecting the head and neck are localized AL amyloidosis, the most common sites being the larynx, oropharynx, trachea, orbit, and nasopharynx.[2]

Clinical features

Systemic clinical manifestations can include signs and symptoms of heart failure, hepatomegaly, nephrotic syndrome, peripheral and/or autonomic neuropathy (eg, carpal tunnel syndrome), impaired coagulation, and muscular pseudohypertrophy (eg, macroglossia).

Macroglossia can result in indentations from the teeth and protrusion of the teeth resulting in an anterior open bite. Amyloid deposition within the tongue and suprahyoid muscles can result in hypogeusia, dysarthria, dysphagia, dysphonia, dyspnea, and obstructive sleep apnea.[3]

Other manifestations include yellowish, red, blue, or purple papules, nodules, and plaques, petechiae, bullous lesions, vesicles, and ulcers of the oral mucosa; periodontal destruction; and sclerotic lips.[3–7] Infiltration of the salivary glands can result in glandular hypertrophy and xerostomia. Rarely, amyloidosis can present with jaw claudication, temporal area headaches, and visual disturbances.

Dermal involvement in systemic amyloidosis may manifest as a waxy thickening; easy bruising; and subcutaneous nodules, plaques, or purpura developing after minor trauma (characteristically in a periorbital distribution). Localized cutaneous amyloidosis can have a macular, lichenoid, biphasic, or nodular pattern.[8]

Incidence, predilection, genetics

The global annual incidence of amyloidosis is estimated at five to nine cases per million, is highest among adults aged 60 to 80 years, and there is a male preponderance.[9–13]

Hereditary amyloidoses (ATTR and non-TTR) are caused by inheritance of genetic mutations in an autosomal-dominant fashion causing misfolding of amyloid proteins. Some of the

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acquired amyloidoses may also be affected by genetically determined factors.

Histopathology

Tissue biopsy is necessary to confirm the diagnosis in all suspected cases of amyloidosis. The amyloid subtype must then be identified and the extent of systemic involvement determined.

On hematoxylin-eosin examination, amyloid appears as acellular, amorphous, eosinophilic material that accumulates in the lamina propria and in a perivascular manner. Amyloid may also infiltrate and replace minor salivary gland parenchyma and there may be a variable foreign body reaction.[7] Congo red–stained amyloid, examined using polarized light, shows anomalous colors including "apple-green birefringence" (Fig. 1).[14]

In AL amyloidosis, plasma cells may have a normal or atypical morphology; the latter warrants suspicion for multiple myeloma. Further investigation employs immunohistochemical stains, such as in an amyloid panel (ie, kappa and lambda light chains, prealbumin, β_2-microglobulin, and SAA1). The normal kappa/lamba ratio is 2:1. Restricted expression of either kappa or lambda suggests monoclonality and a neoplastic process, such as multiple myeloma.[15]

Differential diagnoses

Consideration for the following differential diagnoses should be entertained based on the shared presenting clinical signs and symptoms:

- Sjögren syndrome (SS): hyposalivation, xerostomia, glandular swelling, or hypertrophy.
- Giant cell arteritis: headaches and visual disturbances, weight loss, fatigue, muscle pain and vascular symptoms including jaw claudication, elevated erythrocyte sedimentation rate, and anemia. Congo red staining of the temporal artery biopsy specimen should be performed to rule out amyloidosis if the initial findings are negative for giant cell arteritis.[16]
- Granulomatosis with polyangiitis (GPA): gingivitis, jaw claudication, airway involvement.
- Macroglossia: neoplasms; acromegaly; idiopathic, traumatic, and iatrogenic causes; tongue enlargement following tooth loss; advanced amyotrophic lateral sclerosis; and lymphangioma or lingual vascular malformations.[17]

Treatment considerations

Treatment of systemic amyloidosis addresses the cause of excess fibril production and ranges from use of high-dose chemotherapy with possible stem cell transplant for multiple myeloma associated with AL amyloidosis, to organ transplant in some hereditary amyloidoses. Localized amyloidosis may be managed symptomatically, depending on the organ involved and the grade of functional impairment.[3]

Surgical intervention may be considered for macroglossia caused by systemic amyloidosis, where there are functional or aesthetic problems; however, tongue enlargement and lesions are likely to recur if cessation of deposition of amyloid is not achieved.[6]

Sarcoidosis including Heerfordt syndrome

Brief description

Sarcoidosis is a nonnecrotizing granulomatous disease of unknown cause that most commonly affects the lungs, skin, lymphatic system, and eyes.

Incidence, predilection, genetics

There is wide geographic and ethic variation in incidence, with increased incidence among persons of Scandinavian, Irish, German, West Indian, African-American, and Afro-Caribbean origin.[18–24]

In the United States, the annual incidence rate among white persons is approximately 10.9 cases per 100,00 but is threefold higher in black patients of African descent at 35.5 cases per 100,000 and is especially high in black women of African descent between the ages of 30 and 39 years at 107 cases per 100,000.[18,19]

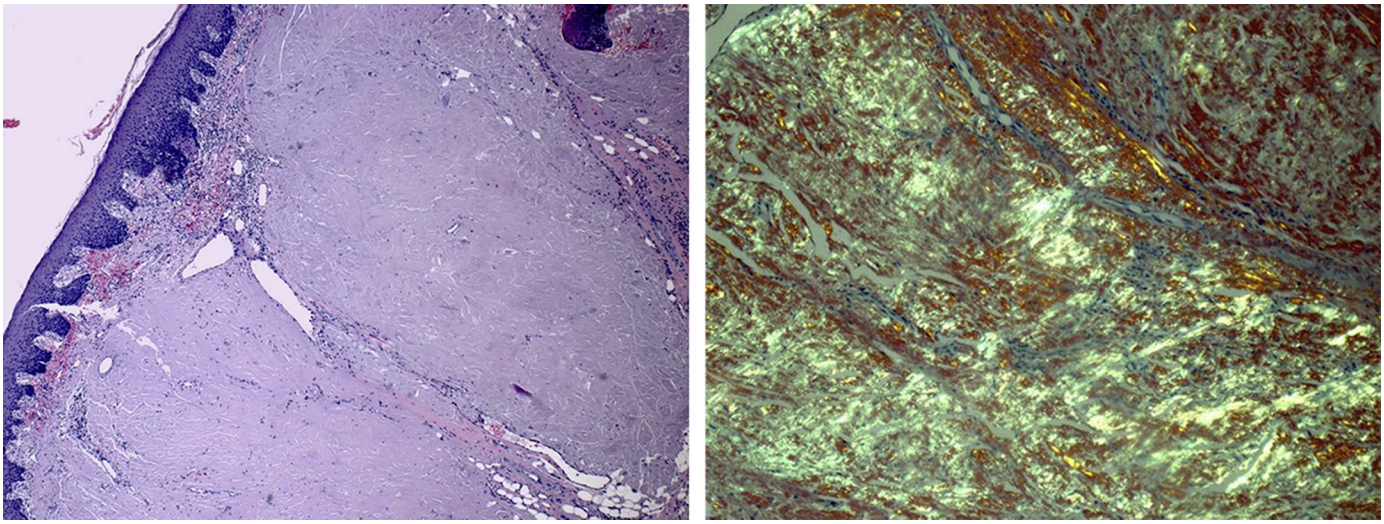

Fig. 1 (*Left*) Oral mucosa demonstrating accumulation of amorphous, eosinophilic material in the lamina propria consistent with amyloid deposition (hematoxylin-eosin, original magnification ×100). (*Right*) Congo red–stained amyloid examined under polarized light showing "apple-green birefringence" (original magnification ×200). (*Courtesy of* Richard Jordan, DDS, PhD, University of California, San Francisco, CA.)