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Amyloidosis: Review and Imaging Findings

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Amyloidosis is a collection of pathophysiologically related disease entities caused by the extracellular deposition of abnormal fibrillar proteins called amyloid. The accumulation of amyloid may be systemic, involving many organs, or localized manifesting as infiltration of individual organs, or in the form of a focal, tumorlike lesion. Amyloidosis may develop in the setting of underlying conditions, usually chronic inflammatory diseases, in which case it is termed secondary, or it may involve no underlying disease and thus be primary or idiopathic. Amyloid infiltration leads to pathology through the disruption of normal tissue structure and function or through cytotoxic effects of intermediate forms of protein aggregates. Clinical manifestations of the disease vary and are nonspecific, increasing the need of imaging during the investigation of the disease. Imaging findings are diverse and not pathognomonic; however, combined with the patient's clinical history they can raise the suspicion of amyloidosis and direct toward its confirmation by biopsy. Radiologists should be familiar with the appearance of amyloidosis in various modalities to aid the early identification of the disease and direct toward prompt treatment planning. Such knowledge would provide the radiologist with an opportunity to contribute to patient care and aid reducing the high morbidity and mortality of the disease.

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Introduction

Amyloidosis' various manifestations share the underlying defect of protein misfolding and extracellular deposition of insoluble protein derivatives.[1] The deposit is formed by three main constituents: (1) a fibrillar protein component prone to aggregation, (2) charged glycosaminoglycans (GAGs) of the extracellular matrix, and (3) the acute phase protein serum amyloid P. The participation of glycosaminoglycans in amyloid (starchlike) formation gives the disease its name, as they stain blue with iodine. Despite the various morphologic and geographic manifestations, all amyloidoses share the same pathognomonic histologic characteristic: an affinity to Congo red stain demonstrating apple-green birefringence under polarized light microscopy and the presence of rigid, 10-12-nm wide non-branching fibrils on electron microscopy, arranged primarily in a β-pleated sheet secondary structure (Figs. 1 and 2).[2]

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The different manifestations of amyloidoses partly depend on the varying behavior of the different fibrillar proteins able to form localized or systemic amyloid deposits in humans.[3] According to the Nomenclature Committee of the International Society of Amyloidosis, the classification of amyloid disease is based on the fibrillar protein component of amyloid among a group of approximately 30 amyloidogenic proteins identified in humans (Table). Such a classification is of vital importance for the exact recognition of amyloid pathophysiology and appropriate management in each case of amyloidosis.[4]

In hereditary and amyloid light chain (AL) amyloidoses, accumulation or aggregation is triggered by mutations that render proteins (ie, transthyretin and immunoglobulin) prone to misfolding. Secondary amyloidosis (AA) and Aβ2-M amyloidosis are characterized by high concentrations of specific proteins such as AA in patients with chronic inflammatory diseases and beta-2 microglobulin in hemodialysis patients. Even concentrations of proteins with a low intrinsic amyloidogenic potential over prolonged periods can lead to amyloid accumulation as in the case of transthyretin in senile amyloidosis.[2] Amyloidogenic precursors typically undergo partial unfolding and assemble into dimeric and then oligomeric aggregates that can have cytotoxic properties.[5] The aggregation of these amyloidogenic oligomers is influenced by

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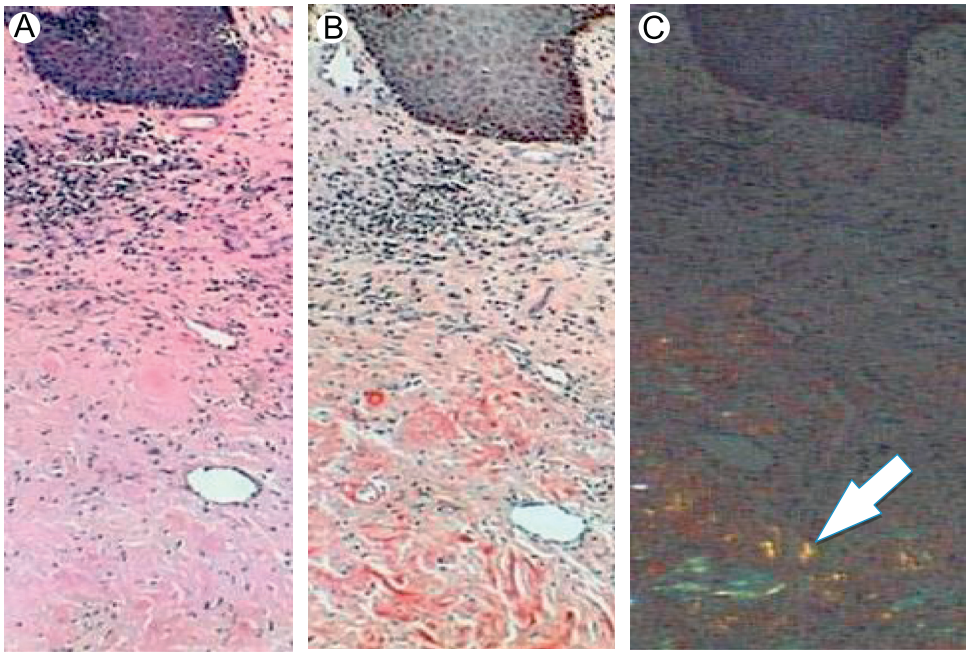

Figure 1 Core biopsy of the tongue in a patient with known involvement. H&E stain (A) shows infiltration of the musculature by pink, collagen-type extracellular material. Congo red stain (B) shows strong affinity for the stain. Same specimen (Congo red) under polarized light microscopy (C) shows apple-green birefringence (arrow), characteristic of amyloid deposition. H&E, hematoxylin and eosin. (Color version of figure is available online.)

local factors (proteolysis, pH, etc.) and leads to cross-β-sheet amyloid fibrils that are 10-12 nm wide.[3]

Amyloidosis can be systemic, affecting more than one organ or tissue type, or less commonly (10%-20% of cases) localized, affecting individual organs such as the intestine and the kidneys.[6] Amyloid deposition becomes clinically significant once the organ function is compromised, either because of cytotoxic effects of prefibrillar aggregates[7] or owing to the replacement of parenchymal tissue by amyloid deposits[3] or by virtue of mass effect. Systemic forms of the disease pose greater

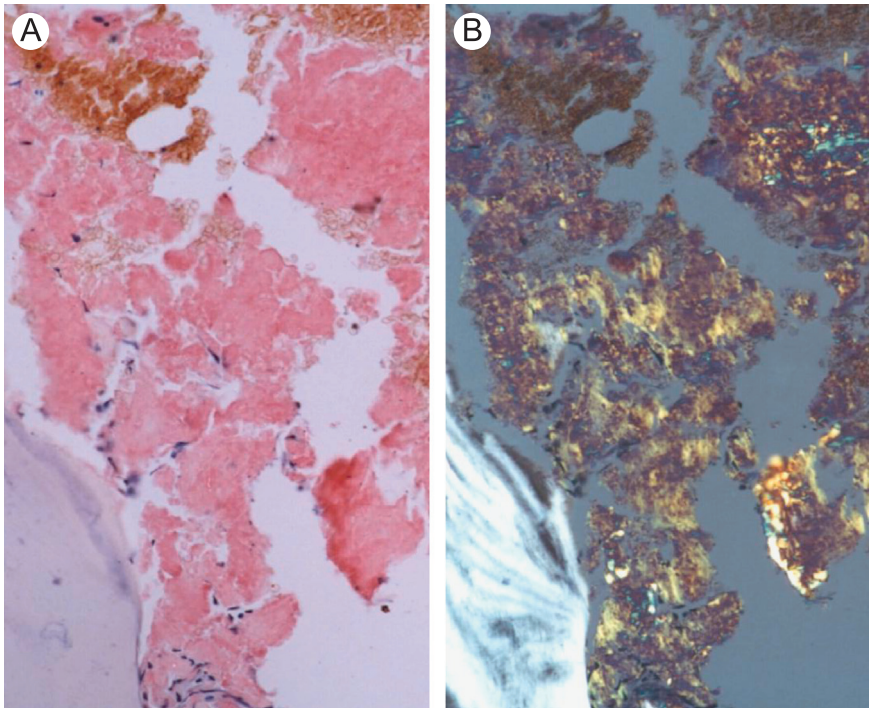

Figure 2 Bone marrow needle biopsy in a patient with primary amyloidosis. Congo red stain (A) shows replacement of the hematopoietic elements by red-staining hyaline-like matrix. Polarized light examination (B) shows the diagnostic green birefringence of amyloid. (Color version of figure is available online.)