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Review Article

Amyloidosis: A cancer-derived paraproteinemia and kidney involvement

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ABSTRACT

Amyloidosis is the general term describing the extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins. There are multiple different human protein precursors of amyloid fibrils. Amyloid deposits are stained using Congo Red and show typical apple-green birefringence in polarized microscopy. Nowadays, a novel technique LMD/MS technique or laser microdissection combined with mass spectrometry help to diagnose amyloidosis. Amyloidosis of the kidney is typically classified as being either one of two types: AL or AA. Less common is the hereditary amyloidosis. Clinical manifestations are usually determined by the type of precursor protein, the tissue distribution, and the amount of amyloid deposition. Renal manifestation is usually present as asymptomatic proteinuria or clinically apparent nephrotic syndrome. In some patients clinical presentation include impaired kidney function with no or mild proteinuria. Patients with renal amyloidosis who progress to end-stage renal disease (ESRD) can be treated with either dialysis or renal transplantation. Diagnosis of amyloidosis is prerequisite to consider treatment options to avoid unnecessary chemotherapy. Treatment of amyloidosis is aimed at decreasing the precursors of fibrillary proteins and/or decrease in synthesis/deposition of amyloid fibrils. It depends upon the type of amyloidosis and cause of excess fibril production.

Contents

1. Introduction

Amyloidosis is the general term used to refer to the extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, many of which circulate as constituents of plasma. These deposits may result in a wide

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range of clinical manifestations depending upon their type, location, and the amount of deposition. It is due to the Janus nature of protein, being in two different forms: fibrils or granules. Soluble precursors undergone conformational changes form amyloid deposits with predominantly antiparallel beta-pleated sheet configuration. There are multiple different human protein precursors of amyloid fibrils.

2. Review

2.1. Past and present of diagnosis of amyloidosis

In 1854 Rudolph Virchow used the term "amyloid," first introduced by Schleiden in 1838 to describe plant starch, to tissue deposits of material that stained as exposed to iodine cellulose [1]. Rokitansky originally described amyloid deposits as "waxy" or "lardaceous", when Virchow showed them to be amorphous and hyaline on light microscopy. Accurate typing of amyloid is necessary since treatments for different types of amyloid are themselves very different. In 1883 Paul Bottinger developed a technique to stain for amyloid deposits using Congo Red, a direct cotton dye and pH indicator. In the 1920s Bennhold introduced polarized microscopy and showed typical apple-green birefringence. The use of thioflavine T, producing an intense yellow-green fluorescence, was popularized in the 1950s. In 1959, electron microscopic examination of amyloid deposits was performed for the first time and showed straight and unbranching fibrils 8–10 nm in width, which may be composed of protofilaments at higher resolution [2,3]. The transmission electron and atomic force microscopy elucidated the three dimensional structure of these macromolecular aggregates and defined folding intermediates, including small oligomers and amorphous aggregates [4]. Additionally, other techniques such as immunofluorescence or immunoenzymatic techniques or by immunoelectron microscopy were used to define the type of amyloid fibril [5,6] (Fig. 1).

Nowadays, a novel technique has come into light in helping to diagnose amyloidosis [7]. It is the LMD/MS technique or laser microdissection combined with mass spectrometry. It is great importance to have access to new techniques as even rare cases that might not have been picked up on regular staining via AA or AL and perhaps even medullary amyloidosis. Thus, in such setting, LMD/MS can sensitively diagnose and type amyloidosis, especially in problematic cases. In this method, ~10-μm-thick sections of formalin-fixed paraffin-embedded tissues are Congo Red stained, and glomeruli with Congo Red deposits are subjected to LMD. The microdissected material collected is analyzed by liquid chromatography electrospray tandem mass spectroscopy. The output includes the total number of mass spectra that can be matched to protein using proteomic software. A higher number of mass spectra denotes greater abundance and will generally provide more extensive amino acid sequence coverage [7].

2.2. Types of amyloidosis

According to the nomenclature given in the editorial in 2014, there is an alphabet soup that one needs to recognize in the various forms of amyloidosis [8].

Amyloidosis is typically classified as being either one of two types: AL [9] or AA [10]. These types are differentiated by their immunofluorescence and immunohistochemistry studies. AL (amyloid light chain) amyloidosis or AH (amyloid heavy chain) amyloidosis are plasma cell diseases and made up of either light chain or heavy chain predominance. AA amyloidosis is usually secondary to chronic illness such as rheumatoid arthritis (RA), familial Mediterranean fever (FMF), infections, and sometimes malignancies like renal cell carcinoma and Hodgkin lymphoma. Besides these two forms, other major forms of amyloid seen clinically include dialysis-related amyloidosis, due to accumulation of beta-2-microglobulin in chronic dialysis patients, typically after 10 or more years on dialysis [11], heritable amyloidoses, age-related systemic amyloidosis and organ-specific amyloid (i.e., isolated bladder amyloidosis, leukocyte cell-derived chemotaxin 2 (LECT2)-associated amyloidosis with liver and kidney involvement, etc.) which also may have kidney involvement [12,13].

Several types of amyloidosis are clearly hereditary, and clinical disease has been linked in most familial forms to missense mutations of the precursor proteins i.e., transthyretin (FAP) (ATTR), cystatin, Apo AI (apolipoprotein AI), gelsolin (Gel), lysosome, fibrinogen Aα chain, Apo AII, LECT2 (?) [12,13]. One should distinguish "hereditary amyloidosis" from "familial amyloidosis". The former is of genetic origin, due to mutation in gene responsible for the synthesis of fibrillary protein such as fibrinogen (Afib) or transthyretin (ATTR), while the latter is found in families due to mutation(s) in genes responsible for protein expression, but not amyloid, including a number of genetic disorders associated with chronic inflammation and deposition of precursor protein in susceptible populations (e.g., pyrin and cryopyrin mutations in FMF, hyperimmunoglobulinemia D syndrome (HIDS), and Muckle Wells syndrome, tumor necrosis factor (TNF) receptor mutations in the TNF receptor associated

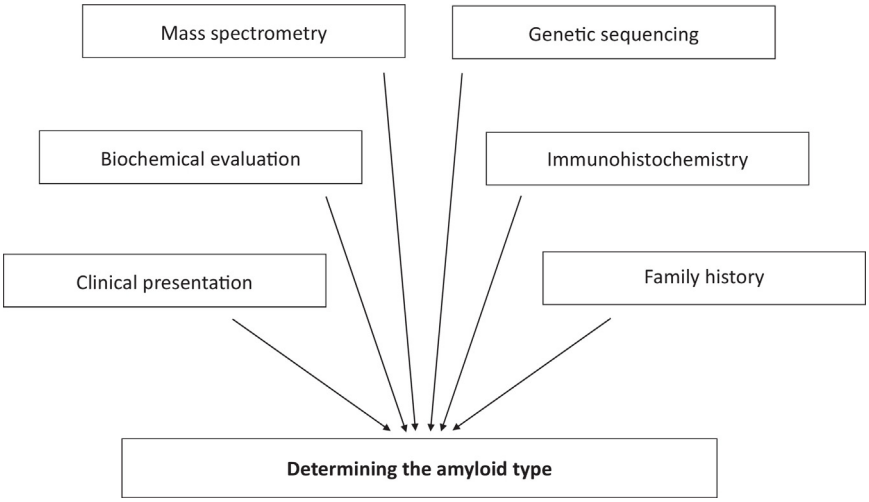

Fig. 1. Methods used to determine amyloid type (modified from Ref. [29]).