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Original Contribution

Abdominal fat pad excisional biopsy for the diagnosis and typing of systemic amyloidosis ☆

Yessica Garcia BS, A. Bernard Collins BS, James R. Stone MD, PhD*

Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

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Summary In the past, the diagnosis and typing of amyloidosis often required an invasive biopsy of an internal organ, such as the heart or kidneys. Abdominal fat pad excisional biopsy (FPEB) offers a less invasive approach, but the sensitivity of this technique has been unclear. To determine the sensitivity of FPEB for immunoglobulin light chain (AL) and transthyretin (ATTR) amyloidosis, we performed a retrospective clinicopathologic analysis of 97 patients who had undergone FPEB, of which 16 were positive for amyloid. The most significant pretest feature predicting a positive FPEB was a serum free light chain κ/λ ratio less than .5, and in this group of patients the probability of a positive biopsy was dependent on the size of the biopsy (P = .004). In FPEBs, the amyloid was present in multiple distinct patterns: pericellular, septal, medium-sized vessel, small vessel, and nodular. For patients with AL amyloidosis for which direct typing was attempted using the FPEB tissue, the amyloid was successfully typed in the FPEB in 90% of cases. The overall sensitivity of FPEB was 79% for AL amyloidosis and 12% for ATTR amyloidosis (P = .0003). In patients with AL amyloidosis, the sensitivity of FPEB was dependent on biopsy size, with small biopsies (≤700 mm^3) having a sensitivity of ~50%, and large biopsies (>700 mm^3) having a sensitivity of ~100%. This study demonstrates that FPEB has high sensitivity for AL amyloidosis, and can be routinely used to type the amyloid. However, FPEB has low sensitivity for ATTR amyloidosis in our patient population.

1. Introduction

Amyloidosis is a disease characterized by the deposition of protein with an abnormal extended β-sheet conformation in tissues throughout the body [1]. There are over 20 types of amyloid based on which protein is misfolding into the abnormal conformation. In the United States, the most common types of systemic amyloidosis result from the misfolding and deposition of either transthyretin (ATTR) or immunoglobulin light chain (AL) [2,3]. AL amyloidosis usually occurs in the setting of a lymphoproliferative disease or plasma cell neoplasm that secretes large quantities of monoclonal immunoglobulin into the blood resulting in an abnormal serum free light chain κ/λ ratio. In contrast, ATTR amyloidosis most commonly occurs in either older men with normal (wild-type) transthyretin gene sequence (ATTRwt) or in patients with an amyloidogenic mutation in the transthyretin gene (ATTRm), but most often in the setting of a normal serum free light chain κ/λ ratio [4].

Systemic amyloidosis due to ATTR or AL most commonly involves the heart, but can involve any tissue. Amyloidosis can be suspected by imaging the heart, by echocardiography,

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* Corresponding author at: Massachusetts General Hospital, 149 13th Street, Room 7368, Charlestown, MA 02129.
E-mail address: jrstone@partners.org (J. R. Stone).

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cardiac magnetic resonance imaging (MRI) or in the case of ATTR, pyrophosphate (PYP) nuclear medicine scan [5,6]. Definitive diagnosis of amyloidosis often involves a tissue biopsy such as from the heart or kidney, which can also be used to directly type the amyloid [7-9]. However, biopsies of internal organs are associated with significant cost and the potential for serious adverse events.

Since systemic amyloidosis can potentially involve any tissue, the subcutaneous adipose tissue in the abdomen may be a less expensive and less invasive source of tissue for diagnosis and amyloid typing. While case studies and a few case series have shown fat pad excisional biopsies (FPEB) to be useful in some patients [10-20], the overall sensitivity of this approach in AL and ATTR amyloidosis has not been clarified. Also, the size of the biopsy necessary for diagnosis has not been determined. To address these questions, we performed a retrospective clinicopathologic analysis of patients who had undergone FPEB in our institution.

2. Materials and methods

2.1. Patients

We searched the pathology database at Massachusetts General Hospital for patients who had undergone abdominal FPEB from 2004 to 2016. The results of the biopsies (positive versus negative) and the sizes of the biopsies were obtained from the pathology reports. Patient age, gender, follow-up interval, assessment of other tissue biopsies for amyloid (ie, heart, kidney or gastrointestinal tract), serum analyses (immunoglobulin free light chain (SFLC) assessment, serum protein electrophoresis (SPEP), and serum immunoelectrophoresis), results of imaging studies (echocardiography, cardiac magnetic resonance imaging, and cardiac PYP nuclear medicine scan), transthyretin gene sequencing, the indication for FPEB, and the results of direct amyloid typing by either immunofluorescence (IF) or mass spectrometry (MS) were obtained from the medical records. Direct typing of amyloid by either IF or MS was performed as described previously [7-9]. The study was approved by the Hospital's human subjects institutional review board.

2.2. Patient group classification criteria

Based on the medical records and pathology specimens, the patients were classified into the following systemic amyloidosis groups. When classifying patients, amyloid in tissue biopsies likely representing isolated amyloidosis such as in cardiac atrial tissue or at sites of monoclonal plasma cell infiltration (ie, amyloidomas) were not considered evidence for systemic amyloidosis.

2.3. AL Amyloidosis Definite

(1) amyloid present on a biopsy and (2) direct typing of the amyloid as AL.

2.4. AL Amyloidosis Probable

(1) κ/λ SFLC ratio less than 0.5 or greater than 5 [8] and (2) either cardiac MRI suggestive of amyloid or amyloid present on a biopsy without direct typing.

2.5. ATTR Amyloidosis Definite

(1) amyloid present on a biopsy and (2) direct typing of the amyloid as ATTR

2.6. ATTR Amyloidosis Probable

(1) amyloid present on a biopsy without direct typing or a cardiac MRI or PYP scan consistent with amyloid, (2) a κ/λ SFLC ratio of 0.5 to 5, and (3) an amyloidogenic *ATTR* mutation or a male over 65 years old.

2.7. AA Amyloidosis Definite

(1) amyloid present on a biopsy and (2) direct typing of the amyloid as AA.

2.8. Systemic Amyloidosis Definite, Undetermined Type

(1) amyloid present on a biopsy, (2) no direct typing available, and (3) either no SFLC analysis available or a κ/λ SFLC ratio of 0.5 to 5 in a patient who is not a male over 65 years old.

2.9. Systemic Amyloidosis Probable, Undetermined Type

(1) no biopsies with amyloid, (2) cardiac MRI suggestive of amyloid, and (3) either no SFLC analysis available or a κ/λ SFLC ratio of 0.5 to 5 in a patient who is not a male over 65 years old.

2.10. Negative for Systemic Amyloidosis

(1) Not meeting the above criteria for definite or probable systemic amyloidosis and (2) either another biopsy (ie, heart, kidney, or gastrointestinal tract) is negative for amyloid or cardiac MRI is negative for amyloid.

2.11. Likely Negative for Systemic Amyloidosis

(1) FPEB negative for amyloid, (2) no other biopsies (ie, heart, kidney, or gastrointestinal tract) for amyloid obtained, (3) cardiac MRI not performed, and (4) echocardiography negative for a speckled pattern of reflectance.

2.12. Presence of Systemic Amyloidosis Undetermined

(1) FPEB negative for amyloid, (2) no other biopsies (ie, heart, kidney, or gastrointestinal tract) for amyloid