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Short Communication

Localized amyloidosis: A diagnostic pitfall in breast pathology*

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ABSTRACT

Amyloidosis is characterized by extracellular deposition of insoluble protein fibrils in a beta-pleated sheet configuration. Breast amyloidosis is a rare entity which has previously been reported to present with localized involvement, or as a late manifestation of systemic amyloidosis. However, descriptions of the clinicopathologic features of localized breast amyloidosis remain limited. A retrospective search for breast amyloidosis diagnosed at our institution yielded 10 cases of breast amyloidosis. All patients were female, with a mean age of 69. Median follow-up for survival or progression was 13 months. Indications for breast or axilla biopsy included mammographic calcifications, mass, and axillary lymphadenopathy. Amyloid showed positive staining with Congo red in all cases, and amyloid typing revealed light chain lambda in 3 cases, amyloid transthyretin in 2 cases, light chain kappa in 1 case, and iatrogenic insulin-derived amyloidosis in 1 case. Amyloid occurred within axillary lymph nodes and alongside both benign and neoplastic breast tissue, including atypical ductal hyperplasia, lobular carcinoma in situ and ductal carcinoma in situ. Most cases were associated with predisposing clinical conditions, including autoimmune disease in 4 cases, B cell lymphomas in 2 cases, and diabetes mellitus treated with insulin in 1 case. In contrast to previously published case series, no patient had clinical evidence of systemic amyloidosis. Amyloidosis of the breast should be considered in the differential diagnosis of all mammographic calcifications and masses of the breast or axilla. When recognized correctly on biopsy, the diagnosis of amyloidosis can not only prevent further unnecessary surgical interventions due to radiology-pathology discordance, but initiate the necessary amyloidosis work-up. Although rare, an awareness of the clinicopathologic characteristics of this easily overlooked entity is of great importance for every practicing pathologist reviewing breast biopsies.

1. Introduction

Amyloidosis is a clinical disorder resulting from the abnormal extracellular tissue deposition of insoluble protein fibrils. Amyloid may be composed of a wide variety of soluble low molecular weight precursor subunits, misfolded in an antiparallel beta-pleated sheet configuration. Structural defects in the protein subunits themselves or in the protein folding and chaperone machinery lead to the emergence of an aggregation-prone state, triggering the process of fibrillogenesis and amyloid deposition, with subsequent end-organ dysfunction [1].

Thirty-six different amyloid precursor proteins have been described in humans to date [2].

The most common and clinically significant forms are associated with underlying systemic disease, and commonly present with systemic involvement of organs such as the kidney, heart, gastrointestinal tract and tongue. These include primary immunoglobulin light chain (AL) amyloidosis, which is frequently associated with plasma cell neoplasms. Serum amyloid A (AA) amyloidosis is a complication of chronic inflammatory and autoimmune disease. Underlying causes of AA amyloidosis also include inborn errors of metabolism such as alkaptonuria, where chronic inflammation is secondary to oxidative stress caused by accumulation of homogentisic acid and benzoquinone acetic acid [3]. Beta-2 microglobulin amyloidosis is associated with chronic dialysis [4]. Amyloid transthyretin presents as an age-related accumulation of wild-type protein, or as a heritable transthyretin-related familial amyloidosis associated with accumulation of mutant transthyretin aggregates [5].

Amyloidosis may also less commonly present with localized involvement of a wide variety of tissues, including lymph nodes, urothelium, skin, lung and larynx [6]. Localized cutaneous involvement commonly presents with deposits of intermediate keratin filament (AK) amyloid [7], and pharmacotherapy-associated forms of amyloid associated with the injection of insulin [8] or the HIV fusion inhibitor enfuvirtide have also been described [9]. Other localized organ deposits

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Table 1
Case Demographics and Clinicopathologic Features.

Case	Age	Sex	Specimen	Indication	Type	Amyloid Typing	Previously diagnosed predisposing disease	Associated pathologic findings	Followup
1	64	F	Axillary lymph node biopsy	Axillary lymphadenopathy	AL lambda	LC MS/MS	Nodal marginal zone lymphoma, status post chemotherapy	Small B cell lymphoma with prominent plasmacytic differentiation	2.9 years
2	62	F	Breast biopsy	Calcifications	AL kappa	LC MS/MS	None	Benign fibrocystic change	None
3	84	F	Breast biopsy	Calcifications	ATTRv	LC MS/MS	None	Atypical ductal hyperplasia, bordering on ductal carcinoma in situ	2 years
4	51	F	Breast biopsy	Calcifications	AL lambda	LC MS/MS	Systemic lupus erythematosus	Benign fibrocystic change	12 months
5	71	F	Breast biopsy	Mass	AL lambda	LC MS/MS	None	Low grade B-cell lymphoma with plasmacytic differentiation	12 months
6	67	F	Breast biopsy	Calcifications	N/A	None	Sjogren syndrome, status post renal allograft	Benign breast tissue	13 months
7	78	F	Mastectomy	Calcifications	N/A	None	None	High grade ductal carcinoma in situ with comedonecrosis, lobular carcinoma in situ	None
8	78	F	Partial mastectomy	Mass	ATTR	IHC	Polymyalgia rheumatica	N/A	10.1 years
9	73	F	Partial mastectomy	Mass	N/A	None	Rheumatoid arthritis	N/A	5.5 years
10	66	F	Axillary lymph node biopsy	Axillary lymphadenopathy	alnsulin	LC MS/MS	Diabetes mellitus treated with insulin	N/A	6 months

AL = amyloid light chain, ATTR = amyloid transthyretin, LC MS/MS = liquid chromatography tandem mass spectrometry, IHC = immunohistochemistry.

are commonly comprised of AL amyloid, often occurring as peritumoral deposition surrounding a B cell lymphoma [10], or secondary to systemic autoimmune disease [6].

Breast amyloidosis is a rare condition which has been described both as a manifestation of systemic amyloidosis and as a localized deposition of amyloid protein [11–14]. The clinical presentation is highly heterogeneous, with cases reported of amyloid forming painless solitary masses, bilateral infiltrates, or axillary lymphadenopathy, or appearing on imaging as grouped calcifications or spiculated masses suspicious for breast carcinoma [15–20]. Histologically, amyloid may deposit within benign breast and lymph node tissue, but has also been reported in conjunction with ductal or lobular carcinomas and B cell lymphomas of the breast [19,21–24]. However, understanding of the clinicopathologic features of breast amyloidosis remains limited. The present study was undertaken to better elucidate the histopathologic appearance and clinical correlates of breast amyloidosis in patients from our institution. The current study suggests that amyloidosis in breast presents most commonly as either mass or calcifications on imaging; and can easily be underdiagnosed microscopically as "benign breast tissue with dense stroma" or "benign breast tissue with microcalcifications", if pink, waxy-appearing extra cellular deposition/hyalinized stroma is not carefully evaluated for amyloid.

2. Materials and methods

2.1. Case histories and histology

A retrospective search for cases of amyloidosis diagnosed in breast or axillary lymph node tissue at NYU Langone Medical Center was performed. The search included all breast biopsies and resections performed between the years 2005 and 2018. The original pathology material was re-reviewed, including 5 μm thick formalin-fixed, paraffin embedded tissue sections stained with hematoxylin and eosin **and 7–10 μm thick sections stained with Congo red in all cases. Congo red staining was performed on a Ventana NexES automated platform using the Ventana Congo Red Staining kit (Roche Diagnostics, Basel, Switzerland).**

2.2. Histochemical methods

In select cases of amyloidosis associated with hematologic malignancy, diagnostic immunohistochemical and in-situ hybridization stains were performed using a Ventana BenchMark Ultra automated immunostainer (Roche Diagnostics, Basel, Switzerland) with Ventana reagents. Tissue pretreatment was performed using Ventana Cell Conditioning reagents 1 and 2 for immunohistochemistry and in-situ hybridization, respectively. Antibodies used included CD3 (clone 2GV6), CD20 (clone L26), and CD138 (clone B-A38). In-situ hybridization was performed for immunoglobulin kappa and lambda light chains (kappa DNP probe 538–567 and lambda DNP probe 826–855). Additional immunohistochemical stains for amyloid P component, kappa and lambda light chains, serum amyloid A and transthyretin were performed in one case for amyloid typing.

2.3. Amyloid typing by mass spectrometry

Liquid chromatography tandem mass-spectrometry (LC-MS/MS) was used to determine the amyloid type in six cases. LC-MS/MS based proteomics was performed at a specialized laboratory as a send-out test (Mayo Laboratory, Rochester, MN). Detailed methods have been previously published [25]. Briefly, 10 μm thick sections of unstained paraffin-embedded tissue were cut and stained with Congo red. **Congophilic tissue deposits were viewed under fluorescent light and laser microdissected. The dissected tissues underwent trypsin digestion and were analyzed by LC-MS/MS using a ThermoFinnigan**

LTQ Orbitrap Hybrid Mass Spectrometer (Thermo Electron, Bremen, Germany) coupled to an Eksigent nanoLC-2D HPLC system (Eksigent, Dublin, CA, USA).

3. Results

3.1. Case series

Ten cases of amyloidosis diagnosed in breast tissue over a period of 14 years were identified in a retrospective search of pathology case reports at our institution. The associated demographic and clinical information is listed in Table 1. Patients were all female, with a mean age of 69 years (range: 51–84). Specimen sources included breast tissue (80%) and axillary lymph node biopsies (20%). Indications for biopsy included breast calcifications (50%), breast mass (30%), and axillary tail mass/lymphadenopathy (20%). Amyloid involvement was unilateral in all cases, with a left-sided predominance (70%). No patient had a prior diagnosis of systemic or localized amyloidosis of other tissues prior to the diagnosis of breast amyloidosis. Four patients (40%) had a medical history significant for autoimmune disease, including systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and polymyalgia rheumatica. One patient had a prior history of marginal zone lymphoma, diagnosed 4 years prior to presentation, and had at that time completed treatment with rituximab and bendamustine chemotherapy with partial response. One patient had a history of type II diabetes treated with subcutaneous insulin injection.

3.2. Histologic features

Amyloid presented with a range of histologic appearances in breast tissue, as illustrated in Fig. 1. Patterns observed in our case series included pink, waxy-appearing nodular amyloid deposits within benign breast tissue (Fig. 1A), diffuse amyloid deposition within fibroadipose tissue mimicking fat necrosis (Fig. 1B), deposits associated with calcification and foreign body giant cells (Fig. 1C), and clustered amyloid deposits surrounding benign breast tissue, mimicking fibroadenomatoid change (Fig. 1D).

In two cases, amyloidosis occurred alongside neoplastic epithelial lesions. In case 3, amyloid deposits were associated with atypical ductal hyperplasia bordering on ductal carcinoma in situ (DCIS). In case 7, amyloidosis was associated with both high grade ductal carcinoma in situ with comedonecrosis and lobular carcinoma in situ in the mastectomy specimen (Table 1).

Within axillary lymph node tissue, amyloid was present as patchy sheet-like deposits interspersed with proliferations of lymphoid cells showing prominent plasmacytic differentiation. Both cases of amyloid within axillary lymph nodes occurred in association with small B-cell lymphomas with prominent plasma cell differentiation (Table 1). Case 1 occurred in a patient with a prior history of treated nodal marginal zone lymphoma. Case 5 was a new diagnosis of primary breast small B-cell lymphoma (Fig. 2A). Immunohistochemistry staining for CD138 was performed on tissue from this case, showing prominent plasmacytic differentiation of the lymphoid proliferation, and in-situ hybridization demonstrated lambda restriction (Fig. 2B–D).

3.3. Amyloid typing

Amyloid deposits stained positive with Congo red in all cases and showed characteristic apple-green birefringence under polarized light (Fig. 2E). Amyloid type was determined by mass spectrometry in 6 cases, and by immunohistochemistry in 1 case (Table 1). 4 cases (57%) were AL, with a predominance of AL lambda (3 cases) over AL kappa (1 case). 2 cases (29%) were composed of aTTR. **Of note, one of the cases of aTTR submitted for proteomic analysis (case 3) showed a V122I mutation of transthyretin, strongly suggestive of familial transthyretin-related amyloidosis (aTTRv), however genetic testing results were unavailable.** One case (14%) of amyloid insulin (aIns) was identified in an axillary lymph node of a patient with type II diabetes treated with subcutaneous insulin.

3.4. Follow-up

Eight of ten patients had reports for subsequent clinical visits. After follow-up times ranging from 0.5 to 10.1 years (median: 13 months), all patients were alive without subsequent diagnoses of systemic amyloidosis or monoclonal immunoglobulin spikes. Amyloid was limited to the breast in seven of the eight cases. One patient (case 8) with a diagnosis of amyloid TTR received a biopsy of a skin nodule which was interpreted as amyloidosis at an outside institution, however LC MS/MS proteomic studies performed were inconclusive.

4. Discussion

Amyloidosis of the breast is a rare entity which has been reported to

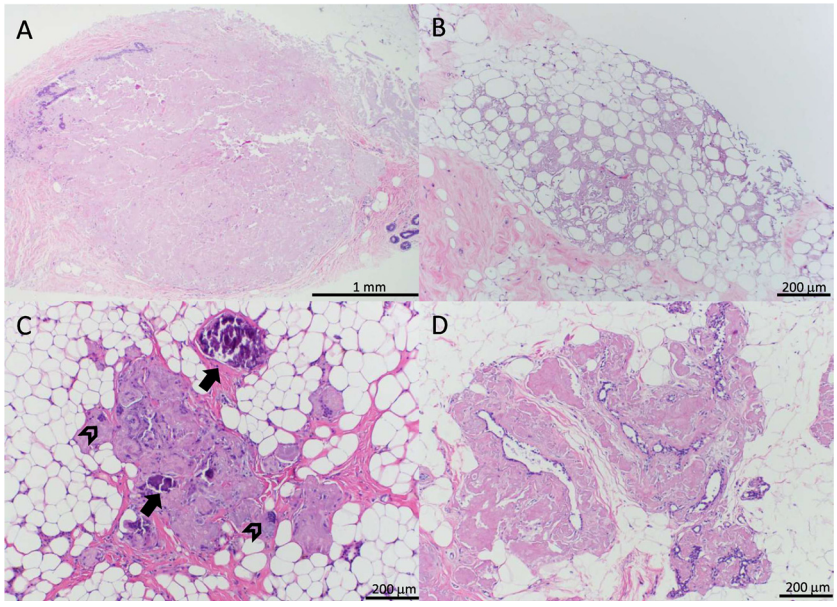

Fig. 1. A spectrum of histologic appearances of localized breast amyloidosis. (A) A nodular AL kappa deposit surrounding benign breast tissue in a biopsy from a 62 year old woman. (H&E; 40x). (B) ATTR deposit within fibroadipose tissue in a biopsy from an 84 year old woman. Neighboring breast tissue had atypical ductal hyperplasia bordering on DCIS (not shown) (H&E; 100x). (C) Amyloid associated with calcifications (arrows) and foreign body giant cell reaction (arrowheads) in a biopsy from a 67 year old woman. (H&E, 100x) (D) AL lambda associated with non-proliferative fibrocystic and focal fibroadenomatoid change/benign breast tissue with dense stroma in a biopsy from a 51 year old woman. (H&E; 40x).

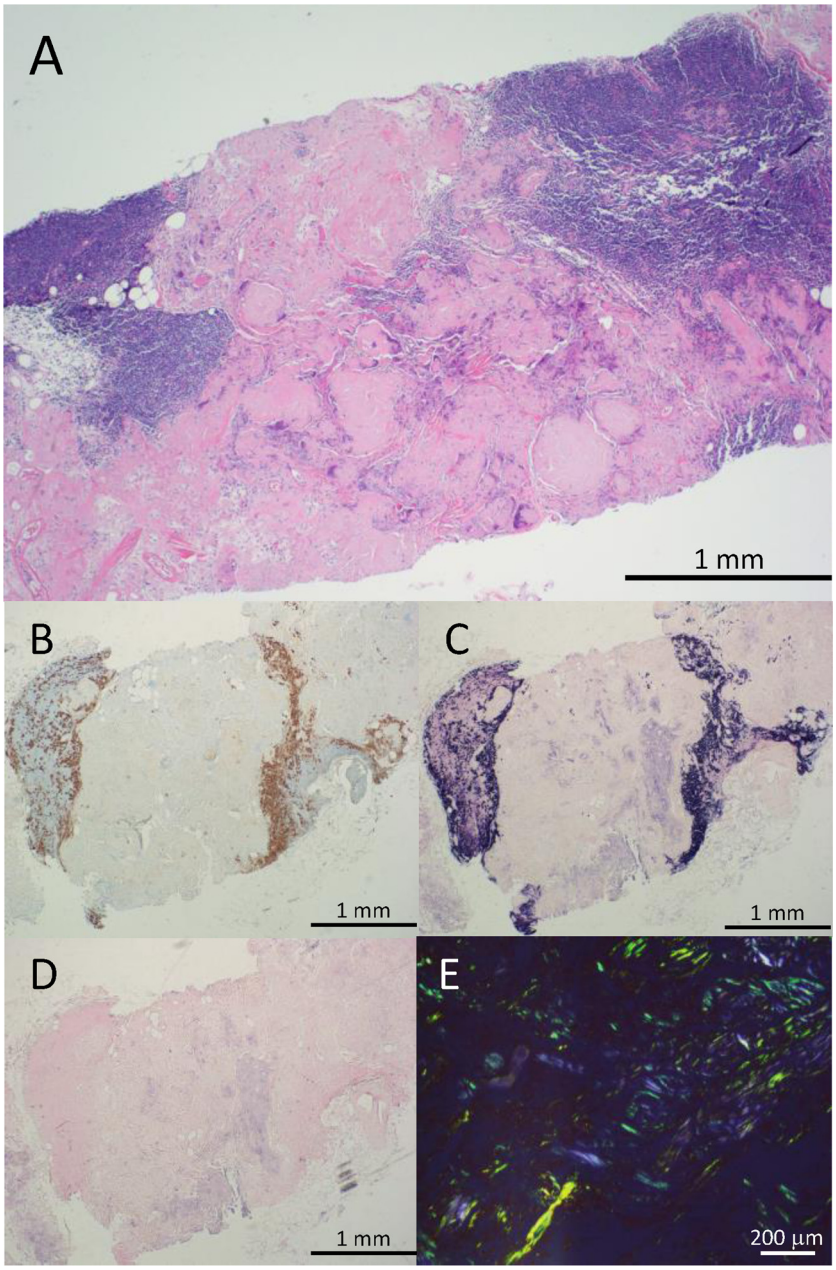

Fig. 2. AL lambda amyloidosis in an axillary lymph node biopsy. (A) A mass-forming AL lambda deposit associated with primary low-grade B cell lymphoma of the breast in a 71 year old woman (H&E, 40x). (B–E) CD138 immunostain on the tissue from (A) confirms plasmacytic differentiation (B, 40x). Lambda and kappa in-situ hybridization demonstrate lambda restriction of the plasma cells (C and D, respectively, 40x), and Congo Red stain of the amyloid deposit shows apple-green birefringence under polarized light (E, 100x).

present as both a localized deposition of amyloid and as a manifestation of systemic disease. First described in the literature in 1973, clinicopathologic studies of breast amyloidosis remain limited, with only four published case series to date [11–14,26]. Here, we present a series of 10 cases diagnosed over the course of fourteen years at a single academic medical center.

Our cases include exclusively female patients, in whom breast amyloidosis presented during middle to old age. Amyloid had a number of clinical presentations which prompted surgical intervention, including calcifications, solitary masses, or axillary mass/ lymphadenopathy. The indication for biopsy was therefore either mass or calcifications in all cases. AL amyloidosis was the most common form detected in our patient population, followed by amyloid TTR, which appeared in both age-related and hereditary mutated forms. **The V122I hereditary mutation of TTR detected in our series is a common variant among the African-American population, with a carrier frequency of 3–4%. This variant is known to form soft tissue deposits, and is a significant cause of cardiac amyloidosis among elderly African-Americans** [27]**.** We also found a single case of pharmacotherapy-associated (i.e. iatrogenic) amyloid in a patient receiving subcutaneous insulin injections for type II diabetes mellitus.

Amyloid displayed a range of histologic appearances, including nodular lesions, diffuse deposition within fibroadipose tissue, and subtle deposition encircling benign glandular tissue. **Because the histologic presentation of amyloid is heterogeneous, it is important to correlate the results of Congo Red staining with LC-MS/MS testing, where available, to rule out amyloid-like mimics observed on H&E or detected by LC-MS/MS alone which do not form characteristic Congophilic amyloid deposits. In our experience, H&E mimics may include materials commonly found in the breast such as**

extracellular matrix or lactoferrin. Additionally, thicker tissue sections of 6–10 μm show reduced rates of false negative staining for amyloid [28].

As previously reported [11,12,21,24], there was a clinical association with B cell lymphomas of the breast and axillary lymph node tissues, with both such cases presenting with AL lambda amyloidosis. **A strong clinical association was also noted with chronic inflammatory and autoimmune diseases** [29]**, which occurred in 40% of the cases in our series. However, we could find no consistent association between autoimmune disease and amyloid type, and we observed no cases of AA amyloid among our series.**

Of note, none of our breast amyloidosis patients had prior diagnoses of systemic amyloidosis or plasma cell neoplasm, and all patients with follow-up lacked evidence of systemic involvement by amyloid. A single patient had a subsequent skin biopsy showing localized amyloid deposition of undetermined type. This differs markedly from a recent large case series of amyloidosis, in which nearly half of patients showed extramammary systemic amyloid involvement, and a majority of cases presented with a concurrent hematologic neoplasm and/or a monoclonal immunoglobulin spike [11]. Our series also showed a predominance of AL lambda over AL kappa in cases of localized AL amyloidosis. This is a similar distribution to systemic AL amyloidosis, but differs from the previously reported predominance of AL kappa in breast amyloidosis [11,12]. These differing features illustrate the variable presentations of breast amyloidosis between patient cohorts and medical centers.

As amyloidosis of the breast carries a wide range of clinical, radiographic and histologic presentations, it is important to include amyloid among the differential diagnosis of all mass-forming lesions and calcifications of the breast. When recognized on biopsy, the diagnosis of amyloid can prevent further unnecessary diagnostic surgical interventions and guide further workup towards potentially associated conditions such as primary breast lymphoma, chronic autoimmune disease, or plasma cell neoplasms. Although rare, an awareness of the clinicopathologic characteristics of this easily overlooked entity is of great importance for practicing breast pathologists.

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