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Case Report

Breast calcifications on mammography from systemic amyloidosis: A case report ☆

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ABSTRACT

Calcifications on mammography from systemic disease at times meet diagnostic criteria for histologic sampling to exclude malignancy. We present a case of bilateral groups of new calcifications on mammography that yielded amyloidosis on core biopsy. Awareness of our patient's known diagnosis of systemic light chain amyloidosis (AL) prompted use of Congo red staining to confirm the histologic diagnosis. Knowledge of systemic diseases with possible manifestations on mammography can facilitate cogent and clinically relevant radiology-pathology correlation.

Introduction

While breast cancer detection remains the primary objective for breast imaging studies, mammography can demonstrate evidence of non-neoplastic systemic diseases [1,2]. Breast calcifications may occur from conditions including collagen vascular diseases, hyperparathyroidism, pseudoxanthoma elasticum, Ehlers-Danlos syndrome, parasitic infection, coronary artery disease, and amyloidosis [1,2]. Today we present a case report of bilateral suspicious breast calcifications on mammography with biopsy proven etiology of amyloid deposition due to systemic lambda light chain (AL) amyloidosis.

Amyloidosis is a rare, heterogenous disease occurring due to tissue deposition of various misfolded proteins [3] and can be systemic or localized to a specific organ. Currently there are 18 recognized human amyloid fibril proteins in systemic amyloidosis and 22 in localized amyloidosis [4]. In an academic center with a large case volume including a consultation service, authors of one retrospective study estimated that less than 0.1% of all breast cases in 2018 and 2019 demonstrated pathology results of amyloid in the breast [5]. In another retrospective review of 1,502 new patients with amyloidosis, only 13% had localized amyloidosis with 6% of those patients presenting with localized amyloidosis in the breast [6].

Although light chain (AL) amyloidosis is diagnosed in the majority of systemic cases [7], it is still considered a rare

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disease with a worldwide incidence and 20 year prevalence of approximately 0.001% and 0.005%, respectively [8]. Presenting clinical signs and symptoms may be non-specific with frequent delays in diagnosis; the affected organ systems account for disease morbidity and mortality, and prognosis largely depends on cardiac function, which is the organ most often affected by amyloidosis [9].

Case report

Verbal and written informed consent were obtained from the patient.

Patient history

We present a postmenopausal 51-year-old black female with a known history of systemic lambda light chain amyloidosis (AL) referred to our imaging center for second opinion reinterpretation of bilateral screening and diagnostic mammography with recommendation for stereotactic biopsy of bilateral calcifications from an outside institution. Personal history is negative for breast carcinoma, and a family history of breast carcinoma was noted in the patient's maternal grandmother at age 80. At the time of presentation, the patient was pending orthotopic heart transplantation for non-ischemic restrictive cardiomyopathy due to amyloidosis (confirmed by endomyocardial biopsy) with gastrointestinal and small vessel involvement (biopsy proven by tissue sampling during colonoscopy). Amyloidosis was initially suspected during a previous inpatient admission for arterial thrombectomy of bilateral lower extremity arterial thrombi at an outside institution when preoperative transthoracic echocardiogram suggested restrictive cardiomyopathy; however, cardiac pyrophosphate (PYP) scan was negative for amyloidosis. Past medical history also includes stage 3 chronic kidney disease and multiple myeloma.

Imaging assessment

Screening mammography demonstrated new calcifications in the upper aspect of the right breast and in the upper outer quadrant of the left breasts (Fig. 1). On magnification views performed for diagnostic mammography (Fig. 2), there are new groups of coarse heterogeneous and amorphous calcifications in the upper aspect of the right breast and a new group of coarse heterogeneous calcifications in the upper outer aspect of the left breast. These were assessed as BI-RADS Category 4 (suspicious) with stereotactic/tomosynthesis guided core biopsy recommended bilaterally. There were also new areas of bilateral benign vascular calcifications present.

Multiple tissue cores were obtained from a single site of biopsy in the right and left breast using digital breast tomosynthesis with a 9 gauge vacuum assisted device. Specimen radiography confirmed the presence of calcifications in the core samples for each breast (Fig. 3). The pathology result for each site of biopsy was benign breast tissue with amyloid deposition and associated coarse calcifications. Amyloid deposition was noted diffusely in both the collageneous stroma and adipose tissue. Biopsy results were assessed as benign and concordant at the time of radiology-pathology correlation.

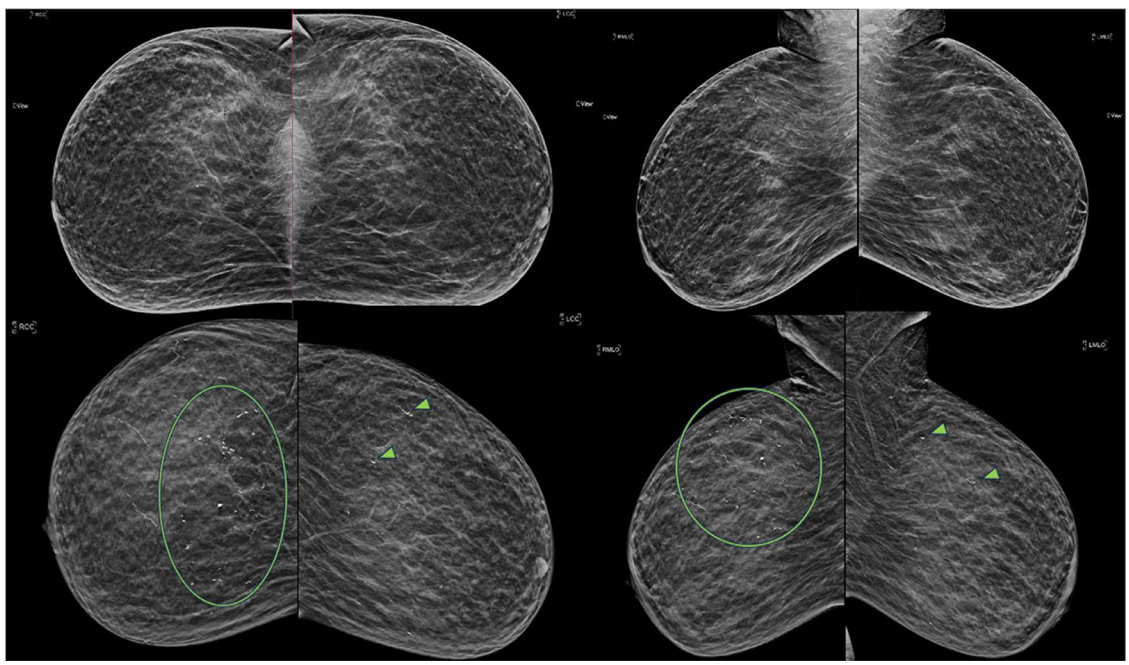

Fig. 1 – New calcifications on screening mammography. Current screening mammogram (bottom row) demonstrates new calcifications in the upper aspect of the right breast (circle) and upper outer quadrant (arrowheads) when compared with prior mammograms (top row).

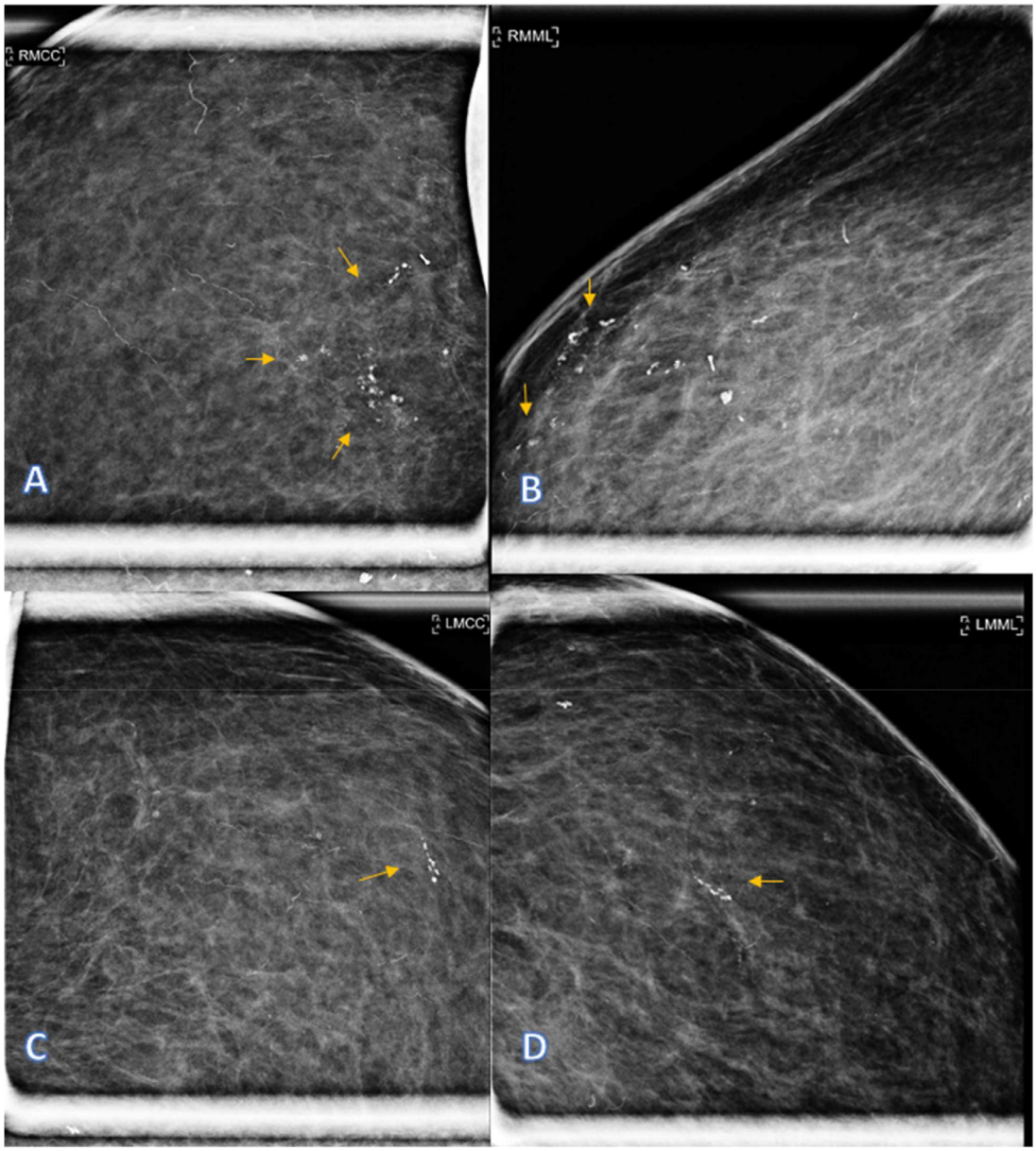

Fig. 2 – Bilateral magnification views of calcifications. Craniocaudal (A) and mediolateral (B) magnification views of the right breast demonstrating new groups of coarse heterogeneous and amorphous calcifications in the upper aspect of the right breast (arrows). Craniocaudal (C) and mediolateral (D) magnification views of the left breast demonstrating a new group of coarse heterogeneous calcifications in the upper outer aspect of the left breast (arrow).

Pathology results

Hematoxylin and Eosin (H&E) stained sections from core biopsies of the left and right breast demonstrated benign breast tissue with amorphous eosinophilic deposits consistent with amyloid in the stroma, adipose tissue, and surrounding vessels. Coarse calcifications were scattered throughout the fibroadipose tissue in association with the amorphous material (Fig. 4A). A Congo red stain performed on both biopsies stained the amorphous material orange-red and demonstrated yellow-green to red birefringence when viewed with crossed polarizer and analyzer supporting the diagnosis of amyloid (Figs. 4B and C). Lambda AL amyloid was identified by tandem mass spectrometry on a prior cardiac biopsy; therefore, amyloid typing was not repeated on the specimens obtained from this breast biopsy.

Therapeutic intervention and outcomes

Due to non-ischemic cardiomyopathy secondary to AL amyloid with an ejection fraction between 20% and 25%, the patient was being considered for orthotopic heart transplantation. After an inpatient admission due to cardiogenic shock, the patient underwent heart transplantation less than two

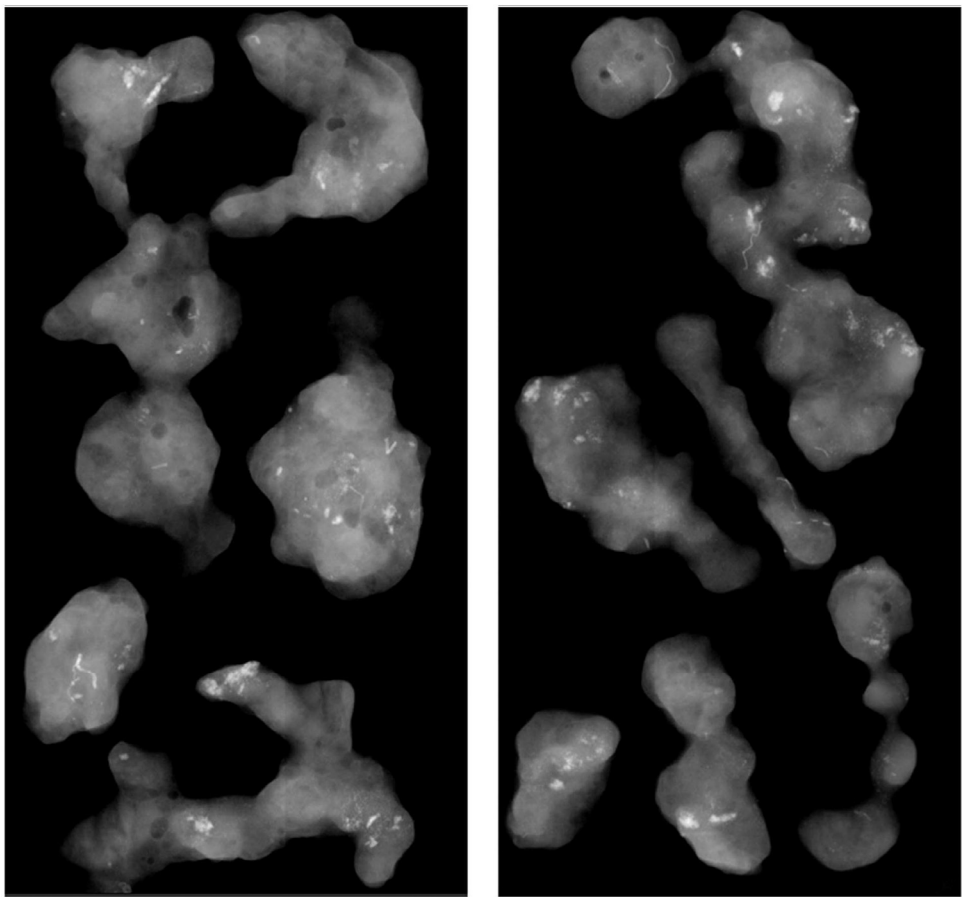

Fig. 3 – Bilateral specimen radiographs. A single specimen radiograph from each breast confirms the presence of representative calcifications in the acquired tissue samples from digital breast tomosynthesis guided vacuum assisted core needle biopsy.

months after stereotactic breast biopsy. After treatment with monoclonal antibody daratumamab, as well as cyclophosphamide, bortezomib, and dexamethasone (CyBorD), the patient had a complete hematologic response. Therefore, high dose chemotherapy and autologous peripheral blood stem cell transplant were not recommended. Since heart transplantation, progression of renal failure was attributed to complications from cardiac transplantation and not amyloidosis. The patient currently has normal functional status with a normal ejection fraction, undergoes hemodialysis routinely, and is waiting for renal transplantation.

Discussion

This case report highlights the utility of formulating a differential diagnosis for mammographic findings including calcifications in the context of the patient's clinical history including salient concurrent systemic disease, such as amyloidosis in our case. Multidisciplinary collaboration facilitated more rapid concordant, benign diagnosis because the referring physician for the biopsy procedure did specifically request evaluation for amyloidosis with Congo red staining. Our case is unique because we already had a high clinical suspicion for amyloidosis prior to biopsy. In addition, this case adds to the existing sparse literature on the imaging manifestations of amyloidosis of the breast. Given that amyloidosis is a rare, heterogeneous clinical condition with unfortunate prognostic implications in some cases if diagnosis is delayed, promoting awareness of its imaging presentation may facilitate more rapid investigation and applicable targeted treatment for the specific underlying pathogenic protein involved in a patient's disease [10].

Histopathology

Amyloidosis of the breast is a subtle finding on H&E-stained sections where the amorphous eosinophilic material can be difficult to distinguish from the collagenous stroma of the breast. Duckworth et al. [5] and Said et al. [11] performed 2 of the largest breast amyloidosis case series where they described amyloid deposits occurring within the fibroadipose tissue and surrounding ducts, lobules, and vessels. Specifically, Duckworth et al reported stromal and perivascular distribution of amyloid, as was seen in this case, in 37% of their cohort. Scattered coarse calcifications were identified within amyloid deposits in the current case which is consistent with

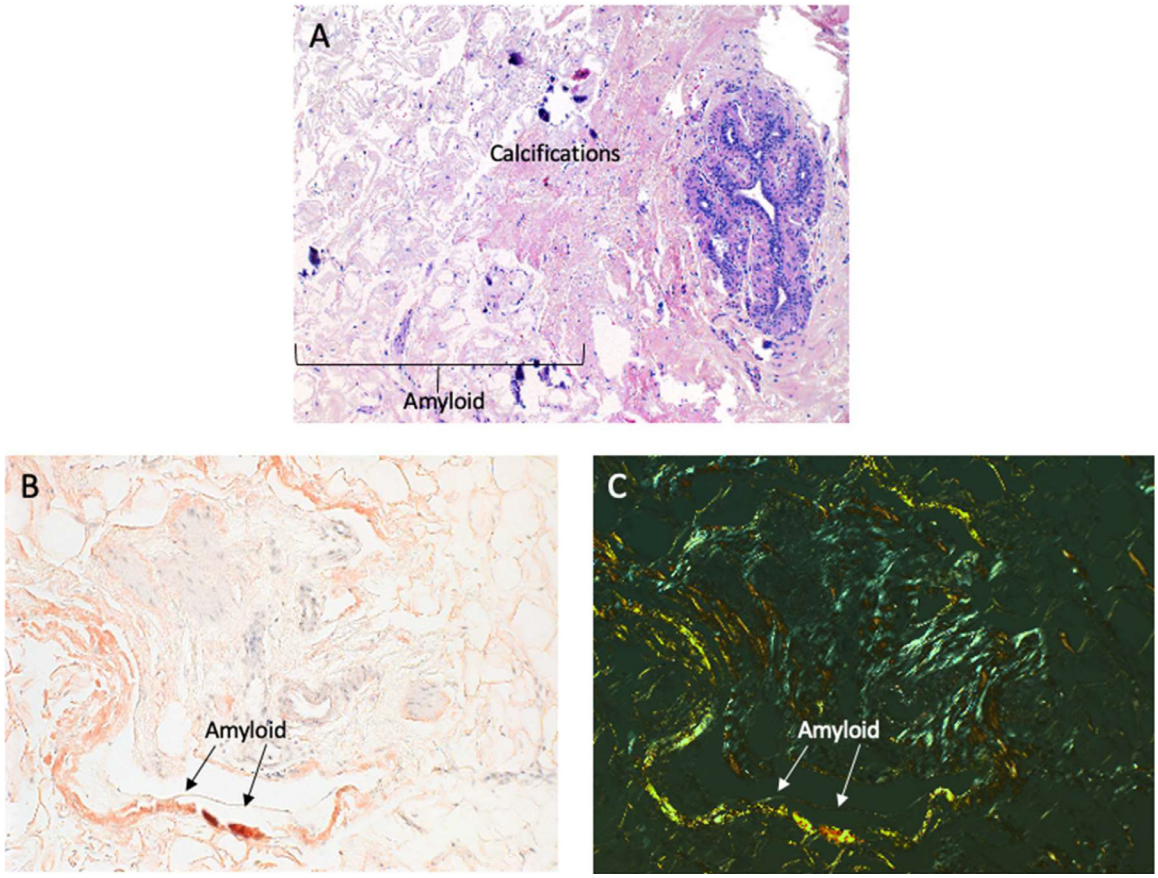

Fig. 4 – Pathology of breast biopsy. Benign breast tissue with eosinophilic amorphous amyloid deposits in the fibroadipose tissue with associated calcifications (A). Congo red stain showing orange-red staining of perivascular amyloid deposits (B), with anomalous birefringence (green, yellow, red) in polarized light (C).

the reported 44% prevalence of calcifications in breast amyloidosis [5]. Due to the subtle relatively nonspecific morphology of amyloid by H&E, the diagnosis should be supported by ancillary studies, most often Congo red. Amyloid has an affinity for the Congo red stain where it is usually described as showing characteristic "apple-green" birefringence in polarized light [4]. However, amyloid displays a variety of colors including green, yellow, and red under polarization because of variable amyloid fibril orientation in the cut section [4]. The H&E morphology, congophilia, and birefringence pattern of the deposits in the current case are consistent with involvement of the breast by amyloidosis. Amyloidosis can either be a localized process or a manifestation of a systemic disease, but the histologic features of amyloid are the same regardless and the distinction often requires clinical correlation.

Imaging presentation

Imaging manifestations of amyloidosis are non-specific on mammography. Amyloidosis has been reported to present on mammography as a mass [12], bilateral masses [13], a mass or masses with associated calcifications, [14-20] calcifications alone [6,21–27], or diffuse skin thickening [28]. Findings may be mammographically occult and only be evident on focused ultrasound evaluation at the site of a palpable mass [29,30]. Axillary lymphadenopathy has also been reported as an indication for biopsy yielding pathology of amyloidosis [20,31,32]. Spontaneous unilateral and bilateral breast skin ecchymosis/hematomas, as well as unilateral and bilateral mastitis were also reported at the time of presentation for breast evaluation in conjunction with an underlying diagnosis of amyloidosis [33].

There are a few notable case series of breast amyloidosis in the literature. Said et al. [11] published data on forty cases of biopsy proven amyloidosis in the breast from the pathology archives at Mayo Clinic in Minnesota. The study cohort included 39 female and one male patient. The indication for biopsy was unknown in over half the cases. Among the patients with known indications for biopsy, breast calcifications (as in our case) were the indication for biopsy in only 15% of the cases, and mass was the more common indication in approximately one-third of the cases. Amyloidosis was found bilaterally (as in our case) only in 5% of the cases (versus unilateral 93% of the time and unknown laterality 3% of the time). Light chain amyloidosis (AL) was the most common type of amyloidosis found (60% of cases) with the lambda type of immunoglobulin found in 40% of cases as in our case (versus 60% of the kappa type). Of the 15 patients receiving care at Mayo

Table 1 – Description of calcifications associated with biopsy proven amyloidosis.

Description on Mammography	Reference	Year
"grouped amorphous, coarse, and round calcifications"	McIntire PJ et al [22]	2023
"group of calcifications demonstrates suspicious coarse heterogeneous morphology and linear/branching distribution"	Roy M et al [34]	2020
"amorphous and irregular"	Kim BM et al [15]	2020
"macrocalcifications and microcalcifications"	Yilmaz E et al [14]	2019
"diffuse coarse dystrophic calcifications"	Eghtedari M et al [16]	2015
"2 foci of linear microcalcifications"	Ngendahalyo P et al [24]	2013
"multiple, irregular calcifications…regionally distributed, generally smooth-branched, linear, and rod-like, and varied in sizes and shape"	Shim Y et al [25]	2013
"groups of suspicious segmentally distributed, irregular and pleiomorphic microcalcifications"	Athanasiou A et al [23]	2007
"small cluster of indeterminate mildly pleomorphic microcalcifications"	Patel B et al [27]	2003
"cluster of fine linear and branching microcalcifications"	Diaz-Bustamante T et al [35]	2001
"grouped, generally smooth branching rodlike calcifications"	Gluck BS et al [26]	2000
"irregularly shaped…course calcifications"	Lynch LA, Moriarty AT [18]	1993

Clinic with available clinical data, 53% had localized amyloidosis to the breast, and 47% had amyloid deposition in one or more extramammary sites. Like our patient, 6 of these 15 patients already had a known diagnosis of amyloidosis in an extramammary site prior to breast biopsy.

Thirty-two cases of biopsy proven mammary amyloidosis in Duckworth et al [5] showed similar trends with a predilection for female patients (100%) and unilateral disease (76% were unilateral and 24% were bilateral). Also similar to the series by Said et al, mass lesion was more commonly an indication for tissue sampling than calcifications (mass in 43%, calcifications in 36%, and asymmetry in 14% of cases).

Unlike Said et al, in which some patients had a prior diagnosis of extramammary amyloidosis, in the retrospective review of 10 cases of biopsy proven amyloidosis of the breast by Lytle et al [31], none had a prior diagnosis of extramammary amyloidosis. In contrast to both larger case series discussed above, calcifications were a more frequent indication for biopsy (50%), followed by breast mas (30%), and axillary tail mass or lymphadenopathy (20%). The diagnosis was unilateral in all cases.

Other individual case reports or smaller case series provide various descriptions of the morphology and distribution of calcifications that were associated with biopsy proven amyloidosis on mammography (Table 1). The calcifications in our case demonstrated coarse heterogeneous and amorphous morphology in a grouped distribution on mammography, which is similar to the calcification descriptions provided within 4 of twelve cases as detailed below [15,18,22,34].

Differential diagnosis

Breast calcifications are characterized by their morphology and distribution with various associated positive predictive values for breast malignancy [36,37]. There is no pathognomonic morphology and distribution of calcifications from amyloidosis in the breast. The suspicious calcifications in our case presented with amorphous and coarse heterogeneous morphology without an associated mass. Amorphous calcifications in the breast are commonly associated with breast histopathology including benign fibrocystic changes, atypia, lobular neoplasia, ductal carcinoma in situ (DCIS), or invasive breast cancer [38]. Coarse heterogeneous calcifications often demonstrate histopathology of fibroadenomata or fibroadenomatoid change and fat necrosis with less frequent histopathology of breast cancer [38]. Although fine linear calcifications very rarely represent amyloidosis within the breast, other diagnostic considerations include DCIS, invasive breast cancer, fibroadenomata, milk of calcium within microcysts, benign secretory disease or plasma cell mastitis, and arterial calcification (medial calcific sclerosis) [38].

Unlike some cases of amyloidosis of the breast reported in the literature, our case did not present with diffuse skin thickening, which may be seen with mastitis, lymphoma, inflammatory carcinoma, or rarely Churg Strauss Syndrome [2], or commonly as a sequela of radiation therapy for breast cancer treatment [1]. Our case also did not present with masses, which may be seen with benign breast disease, in situ or invasive breast cancer, metastatic disease, or other systemic etiologies including Wegener granulomatosis, granulomatous mastitis, sarcoidosis, diabetic mastopathy, lymphoma, leukemia, and fungal infection. [1]

Clinical course

Patients with AL amyloidosis can have a protracted clinical presentation and a complicated diagnostic course with cardiac, renal, and neurologic signs and symptoms with a median time from onset of symptoms to diagnosis of 2.7 years as reported in a recent study [39].

Once the diagnosis of amyloidosis is made, the specific pathogenic protein can be identified and targeted therapies may be initiated if systemic disease warranting treatment is implicated [11]. Current treatment of AL aims to prevent or attenuate the creation and deposition of amyloid fibrils (using proteasome inhibitors and monoclonal antibody therapy) and to provide supportive care for disease complications [10]. Our patient received the monoclonal antibody daratumamab, as well as cyclophosphamide, bortezomib, and dexamethasone (CyBorD), which is a treatment regimen approved

by the U.S. Food and Drug Administration in 2021 for AL amyloidosis [40].

Diagnostic delays can be fatal. Among those with light chain amyloidosis (AL) with a delay in diagnosis of more than 6 months, 63.6% of these patients in one study did not survive beyond 5 years, and greater diagnostic delay was a statistically significant predictor of death [41]. Not all amyloidosis found in the breast is related to systemic amyloidosis such as AL, but the majority of cases of breast amyloidosis in one study were also associated with a plasma cell or other proliferative/hematologic disorder [11].

Future implications

Given rising healthcare costs, professional radiology societies acknowledge and support value-based healthcare, which emphasizes improving patient outcomes without increased expense [42]. Identifying signs of systemic disease on medical imaging studies may inspire novel ways to clinically use imaging data to improve overall health outcomes without inflating cost. Emerging approaches to leverage the value of existing patient data currently incorporate medical images, the electronic medical record, and artificial intelligence/deep learning algorithms [43,44].

More fully characterizing the relationship between mammographic calcifications and systemic disease could represent an opportunity to inform or refine deep learning algorithms for artificial intelligence seeking to improve reader diagnostic performance for breast cancer detection or for additional surveillance for systemic disease.

Although mammography is currently intended for breast cancer screening and diagnosis, opportunistic screening for systemic diseases in mammography is currently being considered, particularly for breast arterial calcifications. Specifically, researchers are evaluating the relationship between breast arterial calcifications and cardiovascular health and cerebrovascular disease [45–47]. Such data may inform additional cardiovascular risk reduction strategies and interventions for women with breast arterial calcifications [48]. However, long-term prospective outcome data for using mammography to screen for diseases other than breast cancer are currently unavailable.

Conclusion

Screening mammography not only represents an opportunity to diagnose breast cancer, but also may play a future role in identifying systemic diseases. Amyloidosis is a rare and heterogeneous disease, and diagnostic delays for systemic amyloidosis can increase morbidity and mortality for some patients. Clinical and imaging presentations for amyloidosis are often non-specific; awareness of this elusive disease as a diagnostic possibility can prompt additional histopathologic evaluation to confirm its diagnosis at the time of core biopsy. When evaluating new calcifications on mammography in a female patient with a history of hematologic or oncologic disease, consider amyloidosis as a diagnostic possibility. If tissue sampling of breast calcifications yields a diagnosis of amyloidosis, and the patient has no known history of hematologic or oncologic disease, consider consultation with hematology/oncology to evaluate for systemic forms of amyloidosis.

Patient consent

Verbal and written informed consent were obtained from the patient.

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