



DOI: 10.32768/abc.202294515-518



Unilateral Primary Localized Cutaneous Nodular Amyloidosis of the Nipple

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ARTICLE INFO

Received:

30 June 2022

Revised:

31 August 2022

Accepted:

31 August 2022

Keywords:

Amyloidosis, nipple, skin changes, case report.

ABSTRACT

Background: Amyloidosis is characterised by extracellular accumulation of an amorphous fibrillary protein and can affect any organ. It is classified into systemic and localised disease according to its sites of presentation and as primary or secondary according to aetiology. Breast amyloid was first described in 1973 and is extremely rare.

Case Presentation: A 61-year-old woman presented in 2020 with a 1-year history of an enlarging tender left nipple with some associated bleeding. Clinical differential diagnoses included a nipple adenoma and an intraductal carcinoma; therefore, a punch biopsy was taken. A full set of screening blood tests were undertaken which were normal, showing no evidence of a plasma cell dyscrasia.

The biopsy showed diffuse replacement of the dermis by acellular eosinophilic material showing fracturing. Congo Red stain was positive showing apple-green birefringence under polarised light. A diagnosis of primary localised cutaneous nodular amyloidosis of the nipple was made.

Conclusion: We present a rare documented case of isolated primary localised cutaneous nodular amyloidosis of the nipple. This can be considered as a differential diagnosis for patients with a new nipple lesion alongside nipple adenoma and intraductal carcinoma

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INTRODUCTION

Amyloidosis is characterised by extracellular accumulation of an amorphous fibrillary protein and can affect any organ. It is classified into systemic and localised disease according to its sites of presentation and as primary or secondary according to aetiology. Breast amyloid was first described in 1973 and is extremely rare.¹ There are only a few case reports and case series in the literature.² Nipple amyloidosis is even less common and only two previous cases have been identified, one currently in press and one published case from 1983.^{3,4}

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CASE PRESENTATION

Our patient is a 61-year-old woman who reported a 1-year history of an enlarged and tender left nipple, with a 2-month history of blistering on the nipple tip and occasional blood spotting on the inside of her bra. She has one child, underwent menopause at age 52 and has not previously taken hormone replacement therapy. Systemically she reported a small degree of lethargy over the previous 6 months and wheezing on exertion. She reported no weight loss, no change in bowel habit and there were no symptoms of peripheral neuropathy nor carpal tunnel syndrome. Her drug history included glucosamine/chondroitin and a multivitamin and she had no drug allergies. She worked as a customer service coordinator for an engineering firm. There was no history of smoking or alcohol use.



On examination, the left nipple was enlarged and on the nipple papilla in the 9-10 O'clock position there was a slight purplish fleshy area (Figure 1). No other abnormalities were noted in either breasts and there was no supraclavicular or axillary lymphadenopathy. Repeat mammogram demonstrated that bilateral dense breast tissue was unchanged from numerous previous mammograms dating back to 2011. Differential diagnoses included a nipple adenoma and an intraductal carcinoma; therefore, a punch biopsy was taken.



Figure 1. Left nipple enlargement with purple discoloration

The biopsy showed diffuse replacement of the dermis by acellular eosinophilic material showing fracturing. Congo Red stain was positive showing apple-green birefringence under polarised light (Figure 2, 3).

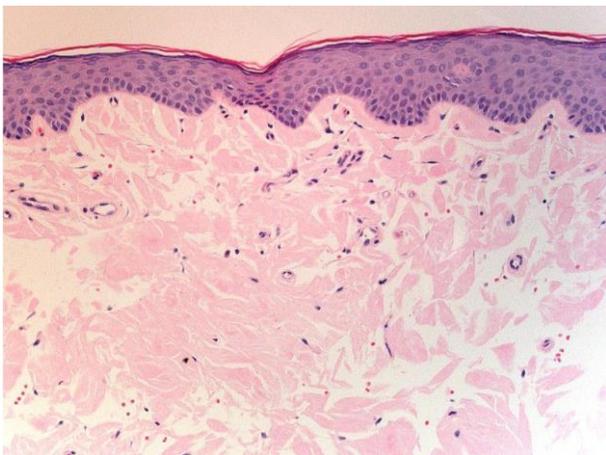


Figure 2. Histopathology of the nipple (Hematoxylin and Eosin x 100)

The cytokeratin stain (CK8) was negative and smooth muscle actin (SMA) stain was positive about the blood vessels. There was only a mild perivascular lymphocytic infiltrate. An initial diagnosis of primary localised cutaneous nodular amyloidosis (PLCNA) of the nipple was made.

Initial blood tests taken were unremarkable, thus supporting localised disease. These included a full blood count, renal function and electrolytes, liver function tests, coagulation studies, C-reactive protein, serum amyloid A, natriuretic peptide tests and cardiac troponins. Further blood tests including immunoglobulins (IgA/ IgG/ IgM) and serum free light chains were also within expected ranges and no serum paraprotein was detected. Urine tests performed included Bence Jones protein, urine protein/creatinine ratio and urine albumin/creatinine ratio, which were unremarkable. Furthermore, the electrocardiogram and echocardiogram were unremarkable.

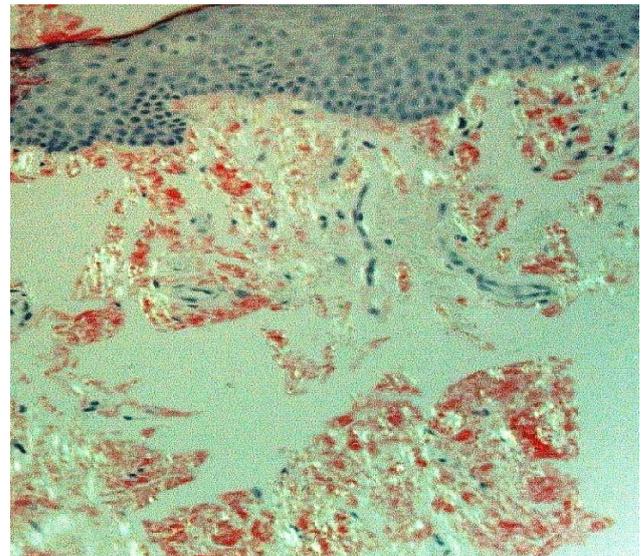


Figure 3. Congo Red staining showing apple green birefringence

The patient was referred to dermatology who subsequently referred the patient onwards to the National Amyloidosis Centre in London (NAC). Biopsy samples were reviewed by the tertiary centre who re-confirmed the presence of amyloidosis and did not identify any evidence of neoplastic or plasma cell infiltrate. The NAC also arranged serum amyloid P (SAP) scintigraphy - a nuclear imaging test that utilizes iodine-123 and SAP to identify any deposits of amyloid in organs throughout the body.⁵ This came back negative and based upon this and the previous investigations described above, the NAC concluded that there was no evidence of systemic amyloidosis and confirmed PLCNA.

The diagnosis of localized amyloidosis with involvement of the nipple was explained to the patient including how unusual it was. The NAC will follow up the patient in one year for review. In the meantime, a Positron Emission Tomography (PET) scan is being arranged to exclude evidence of a lymphoproliferative disorder. If she was to become more symptomatic, complete excision of the affected area could be considered.



DISCUSSION

Breast amyloid is often part of a systemic disease but may be localised to the breast and is often associated with an underlying malignancy.⁶ Localised amyloidosis most commonly occurs in the airway, gastrointestinal tract, bladder and skin whilst breast amyloidosis remains extremely rare.⁷⁻⁹ Most studies to date have found that breast amyloidosis manifests with systemic amyloid involvement, is often associated with haematological malignancy in the breast and is mainly of the light chain amyloidosis (AL) subtype (mainly Kappa).¹⁰

Amyloidosis is classified as primary, secondary or familial with primary and secondary amyloidosis being the most common. Primary amyloidosis and amyloidosis are related to myeloma; light chain amyloidosis (AL) is the most common cause of breast amyloidosis. Secondary 'reactive' amyloid A amyloidosis (AA) is associated with chronic inflammatory diseases such as rheumatoid arthritis or malignancy.¹⁰ Familial amyloidosis is caused by a mutation in the transthyretin TTR gene with ATTR type usually identified.⁶

Clinically, breast amyloid typically presents in post-menopausal elderly women as a painless palpable mass, often unilateral in presentation with or without macrocalcifications on mammography.¹⁰ Radiological findings are thought to be non-specific but one recent report found amyloidosis of the breast demonstrated high signal on T2 and low signal on T1 weighted breast magnetic resonance imaging.¹¹ Initial clinical differential diagnosis includes nipple adenoma and intraductal carcinoma. Therefore, a biopsy must be performed to ensure that there is no underlying malignancy which would necessitate surgical intervention.¹² A positive test for amyloid deposits is via Congo red staining producing apple-green birefringence when viewed under polarized light.⁹ Histopathological differential diagnosis includes systemic amyloidosis and haematological malignancy, thus further investigations are imperative prior to diagnosing PLCNA. Bloods tests should include renal function, inflammatory markers, free light chains, M protein and autoimmune antibodies. Further tests may include urine analysis to look for Bence-Jones protein, assessment of cardiac function,

bone marrow biopsy and biopsy of suspicious sites to name a few.¹³

Liu *et al.* diagnosed PLCNA of the nipple following incisional biopsy as well as blood counts, electrophoresis, immunoglobulins and free light chains to exclude systemic disease. Similar investigations were performed for diagnosis in the case described. Interestingly the authors also described the benefits of using a dermatoscope to identify yellowish- orange globules to aid dermatologists in the initial diagnosis.³

Localised primary amyloidosis itself carries a good prognosis whilst secondary amyloidosis caused by systemic disease has a poor prognosis.¹⁴ The current standard of care for primary amyloidosis of the breast is surgical removal with periodic physical examination and mammograms if deemed necessary.¹⁴

PLCNA is the rarest form of primary cutaneous amyloid. The other more common cutaneous types are lichen and macular amyloidosis. Classic sites of presentation include the face, genitals, trunk and limbs. Associations between diabetes mellitus and Sjogren's syndrome have been suggested in some case reports.² Our patient did not have either of these conditions. Only 7% of PLCNA will progress to systemic involvement. This is excluded using highly sensitive serum amyloid P (SAP) scintigraphy.⁵

Treatment of PLCNA is difficult and recurrence is common compared to other cutaneous types of amyloidosis. Treatment options reported in the literature include surgical excision, cryotherapy, electrodesiccation and curettage, intralesional steroids and CO₂ laser.¹⁵

CONCLUSION

We presented one of the few documented cases of isolated PLCNA of the nipple. This can be considered as a differential for patients with a new nipple lesion alongside nipple adenoma and intraductal carcinoma.

ACKNOWLEDGEMENTS

We would like to thank our patient for her consent.

FUNDING

No funding was associated with this case report.

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How to Cite This Article

Walker H, Reid D, Hunt R, Wainman H. Unilateral Primary Localized Cutaneous Nodular Amyloidosis of the Nipple. Arch Breast Cancer. 2022; 9(4): 00-00.
Available from: <https://www.archbreastcancer.com/index.php/abc/article/view/608>