Pathologic Quiz Case

A 77-Year-Old Woman With Bilateral Breast Masses

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A 77-year-old African American woman presented to the hospital with a pulmonary embolism secondary to bilateral deep venous thromboses, and on physical examination was incidentally discovered to have bilateral breast masses. The mass in the right breast was located at the 4 o'clock position and was larger than that in the left breast. On palpation, the mass was noted to be firm and irregular in shape, so a carcinoma was suspected. The patient had an extensive past medical history, including end-stage renal failure requiring tri-weekly hemodialysis secondary to Wegener granulomatosis, a right upper pole renal mass radiologically suggestive of renal cell carcinoma, monoclonal gammopathy of unknown significance, iron-deficiency anemia, pseudomonal sepsis, postmenopausal bleeding, bullous pemphigoid, and recent-onset chronic diarrhea and pancytopenia.

Mammography of both breasts revealed a 1.7-cm, ill-defined mass containing coarse calcifications in the lower inner quadrant of the right breast (Figure 1) and an uncalcified 1.5-cm lesion in the upper inner quadrant of the left breast. An ultrasound-guided biopsy of the right breast mass was performed. Figure 2 shows a hematoxylin-eosin–stained section of the biopsy. Figure 3 shows the results of Congo red staining, and Figure 4 is the Congo red stain viewed under polarized light.

What is your diagnosis?

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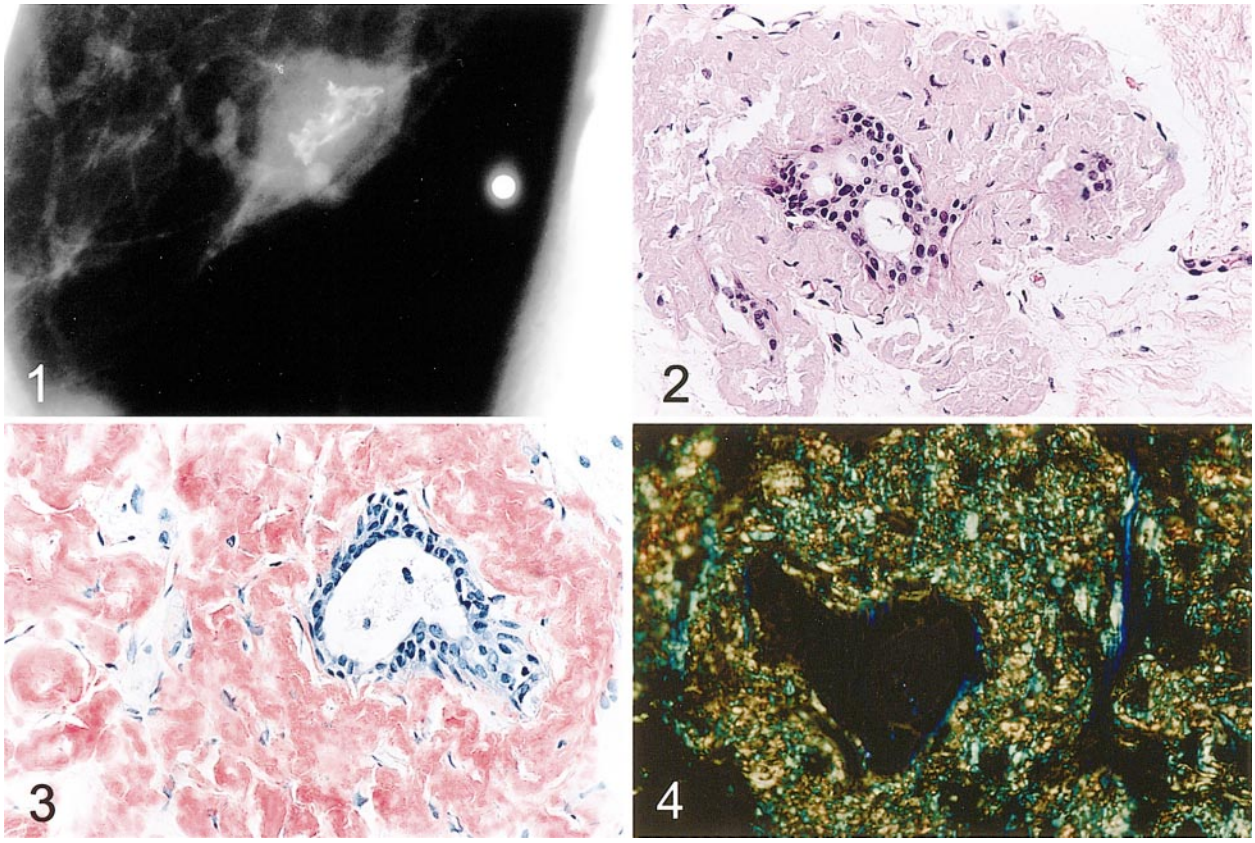

Pathologic Diagnosis: Amyloidosis Involving the Breast

There is a wide range of possible etiologies for bilateral breast masses. Fibrocystic changes and fibroadenomas comprise the majority of cases. Invasive breast carcinoma presents as bilateral tumors less than 1% of the time.[1] Other rare causes include stromal proliferations, such as pseudoangiomatous stromal hyperplasia and diabetic mastopathy, along with metastases to the breast from extramammary malignancy.[2] The literature contains descriptions of several cases of bilateral breast masses due to amyloidosis.

Amyloid deposits are typically closely related to the connective tissue framework of the involved organs and are often found to be interposed between parenchymal cells and their blood supply. This configuration promotes parenchymal cell death via ischemia and pressure atrophy. In the breast, amyloid accumulates surrounding ducts, terminal duct lobular units, vessels, and fat; in the former 2 locations, the differential diagnosis is the far more common periductal stromal elastosis.

Amyloidosis can be divided into systemic and localized forms. Systemic amyloidosis is a relatively uncommon condition and is rare in people younger than 40 years, with less than 1% of the population affected. Systemic amyloidosis can be further subdivided into 2 main types: primary amyloidosis (AL) and secondary (inflammation-associated) amyloidosis (AA). Plasma cell dyscrasias, including multiple myeloma, have long been recognized as being responsible for the AL variety. AL amyloid accounts for 75% of all cases of amyloidosis, and this subtype has a predilection for tissues such as the heart, gastrointestinal tract, peripheral nerves, skin, and tongue. Here, the fibrils are composed of monoclonal κ or λ immunoglobulin light chains. AA amyloid is formed from serum amyloid protein (SAA), an acute-phase protein produced by the liver in response to inflammation. Before the advent of antibiotics, the most common causes of systemic AA amyloidosis were chronic infectious diseases, such as tuberculosis and bronchiectasis. Today these conditions are usually adequately controlled with antibiotics, so chronic inflammatory diseases such as rheumatoid arthritis are now the most common causes of AA-type amyloid. In fact, up to 3% of rheumatoid arthritis patients develop amyloid deposits. Less common types of systemic amyloidosis include that associated with long-term hemodialysis, which affects the joints of 70% of these patients. This subtype of systemic amyloid is derived from a component of the major histocompatibility complex class I molecule, β_2-microglobulin, that fails to be filtered by the membrane used in hemodialysis and therefore accumulates.

In contrast, localized amyloidosis refers to amyloid deposits that are limited to a single organ, such as the lung, larynx, or heart. Localized amyloidosis may also be associated with specific endocrine neoplasms, such as medullary carcinoma of the thyroid, islet cell tumor of the pancreas, and pheochromocytoma; in these circumstances, the amyloid is derived from specific polypeptide hormones.

Amyloidosis of the breast is a rare entity. Fernandez and Hernandez[3] recorded the first case in 1973. Deolekar et al[4] recently reviewed the literature and found 13 well-described cases of localized AL amyloid tumor of the breast, that is, amyloid protein deposits in the breast tissue without any evidence of systemic disease. Of these cases, 2 were bilateral. Our own review of the literature revealed several additional cases of systemic amyloidosis as the cause of bilateral breast masses. One described diffuse amyloidosis involving the lungs and breast, which was associated with a κ-chain restricted gammopathy.[5] Another case reported bilateral amyloidosis secondary to rheumatoid arthritis.[6]

Localized mammary amyloidosis typically presents in postmenopausal patients and has a benign clinical course, although it simulates carcinoma clinically and mammographically.[7,8] The difficulty of this distinction was compounded in 2002, when 3 additional cases of amyloidosis of the breast were reported, 2 of which were found to have breast carcinoma in conjunction with the protein deposits.[9] Overall, AL-type amyloid is more common in the breast than AA-type, and in unilateral cases the right breast is affected 3 times more frequently than the left. κ–Light-chain restriction has been described in mammary amyloidosis more frequently than λ–light-chain restriction.[9]

Our patient's mammary amyloidosis has a number of potential etiologies. Her renal failure and history of hemodialysis make her a candidate for systemic β_2-microglobulin–associated amyloidosis, although her relatively short time on dialysis and absence of joint involvement make this unlikely. Another consideration is the suspected renal cell carcinoma, which has been associated with systemic amyloidosis of the AA variety. The third and most probable consideration is systemic amyloidosis secondary to monoclonal immunoglobulin production. In our patient, serum protein electrophoresis and urine protein electrophoresis demonstrated monoclonal immunoglobulin G λ restriction, but her M-component was quantitatively insufficient to meet diagnostic criteria for multiple myeloma. Immunohistochemistry performed on the biopsy specimens did not demonstrate light-chain restriction, although this is commonly the case due to technical limitations in formalin-fixed tissue. Assuming that the patient's amyloidosis is related to her plasma cell dyscrasia, this patient can no longer be considered to have asymptomatic monoclonal gammopathy of unknown significance, and she is now considered to have systemic amyloidosis. While at the time of discovery of her breast masses the patient had not met the criteria for multiple myeloma, it is possible that her monoclonal gammopathy/plasma cell dyscrasia will progress to multiple myeloma in the future.

In our patient, the diagnosis of amyloidosis in the right breast raises further questions. Her left-sided breast mass was clinically presumed to be amyloidosis due to its similar radiographic appearance to the right breast. As for her renal mass, thought to be a renal cell carcinoma, one wonders if this could be an amyloid deposit mimicking renal cell carcinoma, as has been reported previously.[10] Could the recent-onset chronic diarrhea in this patient be due to amyloid deposits in her colon? It is also possible that her pancytopenia could be the result of amyloid deposition or plasma cell infiltration in the bone marrow.

In summary, we report a rare case of amyloidosis of the breast in the setting of a patient monitored for monoclonal gammopathy of unknown significance. Amyloid should, however, be a differential diagnosis in postmenopausal women presenting with unexplained bilateral breast lesions. Localized primary amyloid tumor of the breast is benign; however, secondary (systemic) amyloidosis involving breast tissue does carry a poorer prognosis.[8] Therefore, it is important to try to seek out and exclude

systemic disease as a causal factor of amyloid protein deposition in these women.

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