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Case Report

Primary lung carcinoid metastatic to the breast

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ABSTRACT

Lung carcinoid tumors account for approximately 2% of lung cancers, with 10% of the tumors represented by the atypical type. While atypical carcinoids are metastatic to intrathoracic lymph nodes in approximately half of the cases on the initial presentation, distant metastases are seen in only 20% of the patients and are found most frequently in bones, liver, adrenal glands, and brain. We present a case of an unusual metastatic disease to the breast in 51-year-old female who developed a new breast mass 2 years after left lower lobectomy due to atypical carcinoid tumor. Atypical pulmonary carcinoid metastases to the breast are exceptionally uncommon, yet they are important considerations for appropriate management, especially with an anamnesis of this neoplasm.

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Introduction

Pulmonary neuroendocrine tumors arise from Kulchitsky cells that are found in the bronchial mucosa and responsible for production and storage of neuroendocrine peptides [1]. Pathologic proliferation of these cells can lead to formation of small tumorlets, low- and intermediate-grade neoplasms, or more aggressive tumors [1]. The biological behavior of these proliferated cells reflects their histologic aggressiveness and ranges from asymptomatic lesions to nefarious malignancies such as small cell lung cancer and large cell neuroendocrine tumors with 5-year survival rate of 21% [2]. Typical carcinoid tumors represent low-grade lung neuroendocrine neoplasms, accounting for 90% of all carcinoid lung tumors [3]. These

tumors usually present as an incidentally discovered or symptomatic noncalcified or partially calcified solid peribronchial or partially or completely obstructing endobronchial lesion in a young individual [4]. The 5-year survival rate is approximately 97%, and the metastatic potential is low: 5%–15% to intrathoracic lymph nodes and only 3% to distant sites [3]. Conversely, atypical carcinoids are considered intermediate neoplasms and account for 10%–20% of bronchopulmonary neuroendocrine tumors [3]. Atypical carcinoids are much more likely to have systemic manifestations and significantly lower 5-year survival rate of 57% [3]; 40%–50% of patients present initially with metastases to intrathoracic lymph nodes, and approximately 20% have distant disease [3]. Both typical and atypical carcinoids occasionally can present with

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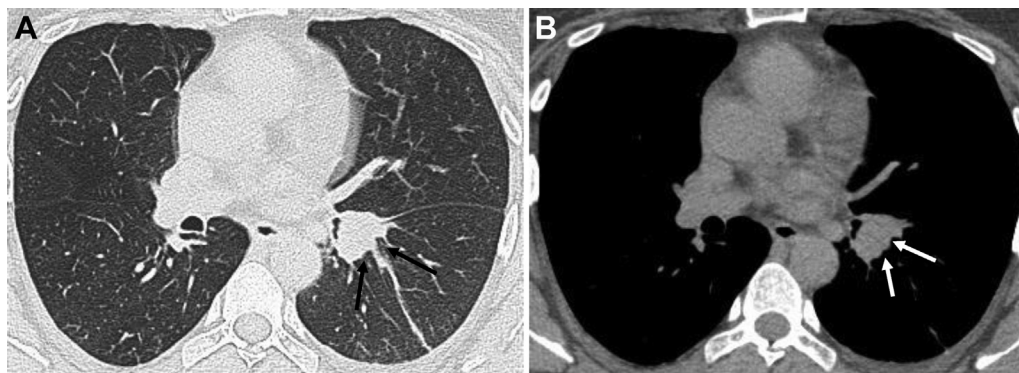


Fig. 1 – Axial chest CT in lung (A) and mediastinal (B) windows shows a medial left lower lobe 2.1 cm nodule (arrows) that abuts and narrows the lobar bronchus. Intraoperatively, bronchial invasion was confirmed.

multifocal deposition of tumorlets along peripheral airways, which may be due to metastatic disease or diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) [5]. Patients with DIPNECH are typically present with symptoms of reactive small airways disease and frequently undergo multiregimen treatment for asthma without improvement [1].

Here, we present a case of a patient with an initial diagnosis of left lower atypical carcinoid and concomitant DIPNECH discovered during workup of chronic cough. Subsequent metastases to the brain and left breast were found after 2 years in remission.

Case report

The patient is a 51-year-old Caucasian female who presented to the pulmonology service with a chronic cough interfering with daily activities. She was referred to pulmonology after numerous years of multiple unsuccessful treatment trials for reactive small airways disease. Upon further workup, CT chest demonstrated medially located 2.1 cm left lower lobe solitary pulmonary nodule, closely abutting and narrowing left lower lobar bronchus (Figs. 1A and B). Subsequent FDG-PET/CT demonstrated significant hypermetabolic activity of the lesion (Fig. 2). The patient underwent bronchoscopy with biopsy with final tissue diagnosis of a neuroendocrine tumor consistent with well-differentiated carcinoid. Intraoperative histopathologic assessment reported staging as pT3N1, with evidence of invasion of the left lower lobar bronchus, the adjacent left inferior pulmonary vein, and a lymph node just medial to the bronchus. Some residual neoplastic tissue was found at the surgical stump, necessitating long-term monthly Sandostatin injections following left lower lobectomy and partial mediastinal lymph node dissection.

Two years later, a routine screening mammogram revealed a new 7-mm indistinct mass (Figs. 3A and B) in the left breast. Subsequent workup with diagnostic mammography and breast ultrasound (Figs. 4A and B and Figs. 5A and B) confirmed the lesion as highly suspicious. Intraoperative histopathologic analysis and special immunostains of the lesion (Figs. 6–9) revealed a neuroendocrine cell origin with positive stains for synaptophysin and chromogranin (markers of

neuroendocrine differentiation) and negative for GATA3 immunostain (marker of primary breast malignancy) [1]. During further metastatic workup, contrasted MRI of the brain demonstrated several focal lesions with biopsy results of neuroendocrine cell metastases as well (Figs. 10A and B).

The patient had since completed whole-brain radiation therapy for metastatic carcinoid tumor to the brain. She then initiated everolimus every other day for her persistent cough. A slowly growing small nodule was noted in the left upper lobe on follow-up CT chest representing either progression of metastatic tumorlets or worsening concomitant DIPNECH (Fig. 11).

Discussion

Atypical carcinoids are categorized as intermediate-grade malignancies, with the designation as atypical carcinoid being based on moderate cytological atypia, necrosis, mitotic

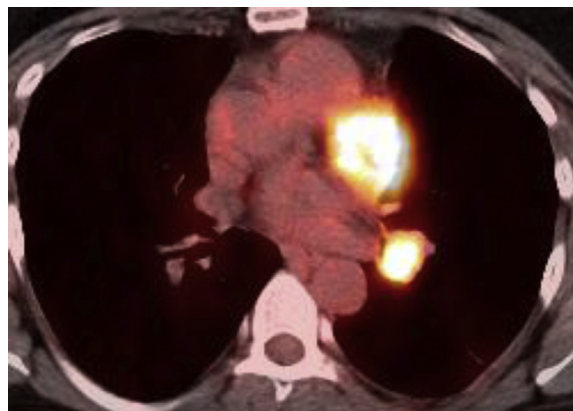


Fig. 2 – FDG-PET/CT shows significant hypermetabolic activity of left lower lobe nodule with a maximum SUV of 8.0. Notice the close relationship to the left inferior pulmonary vein that was found to be invaded in intraoperative examination. FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; SUV, standardized uptake value.

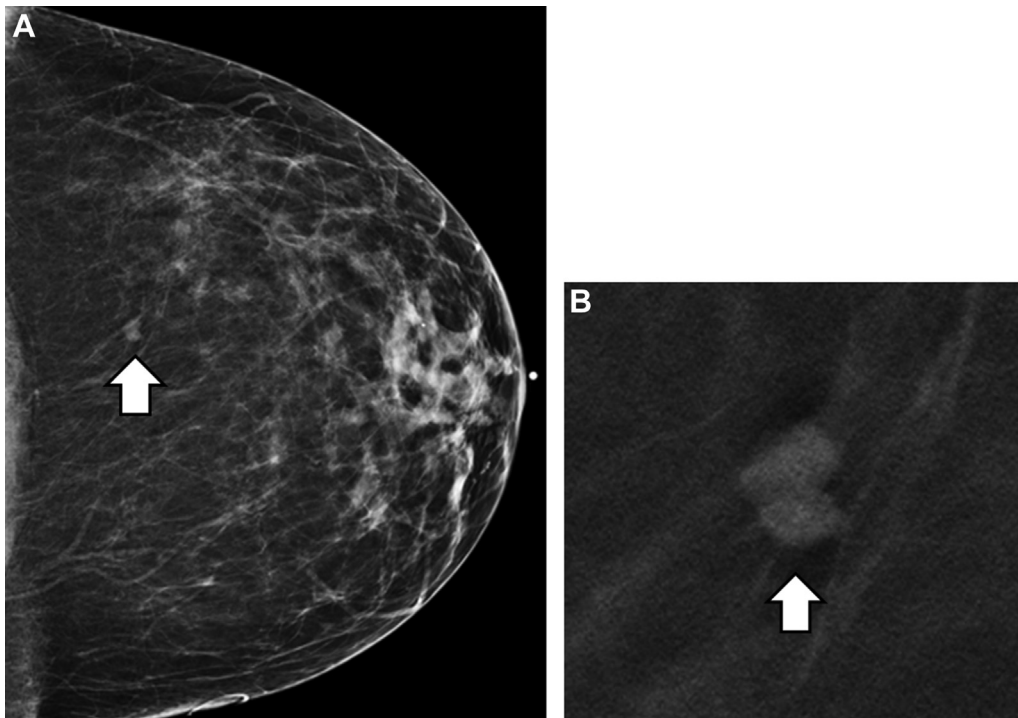


Fig. 3 – (A) Screening mammogram left CC image reveals a new oval mass (arrow) measuring 7 mm in the posterior third of the left breast at the 12:00 position, 10 cm from the nipple. **(B)** Enlarged left CC tomosynthesis view of the new mass shows an indistinct, angular margin. CC, craniocaudal.

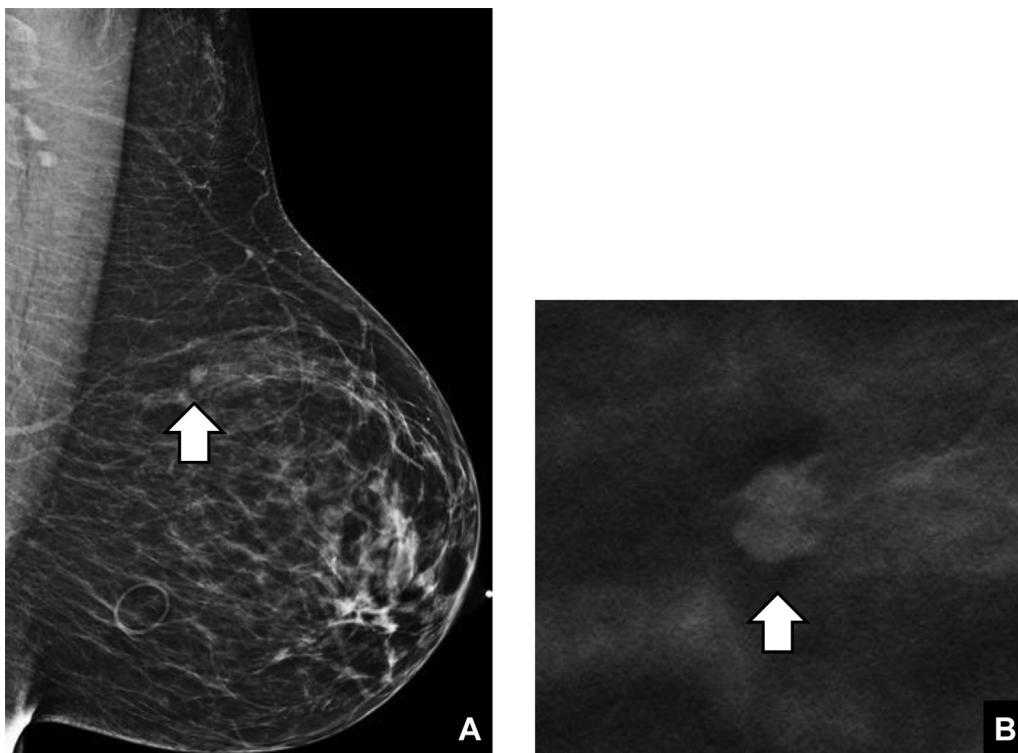


Fig. 4 – (A) Screening mammogram left MLO image reveals a new oval mass (arrow) measuring 5 mm in the posterior third of the left breast at the 12:00 position, 10 cm from the nipple. **(B)** Enlarged left MLO tomosynthesis image showing the new, irregular mass. MLO, mediolateral oblique.

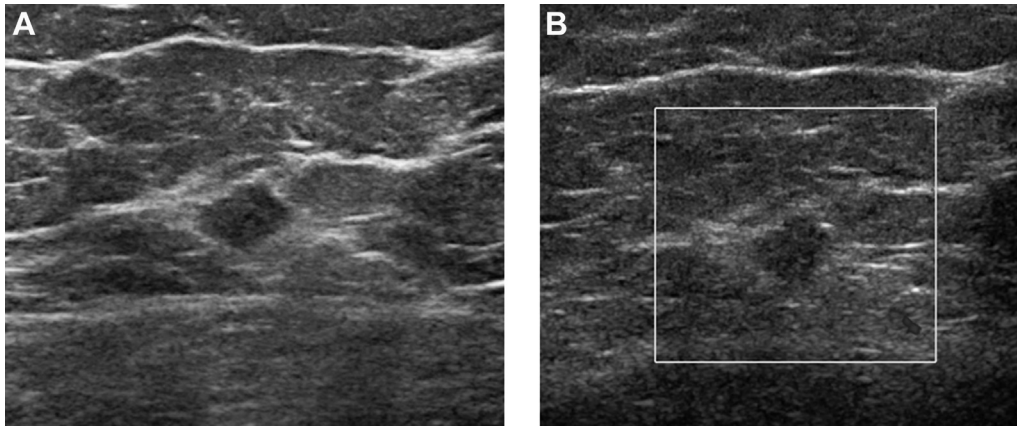


Fig. 5 – Ultrasound performed after initial screening mammogram demonstrates a hypoechoic mass with indistinct margins (A), parallel orientation, without internal vascularity (B), nor posterior acoustic shadowing or enhancement.

activity (greater than 2 but less than 10 cells per high power field), and higher metastatic and invasive potential [6]. Much lower 5-year survival rates are generally present than with overwhelmingly indolent typical carcinoids [6]. Our patient suffered not only from an atypical carcinoid, but concomitant systemic manifestation known as DIPNECH with chronic refractory cough.

DIPNECH was originally described in 1992, when lung surgical pathology specimens revealed neuroendocrine cell hyperplasia surrounding carcinoid foci in patients presenting with small airways disease [5]. Both DIPNECH and carcinoid tumors can present with small multifocal tumorlets [1]. Mosaic attenuation due to air trapping and small scattered solid or groundglass nodules with or without bronchial wall thickening on high-resolution CT chest is classic findings in one-third of symptomatic patients with DIPNECH [1]. Another half of patients with neuroendocrine cell hyperplasia are asymptomatic, with nodules incidentally discovered for other reasons [1]. Frequent coexistence of carcinoid tumor(s) and

nodules from DIPNECH is commonly reported on pathology reports [5]. Symptoms due to DIPNECH resemble refractory asthma and result from constrictive bronchiolitis due to proliferation of neuroendocrine cells along distal airways, leading to intramural and extramural fibrosis [1]. Affected individuals with DIPNECH are almost exclusively middle-aged and older women [5]. It is still unknown why disease manifestation preferentially selects this specific demographic group. On a cellular level, DIPNECH occurs from the pulmonary neuroendocrine cell production of bombesin and gastrin releasing peptide [5]. These ligands kindle exorbitant fibroblastic reaction which induces bronchoconstriction, chemotaxis of other inflammatory cells, and ultimately interstitial fibrosis [5]. Distinction from hypersensitivity pneumonitis or obstructive bronchiolitis can be difficult without clinical insight, since all induce marked endobronchial inflammation [1].

Metastatic atypical pulmonary carcinoid to the breast is exceptionally uncommon, with only 13 reported cases in the English literature. It is generally unknown why breast

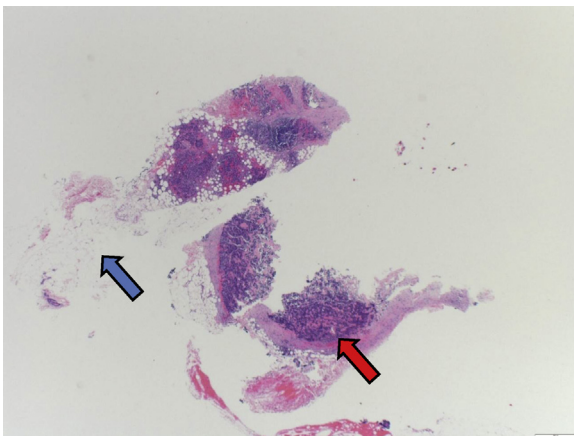


Fig. 6 – Left breast lesion at 12:00, 7 cm from nipple, ultrasound-guided core needle biopsy. Pathology revealed a well-differentiated neuroendocrine tumor. Normal breast tissue (blue arrow) and a well-differentiated neuroendocrine tumor (red arrow) were noted.

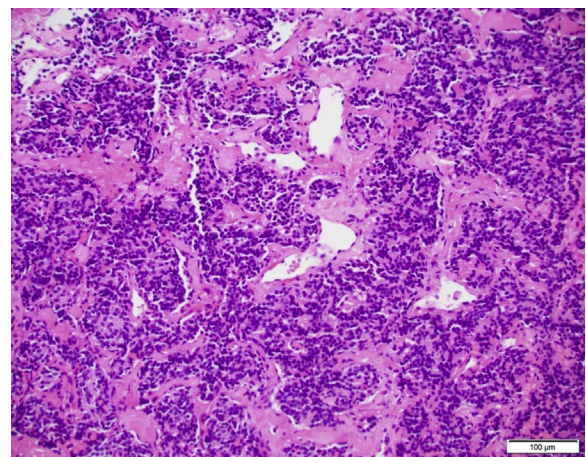


Fig. 7 – The tumor is vascular, with cells arranged in a trabecular and nested pattern. The cells have scant to moderate amounts of cytoplasm with round nuclei and no nucleoli. No atypia, necrosis, or mitoses are present. No normal breast tissue is shown on this image.

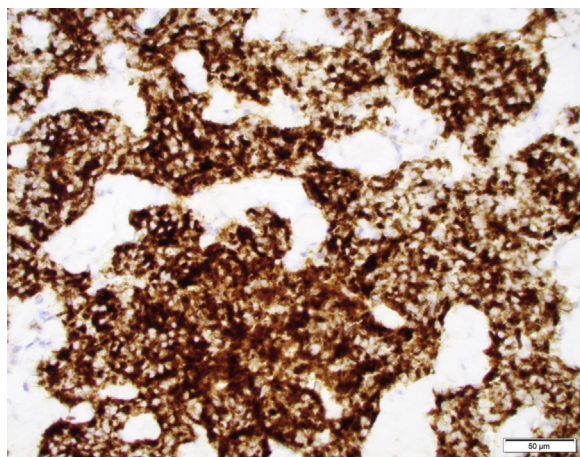


Fig. 8 – Tumor cells are positive for chromogranin (shown), synaptophysin, and CD56 which are markers of neuroendocrine differentiation.

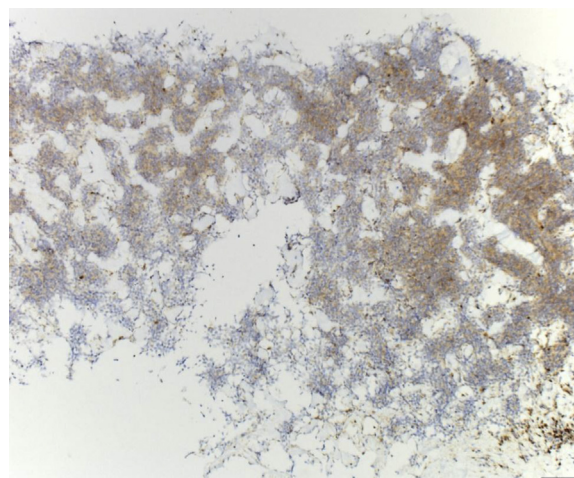


Fig. 9 – The tumor cells were negative for GATA-3 which is a breast marker. Only nonspecific bluish background staining is noted. This finding argues against a primary breast lesion.

metastases are so infrequent; however, it is postulated that since survival time interval is relatively constricted, many cases go unreported. The histopathologic and immunohistochemical distinction is crucial for distinguishing metastatic neuroendocrine neoplasm to the breast from invasive mammary carcinoma as appropriate clinical management can differ. Histologically, nearly all metastatic neuroendocrine tumors to the breast are strongly and diffusely positive for neuroendocrine markers, synaptophysin and chromogranin [7]. In addition, a neuroendocrine metastasis will be estrogen receptor negative and GATA3 negative. Breast neuroendocrine metastasis from a lung primary is commonly thyroid transcription factor-1 positive, as opposed to negative in a primary breast carcinoma [7]. The median survival for metastatic atypical pulmonary carcinoid is 3.3 years, with a 5-year

survival rate at a dismal 24% [6]. However, newer treatment therapies have shown promise. Newer treatment therapies primarily consist of chemotherapeutic agents such as adjuvant platinum–etoposide chemoradiation, temozolomide-based therapies, and octreotide-based therapy, for those with octreotide avid disease [6]. Results are promising, with 10% treatment response, and 70% nonprogression in patients receiving octreotide-based therapies [6]. The average patient treated with this regimen remained stable for a median time of 15 months [6]. For patients with nonoctreotide avid disease, adjuvant platinum–etoposide chemoradiation and temozolomide-based therapies also have had promising rates

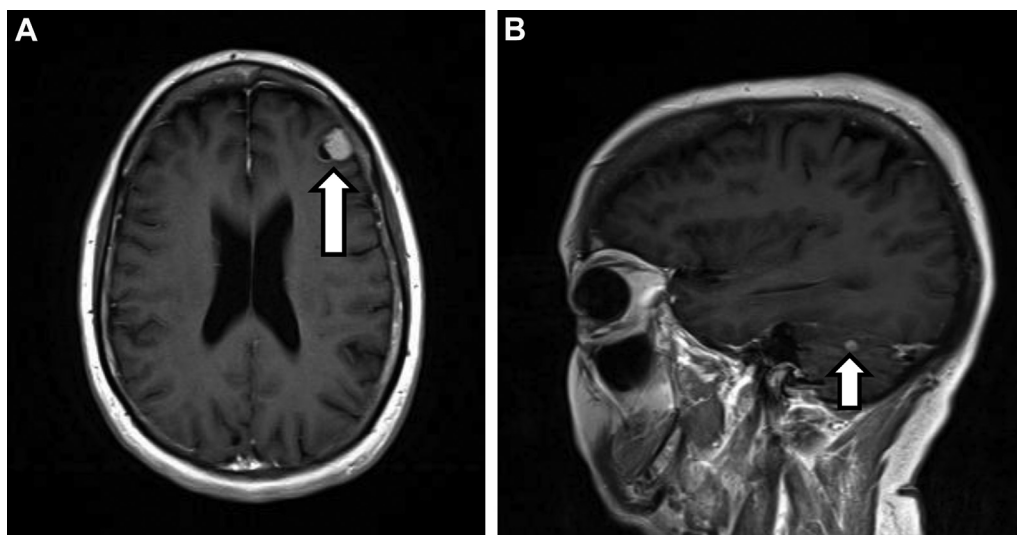


Fig. 10 – Axial T1 postcontrast image (A) shows metastatic disease with an 17 × 16 mm enhancing dural-based lesion in the peripheral left frontal lobe and an additional 6-mm lesion in the right cerebellum (B).



Fig. 11 – Two years after left lower lobectomy, an axial CT chest revealed a new 6-mm left upper lobe nodule indicative of pulmonary disease progression.

of treatment response and disease nonprogression. These patients on average experience a median time of 7 and 10 months of progression-free disease, respectively [6]. Because these tumors are so rare, there is no clear recommendation for surgical management. Historically, patients with breast metastases typically underwent mastectomy because the lesion was often incorrectly diagnosed as a primary carcinoma [8]. In a patient with a few metastatic lesions that are amenable to resection, lumpectomy alone would be acceptable [8]. Axillary lymph node dissection would only be necessary if there was palpable lymphadenopathy [8].

Conclusion

Atypical carcinoid with concomitant DIPNECH is not common. Furthermore, metastasis to the breast is exceptionally infrequent with only a few reported cases in the modern literature. In the past, metastatic atypical carcinoid has shown a meager 5-year survival rate. However, newer treatment modalities are offering hope to those suffering from this disease. Although rare, this case report demonstrates the importance of considering metastatic disease in the differential diagnosis for

a new breast mass in a patient with prior history of invasive carcinoid tumor. Current established histopathologic immunostain analysis would aid to definite diagnosis and timely management.

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