

Case Report

Rare presentation of metastasized primary neuroendocrine breast carcinoma to the right colon and literature review of primary neuroendocrine breast carcinoma metastasized to other organs of the body: case report

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Received: 12 August 2020

Revised: 01 October 2020

Accepted: 28 October 2020

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ABSTRACT

Primary neuroendocrine breast tumors account for less than 0.1% of all breast cancers, hence, unique in nature. This paper aims to report a 56 years old female, known case of primary neuroendocrine breast cancer with a metastatic right colonic neuro-endocrine tumor. The article also aims to review and acclaim the literature regarding primary breast neuroendocrine tumors metastasized to other parts of the body. The patient presented complaining of a breast mass, ulceration, and discharge, which was rapidly progressing. Examination revealed a right breast mass with skin erythema and impending ulceration and right axillary lymph nodes fixed with palpable supra-clavicular lymph nodes. Ultrasound-guided biopsy of right breast mass and axilla disclosed a large cell neuroendocrine carcinoma. CT abdomen and chest revealed metastases to the ascending colon. The patient was treated with palliative radiotherapy along with multiple cycles of chemotherapy for the primary breast cancer. She also underwent a laparoscopic-assisted right hemicolectomy with complete mesocolic excision and primary anastomosis for the metastatic colon cancer. The paper compares the reported case to other similar cases using the framework of an analysis based on age of the patient, primary breast cancer location, method of detection, presence of neuroendocrine markers, primary cancer presentation, metastases symptoms, and location and treatment approach. In conclusion, metastasized primary neuroendocrine breast cancer is a very rare presentation. Incidence and prevalence maybe influenced by age, primary breast cancer location, and presence of neuroendocrine markers. Prognosis may also be a product of metastatic location, associated symptoms and treatment approaches.

Keywords: Primary neuroendocrine breast tumors, Metastasized neuroendocrine carcinoma, Literature review, Case report, Radiochemotherapy

INTRODUCTION

Primary neuroendocrine breast tumors are very rare. They account for less than 0.1% of all breast cancers and less than 1% of all neuroendocrine tumours.¹ Immunohistochemical staining for synaptophysin and

chromogranin on whole sections from 1232 consecutive cases showed a neuroendocrine differentiation in 10.4% of tumours in a recently published retrospective analysis.² Chromogranin and synaptophysin have shown to be the most specific and sensitive neuroendocrine markers.¹ A definitive diagnosis is made with core needle biopsy or with surgical specimen itself.¹ Differential diagnoses

include neuroendocrine tumors metastatic to the breast, Merkel cell carcinoma, lymphoma, and melanoma. Analysis has shown that an associated DCIS component gives more credit to the primary nature of the tumor.³ Appropriate imaging, such as a chest and abdomen computed tomography (CT) scan must be used. Positron emission tomography (PET)-CT with gallium-labelled somatostatin analogs also may be useful to exclude a different primary site for well-differentiated neuroendocrine carcinomas, whereas 18-fluorodeoxyglucose PET-CT could be used in the case of poorly differentiated neuroendocrine carcinoma with a high proliferation rate.⁴ In particular, a larger tumor, with no in situ component, the negativity of estrogen and progesterone receptors, and axillary nodal metastasis point towards the likelihood of a metastasized tumor.⁵

Therefore, this paper aims to report a 56 years old female, known case of primary neuroendocrine breast cancer with a metastatic right colonic neuro-endocrine tumor. Given, the exclusivity of primary neuroendocrine breast cancer and the limited number of reported metastatic tumors, the article aims to review and acclaim the literature regarding primary breast neuroendocrine tumors metastasized to other parts of the body. We present the following case in accordance with the 13B care reporting checklist.

CASE REPORT

A 56 years old female presented on 13 June 2019 complaining of a breast mass, ulceration, and discharge which was rapidly progressing. Examination revealed a right breast mass with skin erythema and impending ulceration. The mass is fixed and measures around 20x2 cm. Right axillary lymph nodes were fixed with palpable supra-clavicular lymph nodes.

Past medical history is significant for T2 diabetes mellitus, hypertension, hyperlipidemia, and hypothyroidism. Analysis for breast cancer related history is significant for being perimenopausal, attained menarche at age 14, has 4 children (first was at 20 years), (+) ve breastfeeding history. Medication history includes lipitor, coversyl, rabizol, metformin and novomix. past surgical history includes laparoscopic cholecystectomy 15 years ago, cervical polyp removal and cataract surgery. Family history is significant for a sister who was diagnosed with breast cancer at 60 years and is undergoing treatment. Father was diagnosed with brain cancer.

Investigations include labs, imaging and pathological work. Labs were significant for thrombocytosis and hyperglycaemia.

Radiological investigations done include US bilateral breast, ultrasound-guided biopsy of right breast mass and axilla, MRI Brain, CT/PET, U/S abdomen and MRI abdomen. US bilateral breast showed a right whole breast malignant looking mass, and malignant looking fixed

right axillary lymph nodes (BIRADS 5), and left breast retro areolar suspicious-looking duct-ectasia (BIRADS 4).

Pathological work included ultrasound-guided biopsy of right breast mass and axilla that disclosed a large cell neuroendocrine carcinoma (Figure 1). The IHC profile was as follows: ER; negative, PR; negative, HER-2/neu 4B5; negative, chromogranin; negative, synaptophysin; positive, CK5/6; negative (Figure 6), p63; staining in one area. Ki-67; 95%, CK14; negative, MLH-1; expression loss not identified, MSH-2; expression loss not identified, MSH-6; expression loss not identified, PMS-2; expression loss not identified, no immunohistochemical staining in favor of MSI.

MRI Brain was negative for metastases. PET scan on 28 October 2019 showed evident metabolic regression and mild size regression of the known large infiltrating and ulcerative right breast mass as well as the right axillary and sub-pectoral necrotic nodal lesions. Also, two newly developed adjacent hypermetabolic right posterior cervical necrotic nodal lesions were revealed, likely metastatic. Besides, a hypermetabolic segmental wall thickening of the ascending colon associated with an adjacent hypermetabolic precaval nodal lesion was also noted (Figure 7). Differential diagnosis includes metastasis and metachronous malign process for histopathological correlation. Otherwise, the rest of the scanned body keeps free. US abdomen showed dilated CBD with intraluminal hyperechoic focus that could be stone/mud, but, was not worked up with MRCP due to no clinical indication.

CT abdomen and chest suggested sealed perforation with abscess formation of the ascending colon on top of marked wall thickening and an exophytic mass (necrotic) in the medial aspect with suspicious lymph nodes (Figure 8). CT chest revealed the right breast mass (Figure 9). Hence, the final diagnosis is a primary neuroendocrine tumor of the right breast that has metastasized to the right colon as a right colonic sided neuroendocrine tumor.

In terms of management, the patient received 1 cycle of carboplatin etoposide on 30 July 2019. When she was due for her second cycle, she was admitted due to an infection in her breast wound and received multiple antibiotics. In September 2019, the patient received breast palliative radiotherapy along with capecitabine. On 29 October 2019, the patient underwent laparoscopic-assisted (later converted to open) right hemicolectomy with complete mesocolic excision and primary anastomosis. On 24 November 2019, she received her second cycle of chemotherapy. She later was hospitalized for tachycardia then developed fever and received antibiotics. The chemotherapy was shifted to AC.

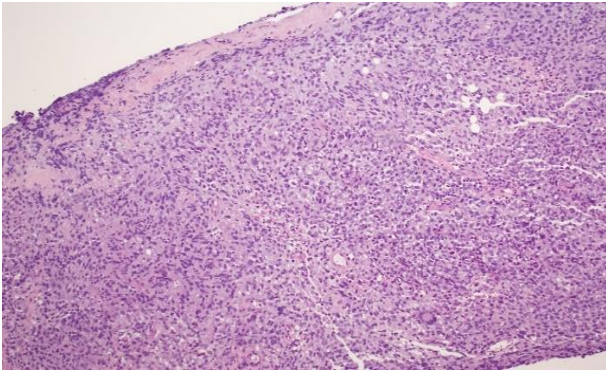


Figure 1: Core biopsy of the breast showing diffuse neoplastic cells.

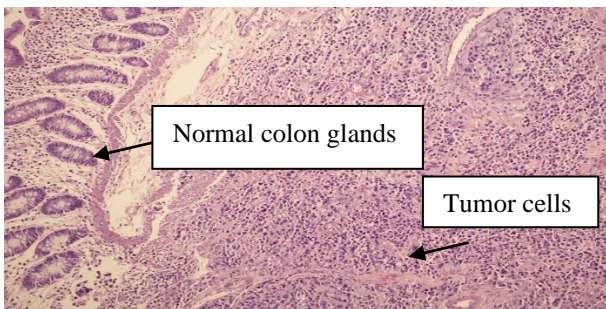


Figure 2: Core biopsy of right sided colon showing tumour cells.

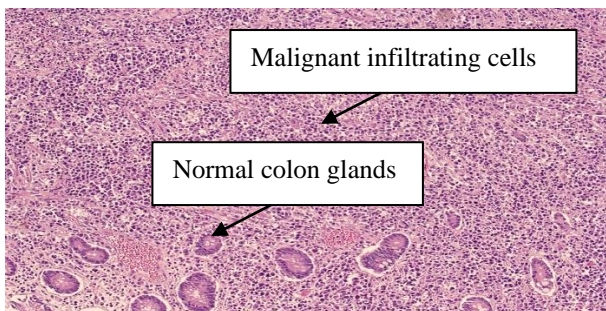


Figure 3: Core biopsy of right sided colon showing malignant infiltrating cells.

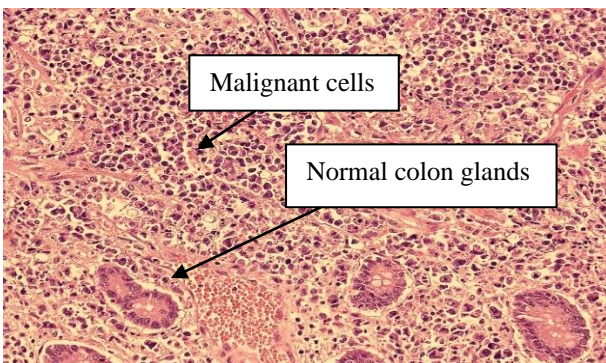


Figure 4: High power slide of core biopsy of right sided colon showing malignant cells.

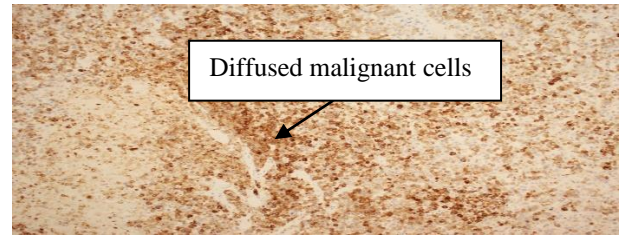


Figure 5: Immunohistochemistry of the colon-CD 56 (neuroendocrine marker).

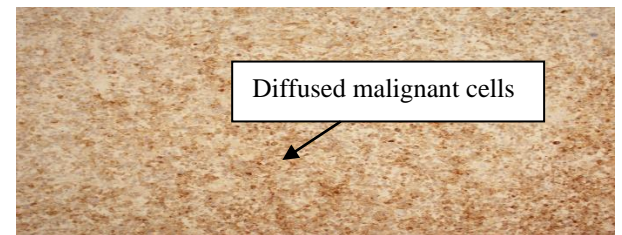


Figure 6: Immunohistochemistry of the colon-synaptophysin stain (neuroendocrine marker).



Figure 7: PET scan.

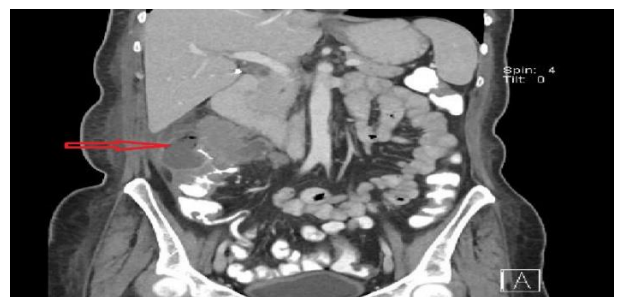


Figure 8: CT scan abdomen.



Figure 9: CT chest.

Table 1: Analysis of selected literature (17 cases) and metastases locations.

Case report ref. no.	Age, sex	Location of primary breast cancer/ Histology	Metastasis location	Treatment primary	Treatment metastasis
8	73 y, F	Location: right breast Histology: invasive ductal breast carcinoma with neuroendocrine differentiation.	Pelvic bone, right femoral bone, lumbar spine, sternum left clavicle. Modality: MRI. Hypodense lesion in the transition zone between the neck and head of the pancreas. Modality: contrast-enhanced CT, several suspicious nodules in lungs. Modality: contrast-enhanced CT, subcutaneous metastases in the face, back, and trunk.	Lumpectomy axillary, LN dissection.	Resection, radiation, chemotherapy.
9	63 y, F	Location: left breast Histology: multifocal CIS carcinoma with neuroendocrine features (chromogranin and synaptophysin), focal positive for estrogen receptor.	Liver+buttock metastases, cardiac metastases.	Left mastectomy and sentinel LN biopsy.	Cytotoxic chemotherapy and tamoxifen.
10	80 y, F	Location: left breast Histology: lobular carcinoma with neuroendocrine differentiation.	Intraluminal mass at the ileocecal valve. Modality: AXR: intestinal air-fluid levels CT: distended intestinal loops (from the ligament of treitz to 10 cm proximal to ileocecal valve) and thickening of the intestinal wall bone metastases. Modality: bone scintigraphy.	Mastectomy.	Ileal mass resected and continuity re-established with end to end anastomosis, continuous administration of letrozole and zoledronic acid.
11	76 y, F	Location: right breast Modality: mammography. Histology: poorly differentiated small round blue cells with high nuclear: cytoplasmic ratio, finely granular chromatin, and scant cytoplasm consists tent with MCC.	5 cm brain metastases.	Partial mastectomy and axillary LAD.	Received 4 cycles of adjuvant cisplatin/etoposide and post-op. Radiation.
12	69 y, F	Location: left breast Modality: mammography Histology: neuroendocrine carcinoma, large cell type, grade 2 and triple-negative.	Tubular adenomas in cecum. Modality: routine colonoscopy, hepatic metastases, pancreas (head and proximal body), tissue mass at root of mesentery near duodenum and adjacent to ascending colon. Modality for 2-4: CT.	Selective internal radiation therapy (SIRT) to debulk tumor for palliation.	Systemic chemotherapy options discussed

Continued.

Case report ref. no.	Age, sex	Location of primary breast cancer/ Histology	Metastasis location	Treatment primary	Treatment metastasis
13	68 y, F	Location: two suspicious lesions of the left breast. Modality: US following auto-detection Histology: showed moderately differentiated, G2, pT1BN1 neuroendocrine tumor.	Post-op. total body CT showed, bilateral mediastinal pathological LN, liver, lung, left adrenal metastases, 3 secondary brain lesions, bone lytic secondary lesions in the spine and ribs.	Left breast lumpectomy and sentinel LN dissection+ axillary left dissection.	Received a combination of cisplatin and etoposide and first-line chemotherapy. Later, wait and see strategy adopted and bisphosphonates therapy (zoledronic acid) added for 24 months for liver progression, received 8 cycles of CAV chemotherapy after 2 y, a third line chemotherapy with oral capecitabine and temozolomide every 28 days .
14	57 y, F	Location: left breast carcinoma. Histology: neuroendocrine carcinoma, invasive type: stage T2N0M0) 12 years earlier.	Pterygopalantine fossa CT- lysis of the posterior wall of the left maxillary sinus.	Left modified radical mastectomy with axillary lymph node dissection.	Radiation therapy.
15	79 y, M	Location: right breast. Histology: small-cell carcinoma (SMCC) of the breast.	Metastatic neck lymph nodes, pulmonary metastases, bone metastases hepatic metastases.	Simple radical mastectomy and level I lymph-adenectomy, without sentinel lymph node identification.	2 cycles of irinotecan combined with carboplatin, later, docetaxel for 1 cycle.
16 Case 1	50 y, F	Location: right breast.	Multiple lung metastases.	Underwent 8 cycles of chemotherapy and subsequent radical mastectomy with axillary lymph node resection.	-
16 Case 2	53 y, F	Location: right breast. Histology: solid small-cell neuroendocrine carcinoma, G III with negative estrogen and progesterone receptors. IHC: CK AE1/AE3 positive, CD56 positive, TTF1 negative, chromogranin, and	Signs of local recurrence in the form of permeation nodules. CT showed lung metastasis, liver metastasis.	neo-adjuvant chemotherapy.	Radiotherapy was started along with hyperthermia and a new chemotherapy regime was considered.

Continued.

Case report ref. no.	Age, sex	Location of primary breast cancer/ Histology	Metastasis location	Treatment primary	Treatment metastasis
		synaptophysin negative.			
17	83 y, F	Location: primary right breast neuroendocrine.	Metastatic disease in the ribs, thoracic vertebral bodies, and the right hilar lymph nodes. Modality: PET. Histology: poorly differentiated small cell carcinoma.	Mastectomy.	Letrozole changed to anastrozole zoledronic acid (monthly infusion).
18	61 y, F	Location: left breast and left axillary masses. Histology: two lumps SCNC.	A small lesion in the left lung. Modality-PET.	Mastectomy and LN resection, radiation to the chest wall and regional lymph nodes.	Six courses of VP16 and cisplatin.
1	62 y, F	Location: inferior outer quadrant of the left breast (axillary region).	Suspicious supraclavicular adenopathies. Modality-CT.	After chemotherapy, left mastectomy along with an ipsilateral axillary lymphadenectomy followed by adjuvant chemotherapy treatment.	Chemotherapy docetaxel, trastuzumab, and carboplatin (6 cycles, every 21 days).
19	76 y, F	Location: left breast mass with left axillary adenopathy.	Left-sided pleural effusion Modality (CXR and CT), enlargement of the peridiaphragmatic lymph nodes. Modality-CT scan, the left breast, mediastinal, internal mammary, and left axillary lymphatic chains bilateral hilar and mediastinal lymphadenopathy, sternum, left anterior ribs, and post 8 th rib, spleen, staging CT showed 6 and 7, sacral mass, four peripheral parenchymal lung metastases.	Palliative radiotherapy the patient completed 2 cycles of streptozocin capecitabine with no response hence palliative surgical intervention. Later, letrozole 2.5 mg daily and monthly zoledronic acid.	-
20	53 y, F	Location: neuroendocrine breast carcinoma (NBC) 10 years earlier.	Brain tumor. Modality CT-high-grade glioma and primitive neuroectodermal tumor. Histology: poorly differentiated neuroendocrine carcinoma.	Unknown (UK).	UK.
21	65 y, F	Location; left breast density. Histology grade 2 ductal carcinoma with neuroendocrine differentiation ER	Sacrum. Modality-MRI.	UK.	UK.

Continued.

Case report ref. no.	Age, sex	Location of primary breast cancer/ Histology	Metastasis location	Treatment primary	Treatment metastasis
		positive (8/8), weakly positive for progesterone receptor (PR) (2/8) and human epidermal growth factor receptor-2 (HER-2) negative.			
22	57 y, F	Location: right breast Histology: poorly differentiated NE carcinoma of the breast.	Osteolytic lesion in the right acetabulum presented with right hip pain for 3 weeks. Modality- X-RAY, proximal ascending colon Modality-PET.	Total mastectomy of her right breast with biopsy of the sentinel lymph nodes.	Radiotherapy for hip pain followed by etoposide and cisplatin (EP) with hormone therapy (tamoxifen). Later, salvage treatment with second-line chemotherapy with the FEC regimen (5FU/epirubicin/cyclophosphamide) followed by paclitaxel in addition to letrozole.
Metastases locations					
Location	No. of cases	Case references			
Bone	9	Christensen and Mortensen (2016), Spiridis and Kambaroudis (2011), Salvia and Brizzi (2019), Takanami and Ota (2017), Jiang and Wang (2014), Alkaied and Harris (2012), Vidulich and Donley (2007), Okines and AF (2010), Hsien Tai and Hsieh P (2018). ^{8,10,13,15,16,18,19,21,22}			
Pancreas	2	Christensen and Mortensen (2016), Amin A and Kong A (2011). ^{8,12}			
Skin/fat/muscle	2	Christensen and Mortensen (2016), Hennessey and Gilcrease (2007). ^{8,9}			
Liver	4	Hennessey and Gilcrease (2007), Amin A and Kong A (2011), Jiang and Wang (2014), Puscas and Lisencu (2013). ^{9,12,15,16}			
Heart	1	Hennessey and Gilcrease (2007). ⁹			
Bowel	3	Spiridis and Kambaroudis (2011), Amin A and Kong A (2011), Hsien Tai and Hsieh P (2018). ^{10,12,22}			
Lungs	6	Christensen and Mortensen (2016), Salvia A and Brizzi M (2019), Jiang and Wang (2014), Puscas and Lisencu (2013)-Case 1 and 2, Adegbola and Connolly (2005)-Case 3, Vidulich and Donley (2007). ^{8,13,15,16,18,19}			
Brain	2	Nambudiri VE, Vivero M, Watson AJ (2016), Zanin and Poliani (2019). ^{11,20}			
Lymph nodes	4	Salvia A and Brizzi M (2019), Jiang and Wang (2014), Alkaied and Harris (2012), Vidulich and Donley (2007). ^{13,15,17,19}			

DISCUSSION

Breast tumors with neuroendocrine features are divided into three groups; neuroendocrine tumor-well differentiated (carcinoid like), neuroendocrine tumor-poorly differentiated, the patient in our case falls in this category and invasive carcinoma with neuroendocrine features.⁶

Primary NECB presents similar to other breast cancers. They could present as a lump with or without axillary lymphadenopathy. In our case, the patient presented with a breast mass that had an erythematous appearance and ulceration. Also, the right axillary lymph nodes were fixed along with palpable supraclavicular lymph nodes found on examination. The patient may experience symptoms due to paraneoplastic syndromes from the ectopic production of adrenocorticotrophic hormone, norepinephrine, or calcitonin.⁷ However; the patient in the reported case did not report the above symptoms. The

disease is most commonly diagnosed in women in their sixth or seventh decade of life. The radiological features do not have an identifiable or unique set of features. Although, reported cases have been described to appear on mammography as a round, sharply circumscribed, hyperdense mass. Breast US shows a hypoechoic solid mass with irregular margins, more vascularity, more posterior echo, and a cystic component. MRI shows even low signal intensity with spaced out rapid initial enhancement on the T1-weighted image.⁴

This report aims to analyze the existing cases on metastasized primary neuroendocrine breast tumor. The first aspect is age. Out of the 18 cases included in this review, 6 cases are between 50-60 years including our index case, 6 cases are between 60-70 years, 4 cases are between 70-80 years, and 2 cases between 80-90 years. Hence it can be derived that majority of the cases are between 50-70 years (12 cases) with relatively few cases in older year groups in this cohort of patients. However, all the cases are more than 50 years. Hence, statistically most patients are in the 50-70 years age group but the size of the study may limit its applicability in the bigger context.

The second aspect is the location of the neuroendocrine cancer of breast (NECB). 8 of the review cases affected the right breast including our index case. 8 cases involve the left breast and 1 case does not have the information available is it was a retrospective finding. Hence, primary breast cancer location does not have a characteristic location with regards to metastasized NECB.

The third aspect is how the breast cancers were first suspected. Out of the 18 cases, 14 cases were self-detected as a mass and brought to medical attention upon suspicion. 1 case was detected by screening mammography. A related aspect is confirmation through a diagnostic modality. 14 out of 18 cases including our index case was diagnosed by core biopsy without a previous radiological investigation while 4 cases were found by mammography/US and then biopsied later. Hence it can be concluded that the majority of cases are identified on self-inspection as masses and then conformed by core biopsy with regards to NECB.

The fourth aspect is the presence of neuroendocrine markers such as synaptotrypsin or chromogranin. With regards to histology, 13 out of the 18 cases have explicitly stated neuroendocrine differentiation. 2 cases including our review case have clearly stated positive synaptotrypsin/chromogranin tumor markers. Hence, it can be concluded that majority of breast cancers have clear neuroendocrine differentiation.

The fifth aspect is the timing of presentation of the primary breast cancer. 15 cases including the index case presented first with breast cancer features. While 3 cases presented with symptoms resulting from the respective metastases. The first of those cases presented as acute

abdomen.¹⁰ The second case was detected on routine colonoscopy showing tubular adenomas in cecum before screening mammography.^{11,12} The third case presented as hip pain for 3 weeks.⁹ The next part of the review is to compare the metastases location and derive the most common location. The most common metastases location is the bone particularly the spine and the ribs. The lung is next in the list for the most probable location. The heart is the least likely location.

The seventh aspect of the analysis is with regards to single vs. multiple metastases. 8 cases including the index case has single region metastasis while 10 cases had metastases to multiple locations. Therefore, statistically primary NECB tend to have multiple metastases.

The last but not the least is the mode of treatment undertaken to manage each case. The treatment can be looked at with regards to primary breast cancer and the metastasized cancer separately. Lumpectomy with LN dissection was reported in the case by Christensen et al.⁸ Hennessey et al reported mastectomy and sentinel LN biopsy.⁹ It can be summarized the major choice of treatment was lumpectomy or mastectomy with or without LAD dissection as directed by the stage of cancer (TNM). The case by Puscas et al reports that the patient underwent neoadjuvant chemotherapy, 4 cycles with farmorubicin, cyclophosphamide, and taxotere to reduce the size of the tumor.¹³⁻¹⁶ Examples of the use of targeted therapy such as letrozole and later anastrozole can be seen used in the patient reported by Alkaied et al.¹⁷ Adegbola et al reported the combined usage of radiotherapy and chemotherapy specifically radiation to the chest wall and regional lymph nodes and six courses of VP16 and cisplatin.¹⁸

Treatment for the metastatic cancer was discerned by location, relative involvement of surrounding structures, comorbidities of the patient, available facilities, and presence of single or multiple metastatic locations. Len et al reported resection of metastatic lung nodules. While Hennessey et al report cytotoxic chemotherapy and tamoxifen as per standard treatment protocol for metastatic breast cancer.¹⁹ Amin et al reported a clinical trial of selective internal radiation therapy (SIRT) to debulk the tumor for palliation along with systemic chemotherapy.¹² It can be inferred that treatment teams preferred to adopt chemoradiotherapy in the cases of metastatic breast cancer, resected if accessible for palliation and better response to chemo and wait and see strategy if the patient was not suitable for intervention as suggested by the performance status.

CONCLUSION

Current paper focuses on reporting a case of primary neuroendocrine breast cancer that presented as a right breast large mass with skin erythema and impending ulceration that metastasized to the ascending colon identified on CT abdomen as perforation with abscess

formation of the ascending colon. The paper also attempts to conduct a literature review of the primary breast neuroendocrine tumors that have metastasized elsewhere. This review was analysed with regards to age, primary breast cancer location, presentation with metastases symptoms, diagnostic modality, metastases location, single metastases vs. multiple metastases, and approach. Firstly, age is a major determining factor with regards to metastases. Secondly, the location primary neuroendocrine breast tumor is equivocal. Thirdly, the majority of the cases were self-detected as a lump or a mass and biopsied before radiological investigation. Core biopsy was the preferred first investigation due to late presentation. Fourthly, the presence of neuroendocrine differentiation was present in the majority of cases. Next, most of the reviewed cases presented with breast cancer first. With regards to metastases, most were to the bones, secondly the lungs. Majority of the cases tend to metastasize to multiple regions/organs. It can be summarized that the major choice of treatment was lumpectomy or mastectomy with or without LAD dissection as directed by the stage of cancer (TNM). It can be inferred that treatment teams preferred to adopt chemoradiotherapy in the cases of metastatic breast cancer, resected if accessible for palliation and better response to chemo, and wait and see strategy if the patient was not suitable for surgical intervention. This paper enhances knowledge and understanding in the field by reporting a detailed rare case of primary neuroendocrine cancer of breast that has metastasized to the right side of the colon thereby giving an opportunity to members of the surgical fraternity to witness how patients may present, diagnostic approaches and management approaches. The Literature review on metastasized primary neuroendocrine breast carcinoma enables those examining the literature to familiarize with similar rare cases and learn about the different factors (dependent, independent) that may have an effect on the presentation of these cases, thereby, allowing healthcare professionals to be better prepared in providing early, prompt and well-suited care for their patients. In conclusion, metastasized primary neuroendocrine breast cancer is a very rare entity with a lot of scope for research and review eventually enabling better streamlining or derivation of diagnosis and treatment guidelines that will help achieve the most optimum prognostic potential.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Saeed MF, Juma IM, Varkey RG, Mathew KP, Kamali MA. Rare presentation of metastasized primary neuroendocrine breast carcinoma to the right colon and literature review of primary neuroendocrine breast carcinoma metastasized to other organs of the body: case report. *Int Surg J* 2020;7:4188-97.