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A case report on metastatic ileal neuroendocrine neoplasm to the breast masquerading as primary breast cancer

A diagnostic challenge and management dilemma

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Abstract

Rationale: Metastatic neuroendocrine neoplasms (NENs) to the breast are very rare entities comprising only 1% to 2% of all metastatic breast tumors. In this article, we describe a case of a neuroendocrine ileal neoplasm metastatic to breast and liver, with breast metastatic tumor to be the initial manifestation of the disease.

Patient concerns: We herein report a rare case of a female patient admitted to our department with a palpable painful mass on her left breast.

Diagnosis: The surgical and histological investigation revealed a metastatic neuroendocrine neoplasm to the breast originated from terminal ileum.

Interventions: A left lumpectomy, right hemicolectomy, cholecystectomy, left hepatectomy along with liver metastasectomies (V, VI, VIII) plus radiofrequency ablation of lesions to the right liver lobe plus standard lymphadenectomy was performed.

Outcomes: Considering the advanced stage of the disease, the patient received an adjuvant therapy of somatostatin analog plus everolimus. Under the guidance of oncological consultation, patients follow-up with CT and MRI scan and clinical re-evaluations in the first 3 and 6 months, substantiates no evidence of recurrence and she presents herself asymptomatic.

Lessons: An appropriate level of suspicion and selective immunohistochemistry in these cases, particularly where no prior history of a known primary neuroendocrine neoplasm occurs, may help to diagnose a previously undetected neuroendocrine tumor elsewhere in the body and provide guidance for the appropriate treatment selection.

Abbreviations: *5-HIAA = 5-hydroxyindoleacetic acid,* BI-RADS = breast imaging-reporting and data system, CAP/TEM = capecitabine plus temozolomide, CgA = chromogranin, CT = computerized tomography, ER = estrogen receptors, *FISH* = fluorescence in situ hybridization, HER2 = human epidermal growth factor receptor 2, *HPF* = high-power field, MRI = magnetic resonance imaging, NENs = neuroendocrine neoplasms, NSE = neuron-specific enolase, PR = progesterone receptors, SRS = somatostatin receptor scintigraphy.

Keywords: breast, breast carcinoma, carcinoid, metastasis, neuroendocrine neoplasm

1. Introduction

Neuroendocrine neoplasms (NENs) are rare entities considered to arise from enterochromaffin cells throughout the diffuse endocrine system. These tumors are usually characterized by the presence of neurosecretory granules containing serotonin and various other vasoactive substances, and may be associated with secretory syndromes, such as carcinoid syndrome, characterized by flushing, diarrhea and wheezing.[1] Given that these cells are distributed widely throughout the body, neuroendocrine neoplasms can arise anywhere. Their presence has been documented in a large variety of systems, including most commonly the lungs, bronchi and gastrointestinal tract. The gastrointestinal tract is the most frequent site for NENs.[2] After the appendix, the small intestine is the second most commonly affected site in the gastrointestinal tract, usually within the last 50 cm of the ileum, with a median age of manifestation of approximately 6th to 7th decade of life. The annual incidence of NENs is approximately 2 to 5 cases per 100,000 people, while their true incidence is most

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likely higher given the indolent nature of these neoplasms, also suggested by their incidental finding in autopsies at a rate of 0.5% to 1%.[3]

The primary significance of NENs is the malignant potential of the tumors themselves which is related to their primary location, size, depth of invasion and growth pattern. Even though they are relatively slow growing tumors, they have a strong tendency to metastasize, frequently to regional lymph nodes, liver and bone. Distant metastasis at presentation occurs in about 22% of cases, whereas in 50% of these cases, the primary source remains unknown. The prognosis for these patients has improved, presumably due to continuous advance in diagnostic modalities and due to new treatment regimens offered.[4] The overall 5-year survival rate is estimated to be 70% to 80%. The best 5-year survival rate is observed in patients with localized disease (93%), whereas the poorest in patients with distant metastatic disease (20%–30%), indicating that prognosis is greatly influenced by the stage of disease.[5]

Metastasis to the breast is a very rare complication of NENs. Often presenting as a breast mass with nonspecific characteristics on screening breast imaging,[6] it poses a diagnostic challenge for clinicians, as well as a management dilemma on determining the most accurate and effective treatment plan for the patient. In this article, we describe a case of a neuroendocrine ileal neoplasm metastatic to breast and liver, with breast metastatic tumor to be the initial manifestation of the disease.

2. Case presentation

A 52-year-old Caucasian female patient presented to our outpatient clinic with a palpable painful mass on her left breast. The patient's symptoms appeared 12 months ago when she first noticed a small painful mass on her left breast during her self-examination testing. She had not undergone a mammography for the past 2 years and during this period she had lost approximately 6 kg. The remainder of her medical history was unremarkable. A diagnostic mammography was performed which demonstrated 2 suspicious lesions on 11 to 12 o'clock on her left breast (BIRADS IV) and the patient was scheduled for excisional biopsy. At admission, the physical examination—apart from the palpable lesion—and the laboratory examinations were unremarkable. Her carcinoembryonic antigen value was 2.6 ng/mL, a-fetoprotein was 5.1 ng/mL, cancer antigen 19-9 was 24.9 U/mL, cancer antigen 15-3 was 21.2 U/mL and cancer antigen 125 was 23.0 U/mL. Breast magnetic resonance imaging (MRI) displayed no lymphadenopathy and bone scintigraphy was negative for metastatic disease. The patient underwent an excisional biopsy and subsequently a lumpectomy that revealed metastatic neuroendocrine neoplasm (NEN ki-67 pending) of unknown primary origin to the breast. Evaluation for synaptophysin and chromogranin immunoreactivity was 100% positive. Immunostaining for ER and PR was performed and exhibited negative staining for both. Her-2 FISH was conducted, which was also negative for Her-2 amplification (Fig. 1A–F). The Ki-67 proliferative index was deemed 1% to 2%.[7]

A thorough work up was initiated to detect the primary neoplasm site with a chest computer tomography (CT) and brain MRI showing no pathological findings, while abdominal MRI revealed a large lesion of the terminal ileum that caused intussusception plus multiple liver lesions (Fig. 2A and B). Further assessment with colonoscopy verified the presence of a mitotic lesion in the terminal ileum and the histopathological examination was suggestive of a well- differentiated NEN with ki-67: 1% to 2%. Somatostatin receptor scintigraphy (SRS) detected an increased uptake in primary ileal lesion and probable regional metastatic lymph nodes. CgA, NSE, and 5-HIAA levels were increased to the levels of 14.5 nmol/L, 8.55 μg/L, 24.4 mg/24 h, respectively.

Since the patient was asymptomatic displaying no signs of carcinoid syndrome in addition to significant tumor burden of her disease, she was induced capecitabine plus temozolomide (CAP/TEM), followed by everolimus treatment.[8] Two months postinduction pharmacological therapy, patient became symptomatic with partial small intestinal obstruction and were submitted to exploratory laparotomy with intent of complete resection of primary origin plus of liver metastases if it was feasible. A right hemicolectomy, cholecystectomy, left hepatectomy along with liver metastasectomies (V, VI, VIII) plus RF ablation of lesions to the right liver lobe plus standard lymphadenectomy was performed (Fig. 3A–C). Reconstruction of the intestinal transit was achieved with an end-to-side ileocolic anastomosis. Her postoperative course was uneventful, and she was discharged from hospital on the 12th postoperative day in good general condition.

The final histological examination of the specimen was conclusive of a primary well differentiated G1- G2 NEN of terminal ileum with maximal diameter of 4 cm, with a significant subserosal extension without penetration of the overlying serosa. In total, 33 lymph nodes were excised and 14 were infiltrated by the neoplasm. Expression of synaptophysin and chromogranin immunoreactivity was 100%. Liver metastases were histologically confirmed presenting fibrotic reaction as a response to prior pharmacological therapy. Ki-67 was 1% to 2% and mitotic rate was 15–20/ 10 HPF. The neoplasm was staged as pT3N1M1c (WHO 2017).

Considering the advanced stage of the disease, the patient received an adjuvant therapy of somatostatin analog plus everolimus. Under the guidance of oncological consultation, patients follow-up with CT and MRI scan and clinical re-evaluations in the first 3 and 6 months, substantiates no evidence of recurrence and she presents herself asymptomatic.

3. Discussion

Metastases to the breast are unusual, constituting less than 1% of all malignant mammary neoplasms. The majority of the metastatic lesions originate from the contralateral breast or hematopoietic malignancies and may present clinically as single or multiple well- circumscribed lesions. Stomach, kidney, ovary, lung, and skin are the rest of the familiar primary sites. Metastatic gastrointestinal neuroendocrine neoplasms to the breast are very infrequent entities and comprise only 0.5% to 1% of all metastatic tumors to the breast.[6] To the best of our knowledge, <60 cases have been reported to date, mostly in the form of isolated case reports or small case series, with <15 cases as a primary manifestation with no prior known history of NEN disease.[9,10] Breast metastases from ileal NENs are even rarer, account for less 20 cases, including the present one, reported in the literature since 1965 (Table 1). In approximately 50% of the cases, breast metastases preceded the discovery of the primary ileal NENs with an average time of 12 months (range 1–44 months).[5]

The first time a breast neuroendocrine metastasis is reported in the literature dates back to 1957, when Zetzel & Skully

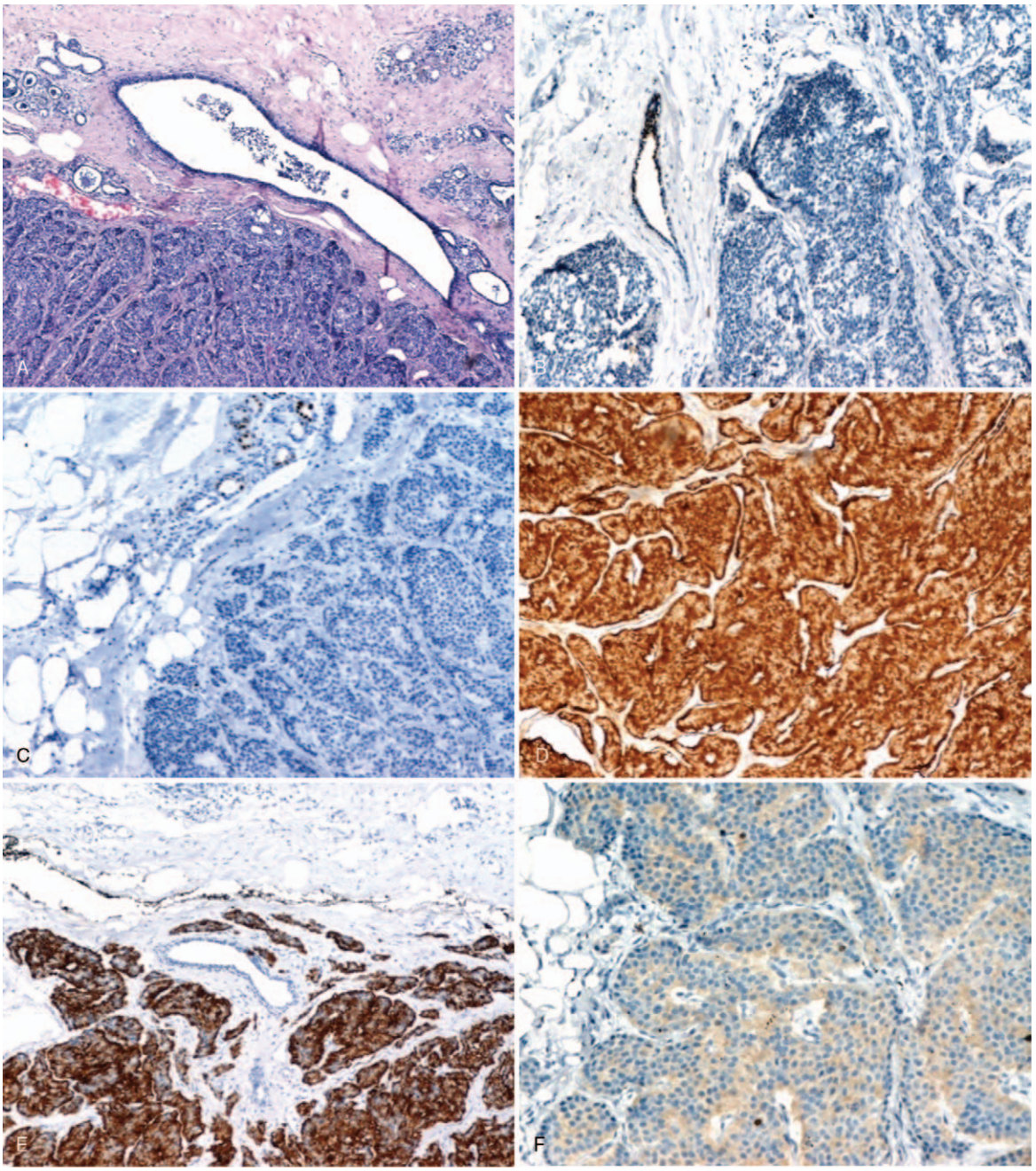

Figure 1. (A) Metastatic NEN breast lesion, trabecular proliferating pattern, ×20 magnification. (B) Metastatic NEN breast lesion, ER (–), ×20 magnification. (C) Metastatic NEN breast lesion, PR (–), ×20 magnification. (D Metastatic NEN breast lesion, Chromogranine immunohistochemistry (+), ×20 magnification. (E) Metastatic NEN breast lesion, synaptophysin immunohistochemistry (+), ×20 magnification. (F) Metastatic NEN breast lesion, Ki 67 (1%–2%), ×40 magnification. NEN = neuroendocrine neoplasm.

diagnosed a patient with primary small bowel carcinoid tumor (former definition of NEN) with metastases to the liver and breast consistent with metastatic carcinoid on autopsy.[11] In 1965, Chodoff reported the first surgical resection in a case of an ileal neuroendocrine tumor metastasizing to the breast in a 72-year-old woman.[12] Schurch, Nielsen, Bohman, and Di Palma report the next 4 neuroendocrine ileal metastatic tumors to the breast[13–16] in 1980, 1981, 1982, and 1988, respectively, as well as Lozowski et al[17] and Stiglich et al[18] in 1989 and 1991 in the form of case reports. Since then, a number of small case series with attempts to reviewing the literature has been conducted both by Kaltsas et al[19] and Rubio et al,[20] with the former to present 2 case reports of midgut and bronchial NEN metastatic to breast, while the latter presented one case of metastatic NEN of unknown primary origin to the breast. From 2000 up till 2010, few case reports were published including Kanthan et al, Gupta

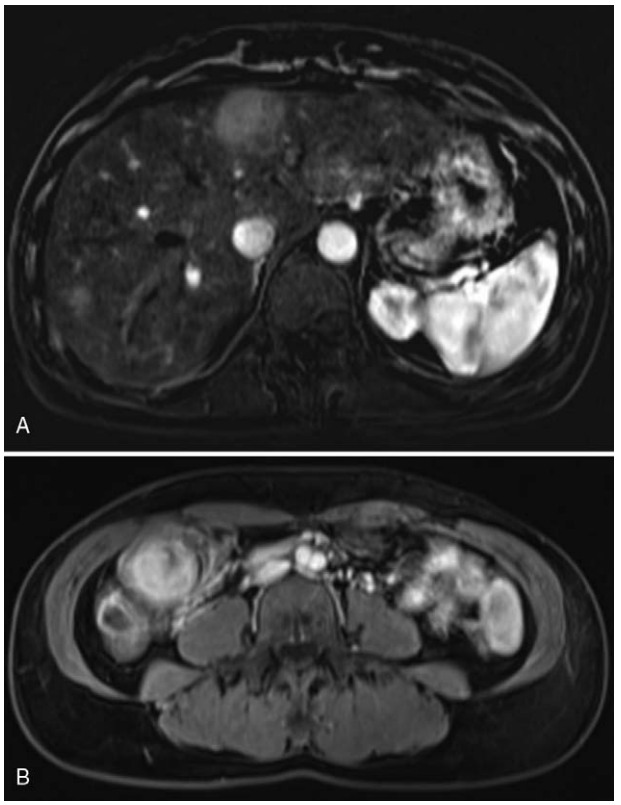

Figure 2. (A) Liver metastases on MRI abdomen. (B) Ileal NEN on MRI abdomen. MRI = magnetic resonance imaging, NEN = neuroendocrine neoplasm.

et al, Upalakalin et al, Geyer et al[21–24] presenting an ileal NEN in each report and Mosunjac presenting one ileal and one midjejunal metastatic NEN[25] pointing out for the first time in literature that metastatic NENs to the breast can seldom express ER, PR (+) stains, complicating even more the differential diagnostic process. From 2011 up to now, researchers have attempted to detect and study larger numbers of metastatic mammary NENs in order to delineate their characteristics, with Glazebrook et al[6] collecting 10 cases, Perry et al[26] collecting 18 cases, Crona et al[27] collecting 20 cases and Mohanty et al[10] collecting 22 cases, all by reassessing their medical centres histopathological databases referring to breast tumors resected in the past.

Due to the rarity of the condition, only a few of the abovementioned publications describe the imaging features of metastatic neuroendocrine tumors of the breast in detail. In general, the metastases tend to be circumscribed masses on mammography with no calcifications, although a few have been reported as spiculated or with irregular margins.[28] Overall, the presentation of metastatic neuroendocrine tumor to the breast is nonspecific, which may lead to misdiagnoses as a fibroadenoma, medullary carcinoma, mucinous carcinoma, or cyst.[9,18,29,30] Metastatic neuroendocrine neoplasms to the breast may additionally show considerable morphologic overlap with in situ and invasive mammary carcinomas, particularly those showing evidence of neuroendocrine differentiation, mainly in the absence of a known clinical history of a primary extramammary neuroendocrine neoplasm.[31] Thus, a metastatic neuroendocrine neoplasm in the breast may potentially be misdiagnosed as an invasive mammary carcinoma in routine surgical pathology practice, and the patient may be subjected to unnecessary mastectomy and/or axillary node biopsy or dissection, with or without radiation/ chemotherapy, based on the mistaken diagnosis.[32] For this reason, prompt histologic examination of the breast tumor is a critical next step to correctly diagnosing a metastatic NEN.

Diagnosis of metastatic NEN is established through histological findings of neuroendocrine features that correspond with the known primary neuroendocrine pathology. Macroscopically, G1-G2 NENs are typically whitish to yellowish or grayish solid tumors with a nodular or polypoid appearance, whereas G3 NENS are generally larger ulcerated masses simulating conventional carcinomas. Typical microscopical neuroendocrine features consist of uniform tumor cells arranged in nests in trabecular, insular, or sheet-like proliferation patterns with abundant eosinophilic granular cytoplasm, round or oval nuclei with stippled ("salt and pepper") chromatin.[33] Noteworthy, both well-differentiated breast carcinoma and NEN show cellular smears with cohesive clusters of bland epithelial cells on aspiration biopsy, while on core biopsy specimens neuroendocrine tumor cells may sometimes grow in nests or strands and thus may be confused with ductal or lobular breast carcinomas, respectively.[34]

Immunohistochemical and ultrastructural analysis can be extremely useful in the accurate recognition of neuroendocrine nature of these neoplasms, with characteristic cytoplasmic granules to be identified through the below mentioned special stains. These include synaptophysin, chromogranin A and B, and neuron specific enolase (NSE). More recent immunostains include prohormone convertase (PC3), CDX-2, and peptidylglycine a-amidating monooxygenase (PGM).[22]

Because of the small number, current treatment recommendations are not well defined.[8]

In most cases of gastrointestinal NENs, curative surgery is the treatment of choice whenever possible; thus localization of the primary tumor and/or metastases is important but is often difficult using conventional imaging techniques, such as ultrasonography (U/S), CT and MR imaging. Successful preoperative localization of neuroendocrine tumors has been achieved using 123I-MIBG, which accumulates in the argentaffin granules, and with 111 In-pentetreotide, which binds to somatostatin receptors commonly present in the majority of patients with neuroendocrine tumors.[19] The recommended treatment for the breast NEN is lumpectomy alone, whereas for the invasive mammary adenocarcinoma, is a modified radical mastectomy or breast-conserving therapy with lumpectomy and axillary lymph node dissection followed by adjuvant radiation at the standard of care.[35,36]

Ileal NENs display a greater predisposition to metastasize and are more frequently multiple lesions therefore, surgery should involve search for additional tumors by inspection and palpation as well as broad lymphadenectomy. In patients with liver metastases, curative surgery should still be attempted, and intraoperative ultrasonography should be performed for detection of all liver metastases. Palliative surgery should be considered for those patients with potentially resectable hepatic metastases and no other medical conditions that can markedly compromise life expectancy or even to prevent complications attributable to the tumor mass in patients noncandidates for curative resection.[37,38]

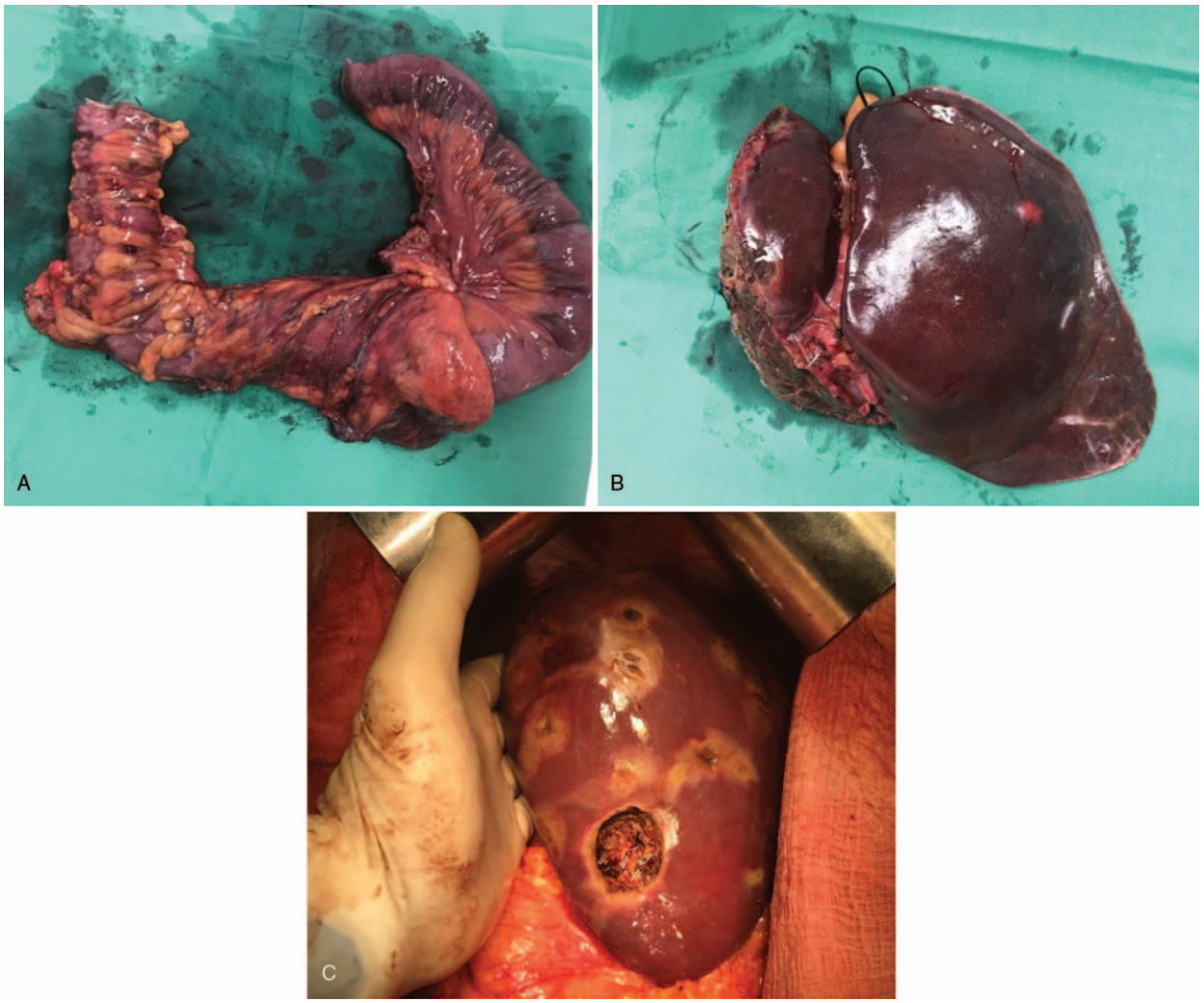

Figure 3. (A) The standard right hemicolectomy specimen. (B) The standard left hepatectomy specimen. (C) Right liver lobe metastasectomies (V, VI, VIII) plus RF ablation.

Table 1

Characteristics of the included studies (articles not written in English were excluded).

Study (Ref.)	Study design	Country	Year of publication	Study period	Number of patients with ileal NEN metastatic to breast
Zetsel et al (11)	Case report	USA	1957	1957	1
Chodoff[12]	Case report	USA	1965	1965	1
Schurch et al[13]	Case report	Germany	1980	1980	1
Nielsen et al[14]	Case report	Denmark	1981	1981	1
Bohman et al[16]	Case series	USA	1982	1972–1982	1
Di Palma et al[15]	Case report	Italy	1988	1988	1
Lozowski et al[17]	Case report	USA	1989	1989	1
Stiglich et al[18]	Case report	Italy	1991	1991	1
Kanthan et al[21]	Case report	Canada	2003	2003	1
Mosunjac et al[25]	Case report	USA	2004	2004	1
Gupta et al[22]	Case report	USA	2006	2006	1
Upalakalin et al[24]	Case series	USA	2006	2006	1
Geyer et al[23]	Case report	USA	2010	2010	1
Glazebrook et al[6]	Case series	USA	2011	2000–2010	1
Perry et al[26]	Case series	USA	2011	1995–2010	NR
Crona et al[27]	Case series	Sweden	2013	1990–2011	NR
La Rossa et al[5]	Case report	Italy	2015	2006	1
Mohanty et al[10]	Case series	USA	2016	1990–2013	2
Policeni et al[28]	Case report	USA	2016	2016	1
Total=					17

NR = not reported.

4. Conclusion

Metastatic neuroendocrine tumors to the breast are rare but must always be considered in the differential diagnosis of similar appearing lesions to the breast with solid papillary and/or neuroendocrine features, or when the phenotype of a neoplasm is discordant with the morphology, particularly when the patient has already a clinical history of neuroendocrine tumor. As there is significant overlap in the radiographic appearance of metastatic neuroendocrine tumors and can easily mimic primary breast carcinoma, it is important to obtain a tissue biopsy, accompanied by a careful tissue examination to distinguish neuroendocrine metastasis from primary breast carcinoma due to the similarities in their histological manifestations. An appropriate index of suspicion and selective immunohistochemistry in these cases may help to diagnose a previously undetected neuroendocrine tumor elsewhere in the body and prevent unnecessarily aggressive local treatments to the breast-potentially detrimental for the patient.

Author contributions

AP and EM equally designed the report and collected clinical data. The hematoxylin and eosin (H&E)-stained slides and immunohistochemical stains were reviewed by pathologist (HS) to confirm the diagnosis. MT and DT were also involved in the pre and postoperative oncologic management of the patient. AP, EM, and DM were involved in review of radiology films, medical records, literature search, and manuscript preparation. MK critically reviewed the manuscript and provided scientific supervision. All authors approved the final version of the manuscript.

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Writing – review & editing: Demetrios Moris.

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