

Case Report

Appendiceal neuroendocrine tumour presenting as bilateral ovarian and breast metastasis

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ABSTRACT

Neuroendocrine tumours (NETs) of the appendix (formerly known 'carcinoids') are rare and are usually detected incidentally after appendectomy. The reported frequency of metastases from appendiceal carcinoids is gradually increasing, may be due to the increased longevity of the patients with benign/malignant diseases. Here we report a case of NET of appendix in an 80 year old female who presented with bilateral ovarian mass, and later developed metastasis in the breast. Though uncommon, NETs producing bilateral ovarian metastasis is well described in literature, the commonest primary being ileum. Only few cases of neuroendocrine tumor metastasis to breast have been reported in the literature, but none from appendix as primary.

Keywords: Appendiceal neuroendocrine tumour, Ovarian and breast metastases

INTRODUCTION

Neuroendocrine tumors (NET) are low grade malignant neoplasms that occur most frequently in the gastrointestinal (74%) and respiratory tract (25%).¹ Appendix is one of the common sites of primary neuroendocrine tumor in the gastro intestinal tract, the commonest being rectum. NETs in the appendix usually arise from the tip and are less than 1cm in size and well differentiated. They have a benign course. But NETs arising from the base of appendix usually grow more than 1cm and are potentially malignant. In European and US referral centers, up to 77% of patients with pancreatic and up to 91% of patients with intestinal NEN present with distant metastases at initial diagnosis, whereas rectal NEN in 40%, gastric in 20-30% and appendiceal in less than 5%.^{2,3} Metastasis to the breast comprises only 1% of all the neoplasms of breast. Majority are from contralateral breast or from hematopoietic malignancies.⁴ Other common reported sites of origin in the literature include the lung, skin, stomach, and ovary.⁵ Breast

metastasis from neuroendocrine tumor is rare accounting for only 1-2% of all metastatic tumours to the breast.⁶

CASE REPORT

80 year old multiparous female presented with lower abdominal distension associated with vague pain since 2 months. On examination her vitals were stable and per abdomen examination showed a 12×7cm lump in right lower quadrant and hypogastrium. On per vaginal examination mass was felt in the right fornix. Per rectal examination was normal. MRI pelvis revealed solid and focal cystic areas in both ovaries suggestive of malignant tumor. Serum CEA was elevated. Patient underwent Total abdominal hysterectomy, bilateral salpingo-oophorectomy and appendectomy. The post-operative recovery was uneventful and the patient was discharged on 5th post-operative day. Gross examination of specimen both ovaries were enlarged left ovary measuring 16x11x11cm and right ovary 13x7x6cm, with intact capsules. Cut section of both showed a solid appearance

with few cystic and mucinous areas. Uterus was atrophic. Appendix measured 3.5cm length, 0.5cm diameter and base showed a thickening of wall 3x0.8x0.5cm. Histological examination of ovaries and appendix revealed nests of uniform cell population with abundant eosinophilic cytoplasm and nuclei with stippled ("salt and pepper") chromatin, mitosis >20%. In the appendix tumour was infiltrating beyond the serosa to subserosal fat and showed vascular emboli.

Tumor cells were positive for synaptophysin in both ovary and appendix and negative for CK 7, Ki 67 index was 20-30%. So a diagnosis of neuroendocrine tumour grade III of appendix metastasizing to both ovaries were made.

After 5 months patient presented with a lump in the breast Mammography showed a mass in right breast upper outer quadrant measuring 3x2cm. Sonomammogram showed a well-defined lobulated hypoechoic lesion measuring 1.6x1.4x1.4cm situated in the upper outer quadrant of right breast (about 11 o' clock position). No internal microcalcification seen. Mild internal vascularity was present. No evidence of focal lesions seen in left breast. Excision biopsy was performed microscopy showed similar histopathology as appendix. Tumor cells were positive for chromogranin, confirming a Neuroendocrine tumor metastasis to breast.

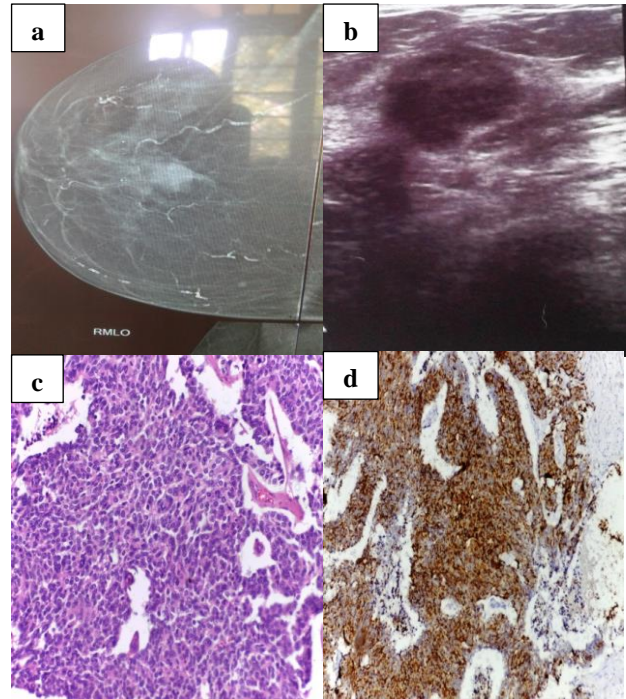


Figure 2: a) Mammography showed a 2x3cm lesion 12 o' clock position. b) USG: Well defined lobulated hypoechoic lesion measuring 1.6x1.4x1.4 cm in the upper outer quadrant of right breast. c) Histopathology showing infiltrative lesion arranged in nest. d) Diffuse tumoral cell positive for cromogranin.

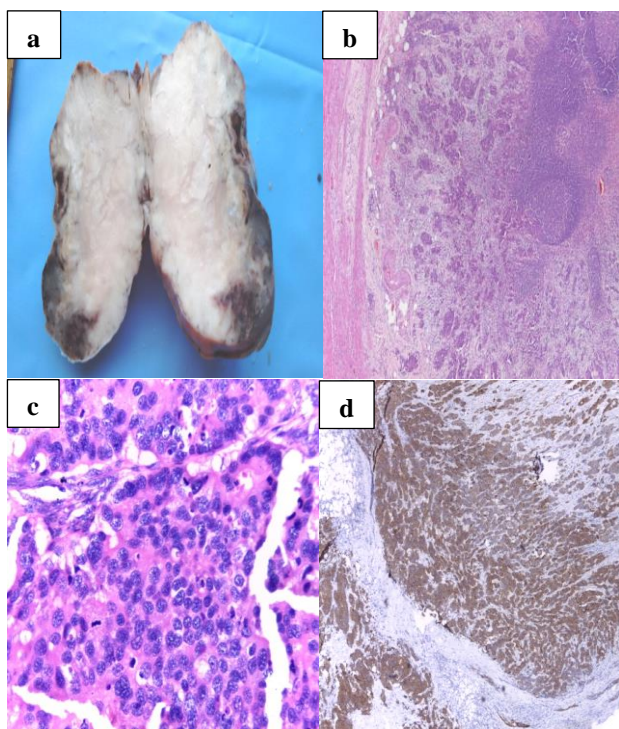


Figure 1: a) Irregular grey white lesion with areas of hemorrhage. b) Histopathology showing infiltrative lesion arranged in nest (10X). c) Higher power showing malignant cells having salt and pepper chromatin (40 xs). d) Diffuse tumoral cell positive for synaptophysin.

DISCUSSION

Carcinoid tumors are slow growing neuroendocrine tumors arising from cells of diffuse neuroendocrine system which are widely distributed throughout the body.¹ The term carcinoid was given by Siegfried Oberndorfer, who was the first person to characterize the nature of tumor as benign and later was reclassified to include the small bowel tumors, which can be malignant and have a metastatic potential.⁴ In review by Motohiro et al authors report on 760 patients, most neuroendocrine tumors of the gut are located in the rectum (94.5%), followed by colon 30 (3.9%) and 12 (1.6%) appendix.⁵ Appendix is no more a common site for neuroendocrine tumors.⁵ Appendiceal carcinoids makeup 50% of tumours in this site occur more frequently in females than in males and the mean age at presentation is 30-50 years.⁶ Majority of appendiceal NETs found incidentally in appendectomy specimens are asymptomatic and located in the tip of appendix (70-75%) while NETs arising from the base (5%) are usually neuroendocrine carcinomas.⁷ At the time of presentation 13-22% of patients with these carcinomas would have metastasized to distant places.⁸ The most frequent sites of distant metastasis, excluding the lymph nodes (89.8%) are the liver (44.1%), lung (13.6%), peritoneum (13.6%) and pancreas (6.8%).¹⁰

Metastasis to breast and ovary are uncommon.¹⁰ NET metastasis more commonly in the right breast as in

present case.⁹ In the review by Kalisher et al, the authors report on 59 cases of neuroendocrine tumors of breast. 39 cases were primary neuroendocrine tumors of the breast, while only 9 were metastases.⁹ There are only a few case reports in the literature with known extra mammary carcinoid tumors who developed breast metastases over a period of time after primary diagnosis.¹¹ To the best of our knowledge less than 50 cases of metastatic NET to the breast have been described in the literature to date.^{12,13} Largest series was published in 2016 from USA by Mohaty et al had described 18 cases of metastatic neuroendocrine neoplasm to breast of which none were from appendix.¹⁴ In some patients metastasis can be the first manifestation of an occult carcinoid tumor in such cases it is to be distinguished from primary NET. The histological features helpful in distinguishing primary versus metastatic NET breast are

- Greater degree of nuclear atypia/pleomorphism, increased nuclear membrane irregularity, increased mitosis favour primary whereas metastatic NETs shows nested/organoid pattern, uniform nuclei, smooth nuclear membrane, 'salt and pepper'- like nuclear chromatin.
- In situ ductal and lobular carcinoma component in the adjacent breast tissue favours primary breast NET.

Rabban et al proposed distinctive clinicopathologic features of primary ovary NET from metastatic.^{13,18}

- Laterality: Primary ovarian carcinoids are reported to be unilateral and bilateral in metastatic carcinoid tumors.
- Multinodular growth: Frequent in metastases, but not seen in primary ovarian carcinoids.
- Size: Primary ovarian carcinoids average 3.4cm in size versus 10.2cm for metastatic carcinoids.
- Presence of teratomatous elements: Supports primary ovarian origin.

Immunohistochemistry using lineage specific markers are also very useful in differentiating primary and metastatic NETs. The main markers that are useful are:¹⁴⁻²⁰

- ER/PR, Mamaglobin, GATA 3 for mammary origin
- TTF1 for pulmonary origin
- CDX2- GIT origin
- PAX8/PAX6- Gastropancreatic/duodenal

In present case, patient had NET grade III of appendix with bilateral ovarian metastasis at the time of presentation itself and developed right breast lump five months post-surgery.

CONCLUSION

Biological behavior of appendiceal NET vary from benign tumors less than 1cm to malignant goblet cell

carcinomas which are usually more than 2cm in size with muscle and serosal infiltration. Metastatic Neuroendocrine tumors with occult primary can have a wide array of presentation leading to diagnostic dilemma and delay in actual diagnosis and treatment. IHC with site- specific lineage markers may be useful in differentiating primary from metastatic NETs.

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