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A RARE HIGH GRADE AGGRESSIVE NEUROENDOCRINE CARCINOID OF RECTUM AND ANAL CANAL

General Surgery

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ABSTRACT

The synchronous presence of rectal and anal canal neuroendoendocrine tumors account for less than 1% of all rectal malignancies. Immunohistochemistry and positivity for markers such as chromogranin A or synaptophysin are used to identify them. The high proliferative index, Ki67, further classifies them as neuroendocrine carcinoid. Here, we present a rare case of a female in her third decade of life who presented with a history of altered bowel habits and was later diagnosed with a high-grade neuroendocrine carcinoid of the rectum and anal canal, Grade 3. The rapidity with which it spreads and metastasizes, combined with the high rate of recurrence, presents a management challenge and a poor prognosis.

KEYWORDS

Grade 3, neuroendocrine carcinoid of rectum and anal canal, Synaptophysin positivity, Ki67 index, platinum based chemotherapy

INTRODUCTION

Neuroendocrine neoplasms in digestive system called GEP-NETs are heterogenous group of tumors with variable and complex clinical presentations arising from neuroendocrine cells considered as neural crest cells of embryological gut.[1]

NETs, which make up around 0.5% of all newly diagnosed cancers, are uncommon. Less than 1% of all rectal and anal canal malignancies are rectal (Rec) and anal canal (AC) NETs. When these tumors are diagnosed, they are frequently asymptomatic and are only accidentally found during a normal lower gastrointestinal endoscopy. Overall, the prevalence of GEP-NETs has generally been rising steadily over the past few decades as a result of better diagnostic methods and more awareness.[2]

NETs, neuroendocrine carcinoid (NEC), and mixed adenoneuroendocrine carcinoid tumors are the three histological categories (MANEC). Based on the proliferation of tumor cells, the Ki67 index, these are divided into three tiers. NETs contain neuroendocrine markers such chromogranin A, synaptophysin, and hormones and have well-differentiated tumor cells with little cellular atypia (G1 or G2) and neuroendocrine differentiation. However, NEC is a poorly differentiated, high-grade malignant tumor that exhibits cellular atypia, frequent necrosis, and high proliferative activity—G3 (6). The size of the tumor, the depth of the invasion, and lymph node involvement are prognostic indicators for metastatic illness.[2]

CASE REPORT

A 35-year-old female came with the H/O altered bowel habits for 6 months duration. H/O bleeding per rectum with mucus discharge for 6 months. H/O tenesmus present for 3months. H/O of pain during defecation for 3 months. H/O weight loss for 3 months. In DRE, a circumferential ulceroproliferative growth with irregular surface was palpable 5cm from the anal verge, which bleeds on touch. The upper limit could not be reached in direct rectal examination. CECT intravenous and rectal contrast are taken for further diagnosis and to know the extent and nature of the disease. In that, a circumferential irregular heterogeneously enhancing wall thickening noted involving the anal canal and lower one third of rectum was noted for a length of about 8cm and for am maximal thickness of about 11.3mm. The lower limit was found to be 4 cm from the anal verge, extending beyond the serosa and was found infiltrating the mesorectal fascia at 9O'-11O' clock position with vaginal invasion. Bilateral internal iliac lymphadenopathy was noted. Radiologically it was diagnosed as carcinoma of rectum with anal canal - $T_{4c} N_2 M_X$. In colonoscopy, multiple ulcerations with growth are seen in the lower rectum and anal canal. Hemorrhages are seen. Mucosa appears markedly friable. (As depicted in the figure 1, 2 and 3). So, possibility of carcinoma of rectum was thought of with a biopsy for histopathological examination taken for confirmation.

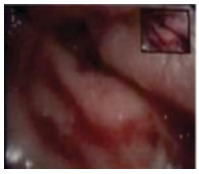

Figure 1

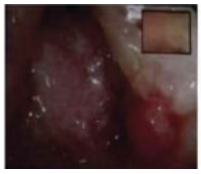

Figure 2

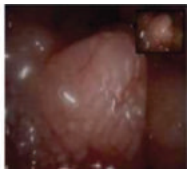

Figure 3

The histopathological examination showed fragments of colonic mucosa with neoplastic cells arranged in nest, sheets composed of round to oval cells, scant to moderate eosinophilic cytoplasm, round to oval cells. Necroinflammatory infiltrates with hemorrhage is also seen. In immunohistochemistry evaluation, diffuse strong positivity of Synaptophysin was found in tumor cells. CK 20 was negative in tumor cells. Ki67 expression was 40% in the tumor cells. So a Grade 3 Neuroendocrine carcinoid was diagnosed with histomorphology and immunohistochemistry.

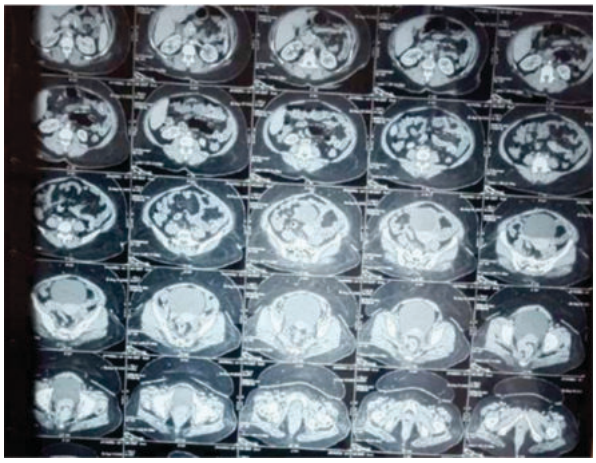

Figure 4 CONTRAST CT ABDOMEN AND PELVIS showing the rectum and anal canal growth

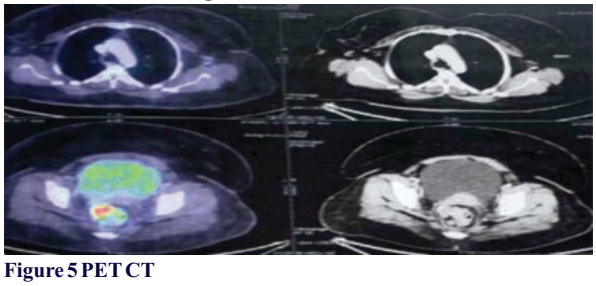

Figure 5 PET CT

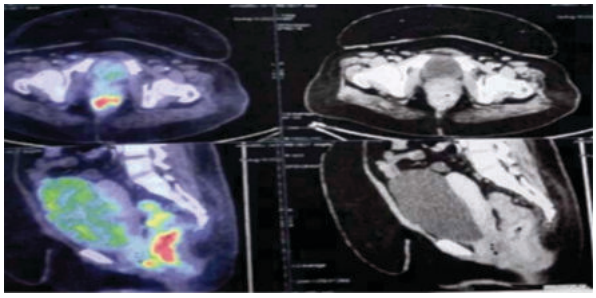

Figure 6 PET CT

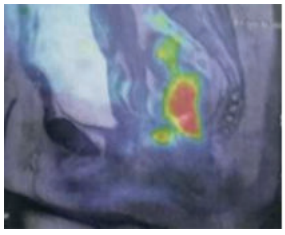

Figure 7 PET CT

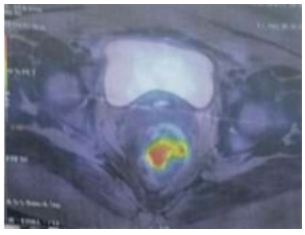

Figure 8 PET CT

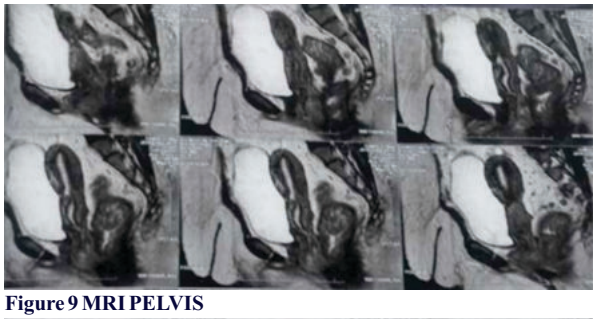

Figure 9 MRI PELVIS

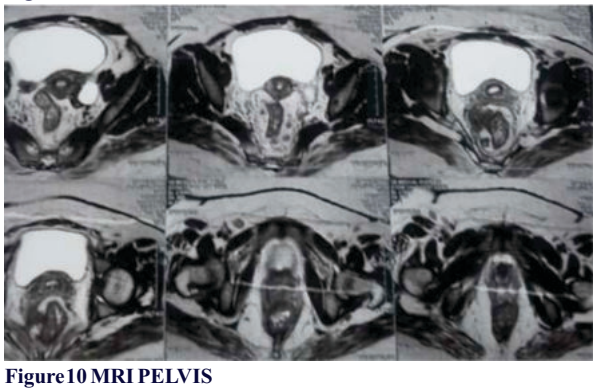

Figure 10 MRI PELVIS

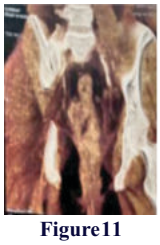

Figure 11

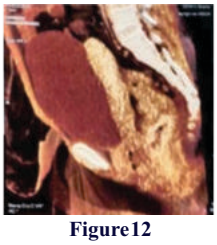

Figure 12

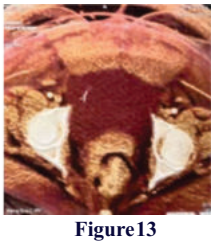

Figure 13

Figures 11, 12,13 Depicting The 3 D Reconstruction Of The Pelvis with The Growth.

PET-CT scan was taken and was found a FDG avid(SUV max 13.3) irregular thickening of lower half of rectum and anorectal junction is visualized for a length of 6cm and thickness of 18mm. The Lower limit of the lesion was 4cm from the anal verge. FDG avid(SUV max 7.3) thickening of lower 3rd of posterior wall of vagina was also visualized. FDG avid(SUV max 9.6) perirectal tumor extension of right side of mid 3rd of rectum was also noticed. Involvement of mesorectal lymph node was observed, with right internal iliac lymph node of size 18*13mm(SUV max 4.4), right inguinal lymph node of size 16*10mm(SUV max 2.7)-likely peritoneal metastasis. So suggestive of Carcinoma of rectum (T_{4b} N_{2b} M_{1c}). Based on the imaging and the histopathological report, the TNM Stage- T4b N2b M1c- STAGE IV, GRADE 3 NEUROENDOCRINE CARCINOMA. Due to its staging and grade, the patient was started on chemotherapy- Cisplatin and Etoposide.

DISCUSSION

Less than 0.1% of all colorectal malignancies are Rectum and Anal canal NECs, which are frequently poorly differentiated and have a poor prognosis. To classify neuroendocrine tumors, the World Health Organization (WHO) and the European Neuroendocrine Tumor Society have developed grading systems. Both allow for grading to be determined by either the mitotic rate or the Ki-67 labelling index.[11]

GRADE	MITOTIC COUNT	Ki67
Grade 1	<2	<3%
Grade 2	2-20	3%-20%
Grade 3	>20	>20%

A neuroendocrine carcinoid (NEC) with a high mitotic rate (>10 mitotic figures by 10 high-powered fields, or a Ki-67 proliferative index >20%) with possible extensive necrosis is referred to as a high grade neuroendocrine tumor. These tumors frequently exhibit rates as high as 40–70 mitoses per 10 high-powered fields, or a Ki-67 index of 50–90%, exceeding these criteria.[4] Recently, Sorbye et al. studied 305 patients who met WHO criteria for poorly differentiated gastrointestinal NECs. The optimal cutoff value for predicting prognosis and treatment response was determined to be Ki-67 55%.

In our case, the histopathological findings revealed segments of colonic mucosa with nests of neoplastic cells, sheets made up of round to oval cells, and sparse to moderate amounts of eosinophilic cytoplasm. Hemorrhage and necroinflammatory infiltrates are both detected. Tumor cells exhibited diffuse, high synaptophysin positivity after immunohistochemistry evaluation. Tumor cells tested negative for CK 20. The tumor cells have a 40% Ki67 expression level. So, using histomorphology and immunohistochemistry, a Grade 3 Neuroendocrine carcinoid was identified.

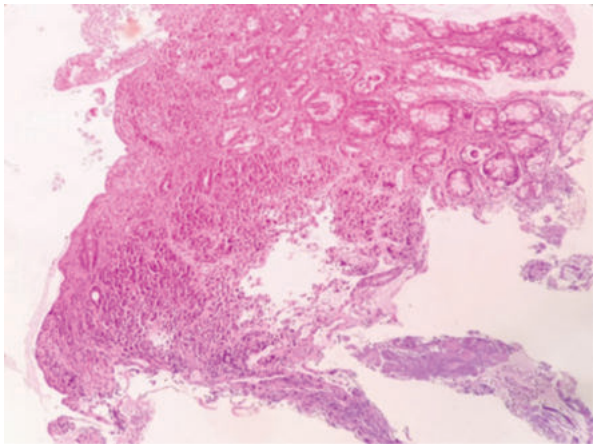

Figure 14- Histomorphology (Low power)

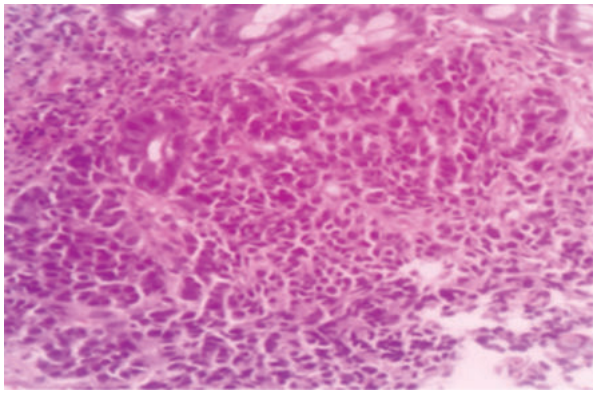

Figure 15-Histomorphology (High power)- section showing fragments of colonic mucosa with neoplastic cells arranged in nest, sheets composed of round to oval cells, scant to moderate eosinophilic cytoplasm, round to oval cells. Necro inflammatory infiltrates with hemorrhage is also seen.

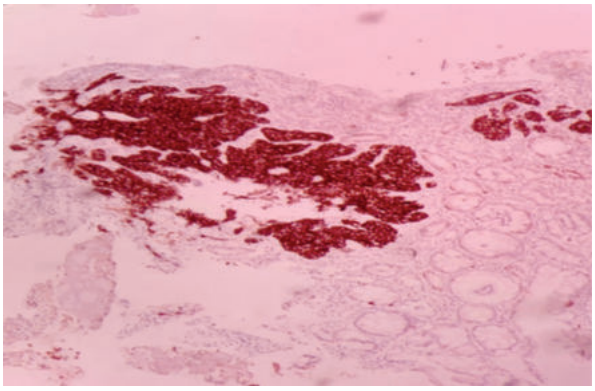

Figure 16-Immunohistochemistry showing Synaptophysin diffuse strong positivity in tumor cells.

According to Teresa Raposo André et al., the likelihood of NET metastatic disease rises with tumor size—2% when 1cm, 10-15% 1-2cm, and 60-80% when 2cm.

High-grade neuroendocrine carcinomas (HGNECs), which are poorly differentiated, fall within the category of aggressive malignancies. Compared to the more frequent well-differentiated neuroendocrine tumor's, HGNECs are clinically unique (NETs; low and intermediate grade).[1] Morphologically and phenotypically, gastrointestinal HGNECs resemble pulmonary HGNECs (large and small cell types).

As a result, platinum-based chemotherapy is the main treatment option for HGNECs.[9,10] Because of the expression of common neuroendocrine markers (such as synaptophysin and chromogranin, which can be seen with immunohistochemistry), well-differentiated and poorly-differentiated NECs are categorized together.[14,15]

Adjuvant chemotherapy is advised for individuals who have symptoms such intestinal obstruction or rectal bleeding but no other symptoms, according to the European Society of Neuroendocrine Oncology recommendations.[11]

The platinum-based regimen combined with etoposide or topotecan is recognized as the first line chemotherapeutic regimen for GEP-NETs with weak differentiation, but the survival duration is less than 16 months.[12,4] Chemotherapy demonstrated that the EP regimen was effective for the primary lesion as the size of the primary lesion decreased and the Ki-67 index and the primary tumor cells' mitotic figures greatly decreased. By interfering with DNA transcription and/or replication, this substance prevents cell division. In our situation, etoposide, a substance that also causes DNA damage, was coupled with cisplatin. Neoadjuvant chemotherapy may slow the rate at which neuroendocrine tumor cells synthesize DNA, restrict their growth, and diminish their mitotic activity, which results in major degenerative alterations in tumor cells.[1]

Less than 0.1% of all colorectal malignancies are Rectum and AC NECs, which are frequently poorly differentiated and have a poor prognosis. Various studies conducted by Sorbye et al and Yamaguchi et al indicate that, independent of the histological characteristics, NECs tend to have shorter overall survival when compared to NETs, and surgical or endoscopic tumor removal has a significant impact on overall survival.

According to data from the study carried out by Smith JD et al, surgery, particularly in the context of metastatic disease, may not deliver a survival benefit for the majority of patients. Emerging evidence, albeit still debatable, suggests that chemoradiation alone may be sufficient for locoregional NECs. This is crucial to take into account because a radical procedure like APR may be necessary.

Second line regimens following platinum-based therapy in the context of metastatic illness are unclear. There was no difference in PFS or OS between 24 individuals treated with surgery versus chemotherapy in a study by Brieau and colleagues.

Patients with Ki-67 55% exhibited a worse response to platinum-based chemotherapy (14 vs. 44%; p 0.001) despite having a longer median survival (15 months) than those with Ki-67 >55% (10 months; p 0.001).[12]

In our case, the response improved and the tumor size shrank once the chemotherapy was started but had recurrence within 1 year. This patient in our case had an 18-month survival period and still on follow up.

CONCLUSION

Due to the rarity in its presentation, the neuroendocrine tumors of rectum and anal canal especially the high-grade neuroendocrine carcinoid poses a major threat as in reducing the overall survival rate of the patient, pertaining to its aggressive nature and poor response to chemotherapy, radiotherapy and surgery with high rate of recurrence. Hence the differential diagnosis of neuroendocrine tumor should be considered and diagnosed with the help of immunohistochemistry for its early and prompt management.

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