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Rectal Neuroendocrine Tumor in a Patient with *CHEK2* Mutation

Introduction

Discovery of a *CHEK2* mutation in cancer patients necessitates discussion about the risk for additional tumors and screening to reduce morbidity and mortality from other concurrent *CHEK2* mutation-related cancers. Rectal neuroendocrine tumors (NETs), formerly called carcinoids, are relatively rare, representing less than 1% of rectal cancers.[1,2] While the *CHEK2* mutation is associated with adenocarcinoma of the colon, it has not been identified in association with NETs, and, to our knowledge, there is only one other case of an appendiceal NET in a patient with *CHEK2* mutation.[3] We report a patient who had ductal carcinoma in situ (DCIS) breast cancer and a *CHEK2* mutation and was later diagnosed with a rectal NET.

Case Presentation

A 67-year-old Caucasian female with a history of estrogen receptor-positive DCIS breast cancer had genetic testing with a panel of 28 actionable genes, including *BRCA1* and *BRCA2*, as the result of a strong family history (her grandmother and sister) of breast cancer. The patient was found to have a germline c1100 del *CHEK2* mutation. Because of the association of *CHEK2* mutation with colorectal adenocarcinoma, she underwent colonoscopy. This was her first colonoscopy as previously, she had refused this procedure, opting instead for occult blood testing as a colorectal cancer screening. Upon colonoscopy, a polyp of less than 1 cm in diameter was discovered in the rectum. Pathology showed that the tumor was characterized by a submucosal neoplastic proliferation of cytologically bland, mitotically inactive cells arranged in cords and nests. The cells stained strongly positive for CD56, synaptophysin, and the cytokeratin cocktail AE1/AE3, which are markers classically associated with NETs (Figures 1-3). Patient consent was obtained for this case report.

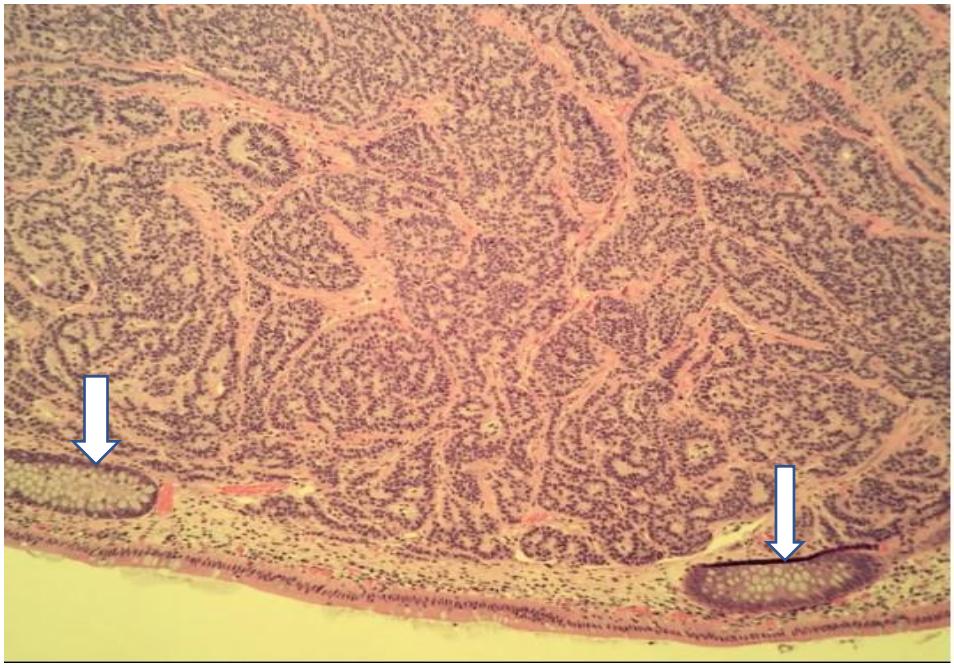

Figure 1. Low-power hematoxylin and eosin-stained image of the colonic mucosa with loss of the normal test tube appearance of colonic crypts due to distortion by the neoplasm. 100x magnification. The arrows indicate a normal crypt.

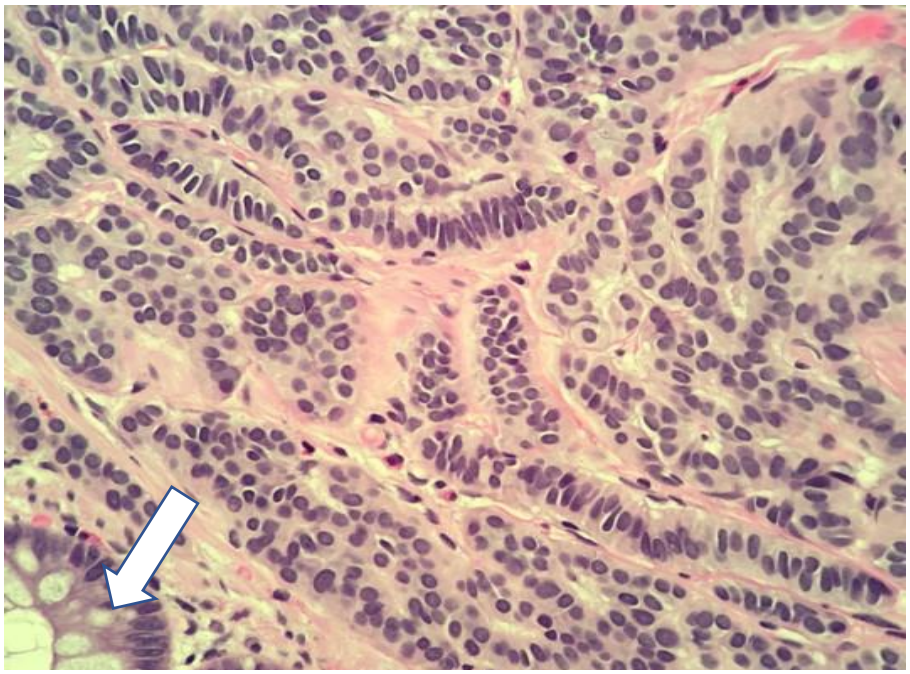

Figure 2. High-power hematoxylin and eosin-stained image of the neoplastic cells within the colonic submucosa. A portion of a normal colonic crypt (arrow) is present. 400x magnification.

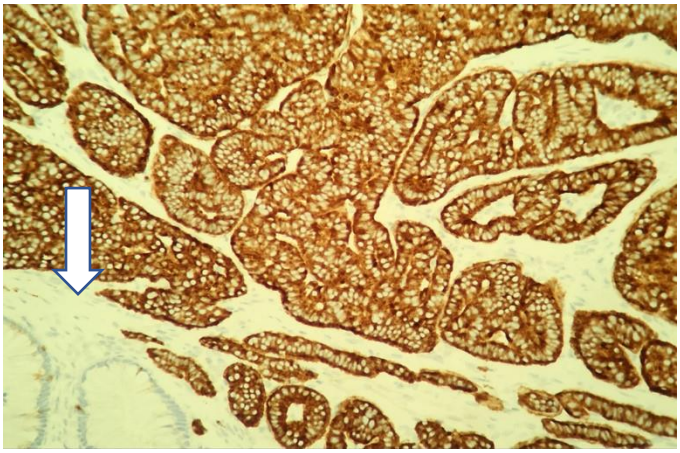

Figure 3. High-power image of the neoplastic cells stained with antibodies directed against synaptophysin, a marker of neuroendocrine differentiation. Normal colonic crypt is indicated by the arrow. 200x magnification.

The rectal tumor was completely removed by polypectomy during colonoscopy, and the location was subsequently tattooed to mark the tumor site. Surveillance for recurrence after 2 and 6 months found no evidence of recurrence.

Discussion

CHEK2 germline mutation is known to be associated with adenocarcinomas of the breast and colon, but only one other case of NET associated with this mutation has been reported.[3] Some providers offer next-generation genetic screening to all cancer patients without limitation by insurance or finances in order to develop a genetic registry.[3] One such group uncovered six cases of NETs associated with different cancer-predisposing genes, including *APC*, *MUTYH*, *MSH-6*, *MLH1*, and *CHEK2*. Only one of the six patients harbored a *CHEK2* mutation. This patient had an appendiceal goblet cell tumor, and immunohistochemical staining yielded a diagnosis of NET.

Gastrointestinal NETs are the most common type (43%), and rectal location NETs account for only 15% of the gastrointestinal NETs. The second most common location for NETs is the lung, representing 31.9% of NET cases reported.[4] Rectal and anal NETs with diameters of less than 1 cm have the best prognosis, so early detection is important.[5] We realize this report will not change practice, because we already perform colonoscopy on patients with *CHEK2* mutation to look for adenocarcinoma; however, confirmation of the association of *CHEK2* mutation with NETs may lead to trials of screening other parts of the body, such as the lung, for early detection and reduction of cancer mortality.

The *CHEK2* gene codes for a protein that acts as a tumor suppressor, regulating excessive cell growth. In response to damage in the cell, CHEK2 communicates with other well-known regulators of mitosis as well such as tumor protein 53 (tp53).[6] It is not surprising that a mutation that limits the action of CHEK2 results in tumor growth because the role of CHEK2 is to limit unwarranted proliferation.[7]

As more genetic testing is performed, we will likely identify additional tumors that are associated with *CHEK2* mutation. For example, a 48-year-old female patient with the *CHEK2* mutation was found to have adrenocortical carcinoma.[8] Surveillance testing discovered an adenocarcinoma in her left lower lung 2 months later. Additionally, a population-based study revealed an increased risk of breast cancer, stomach cancer, kidney cancer, sarcoma, and prostate cancer in patients with *CHEK2* mutations.[9] The NIH website reference to *CHEK2* links this gene with prostate, breast, lung, colon, kidney, thyroid, and ovarian cancers as well as osteosarcoma.[6]

Conclusion

This study provides new information about *CHEK2* mutation in association with a rectal NET, adding to the growing body of knowledge about this mutation. While *CHEK2* mutations are associated with colonic adenocarcinomas, to our knowledge only one other reported case of *CHEK2* mutation in association with a gastrointestinal NET has been reported. Greater knowledge of these associations may potentially lead to earlier diagnosis of cancer in patients with *CHEK2* mutation, due to increased preventive screening in these high-risk patients. As

more genetic testing is performed, we suspect there will be reports of additional cancers associated with *CHEK2* mutation.

Conflict of interest

The authors declare that there is no conflict of interest.

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