Case Reports in Oncology

Case Rep Oncol 2024;17:524–531
DOI: 10.1159/000536052
Received: November 14, 2023
Accepted: December 27, 2023
Published online: April 2, 2024

Case Report

Synchronous Papillary Thyroid Cancer and Colorectal Cancer in a Young Patient with a CHEK2 Mutation

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Keywords
CHEK2 · Colorectal cancer · Papillary thyroid cancer · Synchronous tumors

Abstract
Introduction: Mutations of *CHEK2* are usually inherited and have been implicated in breast cancers, colorectal cancers, thyroid cancers, kidney cancers, and prostate cancers. The CHEK2 gene codes for checkpoint kinase 2 protein which is an effector in the ATM-CHEK2-p53 pathway and responds to DNA double-strand breaks. ***Case Presentation:*** We describe a unique case of a 29-year-old Canadian female who presented with synchronous papillary thyroid carcinoma and rectal adenocarcinoma who was subsequently found to have a sporadic CHEK2 (checkpoint kinase 2) mutation. She presented with an 8-month history of bright red blood per rectum and saw two different physicians who diagnosed hemorrhoids and possible rectal ulcers, respectively. When the symptoms continued, the patient pursued a colonoscopy exam which found a large rectal tumor. Subsequent clinical staging diagnosed a rectal adenocarcinoma and a synchronous papillary thyroid carcinoma. Due to her synchronous tumors, a genetic panel was performed, which revealed a low-risk CHEK2 mutation. Our patient had a full response to neoadjuvant brachytherapy of the rectum and surgical treatment of her cancers. ***Conclusion:*** This is the first case report, to our knowledge, of a patient with a CHEK2 mutation who presented with synchronous papillary thyroid carcinoma and invasive colonic adenocarcinoma. The incidence of colorectal cancers and papillary thyroid cancers in those under 30 with no family history is very low, which signifies the rarity of their simultaneous occurrence at such a young age.

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Introduction

We describe a case of a female with synchronous presentation of rectal adenocarcinoma and papillary thyroid carcinoma with neck node metastasis at the age of 29 years. Given her young age at presentation and synchronous tumors, genetic studies were performed, and *CHEK2* mutation was discovered. The CHEK2 gene codes for checkpoint kinase 2 protein which is an effector in the ATM-CHEK2-p53 pathway [1]. It responds to DNA double strand breaks and serves as a tumor suppressor gene. *CHEK2* mutations are frequently seen as germline mutations and are associated with multi-organ cancer susceptibility. *CHEK2* testing is routinely done when hereditary cancers are suspected as part of genetics panels [2]. Colorectal cancer is increasing in incidence, and it has been shown that many patients with colorectal cancer have multiple primary cancers. Lee et al. [3] found that 36.4% of patients with colorectal cancer had a synchronous primary tumor. Of these, thyroid cancer was the second most common associated tumor. Our case represents a novel presentation of synchronous rectal adenocarcinoma and papillary thyroid carcinoma in the patient with a *CHEK2* mutation. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536052).

Case Report

The case is a 29-year-old nulliparous female who presents in Canada with an 8-month history of increasing bright red blood per rectum. The patient had seen two different family practitioners in the preceding 8 months. Given her age and lack of family history for colorectal disease, the two family practitioners did basic physical examinations only and diagnosed her with hemorrhoids and a possible rectal ulcer, respectively. At 8 months, the patients' symptoms worsened, and she pursued a consultation with a private colonoscopy provider. The colonoscopist found a large rectal tumor located in the posterior rectal vault. Biopsy revealed an invasive rectal adenocarcinoma. The workup radiology included a PET scan which also showed an incidental thyroid lesion. Fine needle aspiration of the thyroid lesion revealed a synchronous papillary thyroid carcinoma.

Her past medical history is unremarkable except for lactose intolerance and intolerance for certain foods. The patient did not consume alcohol or smoke. Her family history is positive for basal cell carcinoma in her father at age 53 years. Both parents and the patient's brother had colonoscopies after the patient's diagnosis which were both normal. The patient's maternal grandfather had a history of multiple cancers including bladder cancer, testicular cancer, non-Hodgkin lymphoma, and multiple basal cell carcinomas. No known genetic testing was performed on his neoplasms. There was no other reported history of gastrointestinal cancers, gynecological cancers, or thyroid cancers in first- or second-degree relatives.

Prior to the surgical treatment to remove the tumor, the patient underwent neoadjuvant ovarian lift procedure and lower abdominal brachytherapy in an attempt to shrink the size of the rectal tumor. Close to 1 year after the onset of symptoms, brachytherapy was completed with positive gross shrinkage of the rectal tumor, and the patient underwent a simultaneous low anterior resection of the rectal tumor and a total thyroidectomy with left neck dissection for pathologic staging of each cancer (Fig. 1).

Histopathology of the thyroidectomy specimen showed a 1.5 cm greatest dimension papillary thyroid carcinoma, classic variant with focal tall cell features in the left thyroid lobe. No extrathyroidal extension, margin involvement, or perineural invasion were identified. Focal lymph-vascular invasion was seen in two of the four lymph nodes examined that were positive for metastatic papillary thyroid carcinoma. The pathologic stage was pT1bN1bM0 (Fig. 2–3).

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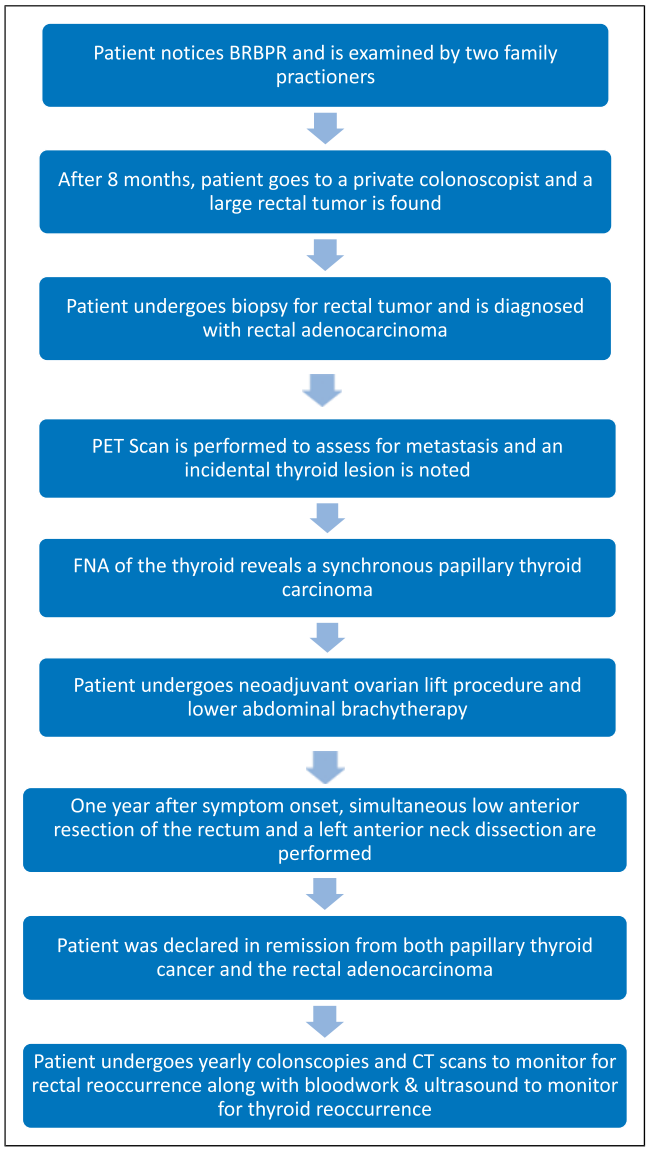

Fig. 1. Timeline of the patient's presentation of symptoms to the end of her treatment.

The low anterior resection specimen showed residual invasive moderately differentiated adenocarcinoma of the rectum. The tumor was 2.3 cm greatest diameter with invasion into the muscularis propria. All margins were negative for carcinoma or dysplasia. Treatment effect was identified with a partial response score of 2. Small vessel lymph-vascular invasion was present. Tumor budding score was intermediate (5–9). Zero of eighteen (0/18) lymph nodes identified had metastatic carcinoma. The pathologic stage for rectal adenocarcinoma was a pT2pN0pMx (posttreatment) (pTNM, AJCC 8th edition). Immunohistochemistry testing for mismatch repair (MMR) proteins showed no loss of nuclear expression of MMR proteins (MLH1, MSH2, MSH6, PMS2) (Fig. 4–5).

Given this presentation and clinical history, genetic studies were performed. The genetic testing was positive for a pathogenic (low penetrance) variant in the *CHEK2* gene, c.470T>C (p.Ile157Thr), and a variant of uncertain significance in the PMS2 gene, c.2559C>G (p.Ile853Met) [1]. This *CHEK2* mutation is considered a low-risk variant. Immunohistochemical staining of the rectal biopsy tumor was normal with no evidence of MMR gene deficiency of MLH1, MSH2, MSH6, or PMS2. No additional sequence variants or

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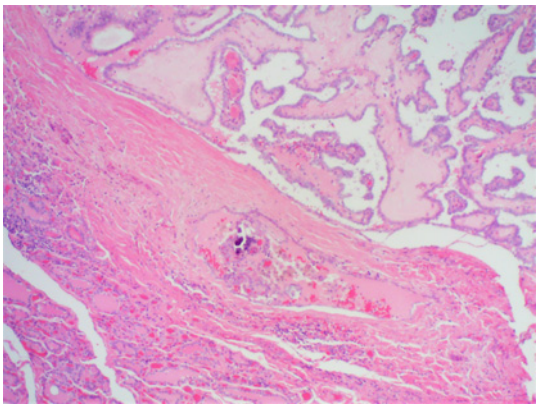

Fig. 2. Papillary thyroid carcinoma – classic nuclear changes of papillary thyroid carcinoma, nuclear.

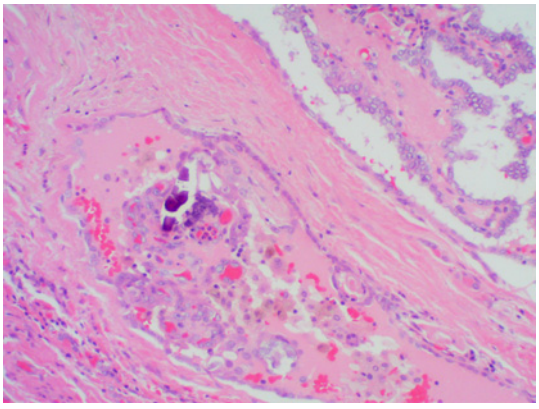

Fig. 3. Papillary thyroid carcinoma – psammoma bodies within the tumor grooves and optically clear chromatin.

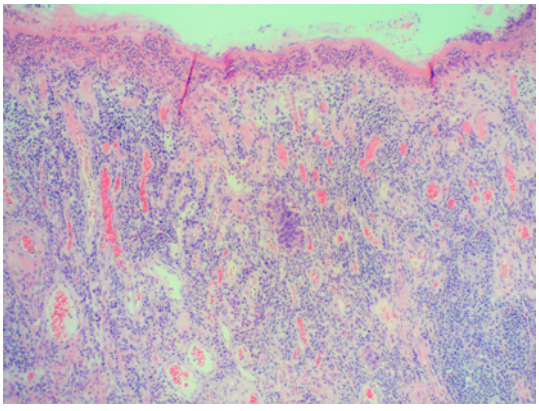

Fig. 4. Invasive moderately differentiated adenocarcinoma from the rectum – ulcerated mucosa with nest of tumor cells.

deletions/duplications were identified in any of the following genes analyzed: APC, MLH1, MSH2, MSH6, PMS2, EPCAM, MUTYH, POLD1, POLE, PTEN, SDHB, SDHD, STK11, TP53. The patient was felt to have a modest increased risk of CHEK2-associated cancers.

Initial molecular testing on the rectal tumor for DNA alterations in 52 genes that are relevant to solid tumors was negative for clinically relevant DNA alterations. RNA alterations were not tested. This test was performed in parallel on DNA and RNA samples obtained from the same tumor specimen using the AmpliSeq for lllumina Focus Panel (see test method).

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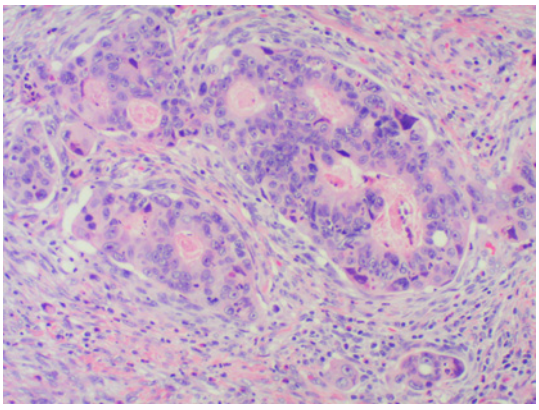

Fig. 5. Invasive moderately differentiated adenocarcinoma from the rectum – the tumor is composed of infiltrating cribriform glands with marked desmoplasia.

Test method: this test is performed in parallel on DNA and RNA samples obtained from the same tumor specimen using the AmpliSeq for lllumina Focus Panel. Targeted DNA and RNA regions are amplified by multiplex PCR. Paired-end massively parallel sequencing of 150 bp fragments is performed with an lllumina MiSeq instrument. DNA sequences are aligned and compared to reference genome GRCh37 to identify SNVs, indels, and CNVs. RNA sequences are aligned to a custom reference containing fusions and other aberrant splicing events of interest. Variants are interpreted and categorized based on their clinical impact, as per standards and guidelines. In the field (PMID: 27993330): tier I, variants with strong clinical significance (level A and B evidence); tier 11, variants with potential clinical significance (level C and D evidence); tier 111, variants with unknown clinical significance; and tier IV, benign or likely benign variants, catalog #20019164.

The patient had no other adjuvant therapy and was declared in remission from both papillary thyroid cancer and the rectal adenocarcinoma in 2019. The patient is monitored for rectal reoccurrence through yearly coloscopies and full body CT scans every 3 to 6 months. The patient undergoes bloodwork and ultrasounds to monitor for thyroid reoccurrence.

Discussion

The *CHEK2* gene encodes for checkpoint kinase 2 which is an effector protein in the ATM-CHEK2-p53 pathway and has been associated with Fanconi anemia DNA damage response pathway [4]. Checkpoint kinase 2 responds to DNA double-strand breaks and functions as a tumor suppressor gene by ensuring that any cells with damage to their DNA do not reproduce [1]. If *CHEK2* becomes mutated, then it allows cells that are damaged to reproduce which increases the risk of development of cancers. *CHEK2* is on chromosome 22 and is usually in its inactive form until there is DNA damage. When *CHEK2* is activated, it then phosphorylates a string of hydrophobic amino acids and then regulates other cell cycle pathways [4].

There are many different variants of the *CHEK2* gene – some pathogenic and some not. The two most common pathogenic variants of *CHEK2* are c.1100delC and C.Ile157Thr [5]. The C.Ile157Thr is a missense mutation present in the patient. C.Ile157Thr has been attributed to a decrease in hydrophobicity. The variant C.Ile157Thr has been shown to cause an increased risk of breast, prostate, colon, kidney, and thyroid cancer [1].

The C.Ile157Thr variant has been shown to increase the risk of colorectal cancer to 0.5% by age 49 years with a cumulative lifetime risk of 12% [2]. Risk for colorectal cancer is deemed low-to-moderate for the C.1100delC variant and low risk for C.Ile157Thr variant [2].

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This is compared to the cumulative lifetime risk of developing colorectal cancer in the general population of 6% [2]. *CHEK2* germline mutation lifetime risk for breast cancer has been shown to range from 20 to 40% in women with and without a positive family breast cancer history [2]. Huszno et al. [6] studied the correlation between *CHEK2* mutations and renal cell carcinoma and found that the variant C. Ile157Thr was associated with increased risk of cancer in family history (breast cancer, gynecological cancer) in renal cancer of the contralateral kidney. *CHEK2's* involvement in the ATM-CHEK2-p53 axis has been shown to be integral to DNA damage response and helps to combat the initiation of cancer [7]. *CHEK2* is considered a moderate penetrance mutation in breast cancer, with an estimated cumulative lifetime risk of breast cancer with the C.Ile157Thr variant displaying an 18% risk at age 80 versus a cumulative risk without the mutation of 3% [4]. A meta-analysis done by Koen et al. [8] was performed to assess the colorectal cancer susceptibility with the C.Ile157Thr variant and found there to be a significant association with this variant and colorectal cancer, both sporadic and familial. Stolarova et al. [9] did a study that showed that 15% of patients with papillary thyroid cancer had some sort of *CHEK2* variant present. They identified 6% specifically that had the C.Ile157Thr variant. When looking at all mutations that are associated with the development of thyroid cancers, SNPs found in CHEK2 have been associated with an increased risk of differentiated thyroid cancer, most of them being papillary as such in our patient [10].

CHEK2 mutations are inherited in an autosomal dominant fashion [2]. The geneticists for the patient believe that she is the first person in her family to have this mutation and that it is sporadic. *CHEK2* mutations can possibly work concurrently with other mutations. CHEK2 is not commonly tested in patients with colorectal or thyroid cancer unless there is a strong family history [2]. The patient was only tested for CHEK2 mutations due to the presence of synchronous cancers with the lack of risk factors present. Common risk factors for rectal cancer are having hereditary cancer syndromes such as Lynch syndrome, familial adenomatous polyposis syndrome. Other risk factors include polyps on previous colonoscopy or whose family members have a history of polyps. Patients with inflammatory bowel disease and cystic fibrosis also have an increased risk for colorectal cancer [11]. Common risk factors for thyroid cancer include childhood radiation exposure, family history, and other things such as environmental exposure, chronic hepatitis C, and being overweight or obese [12].

The *CHEK2* mutation present in the patient behaved as a higher risk variant and arose at a very young age. Due to her lack of family history and risk factors, she was not worked up for malignancy until months after her symptoms appeared. When her thyroid cancer was discovered, it then led her doctors to suspect a genetic mutation and eventually led them to *CHEK2*. As stated, her parents and brother were negative for any CHEK2 mutation.

Conclusion

This is an interesting case report of a young patient with a *CHEK2* C.Ile157Thr mutation that presented with the rare combination of two primary tumors consisting of invasive rectal adenocarcinoma and papillary thyroid carcinoma with regional metastases. The patient's *CHEK2* variant likely contributed to the development of her papillary thyroid cancer and, perhaps to a lesser extent, the development of her colorectal cancer. The geneticists for the patient believe that even though this is normally a low-risk variant for *CHEK2* mutation, it is behaving like a high-risk variant in this patient and will be treated as such. Therefore, the patient rotates between mammograms and breast MRI's every 6 months. It is important to

note that the patient's symptoms were ongoing for 8 months before a colonoscopy was performed due to her age and lack of family history. This rare presentation emphasizes the importance of maintaining broad differentials when diagnosing young patients, even when the clinical probability of them having such a rare condition appears low. The identification of a de novo CHEK2 mutation in this young patient highlights the evolving understanding of genetic predispositions in cancer.

Acknowledgments

Dr. James Small took pictures with his camera of the microscope pathology images in order for us to have high quality images to use for the article. Dr. Rebecca Ryznar looked over the article in beginning stages to see if it was worth pursuing. Jensen Fisher did a full library/database search for us in order to ensure that there were no similar articles and also contributed by recommending articles that may be helpful to us. Alexis Horst helped by looking over the article for grammar errors.

Statement of Ethics

This study protocol was reviewed and approved by the Rocky Vista University IRB, approval number 2023-120. Written informed consent was obtained from this patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Funding was provided by Rocky Vista University in Colorado.

Author Contributions

Dr. Torgerson contributed by obtaining the case report from the patient as well as contacting the hospital that held the medical records of our patient to obtain pathology slides for this case. She also contributed by editing and providing an overview of the manuscript. Student Doctor Sydney Hoskins contributed to the paper by researching CHEK2 and its relevance to our patient's case and writing up the pertinent information on CHEK2 for this case. She also contributed by editing and providing an overview of the manuscript.

Data Availability Statement

The data used for this case report are not publicly accessible due to privacy reasons but are available from the corresponding author upon reasonable request.

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