PJSS Vol. 80, No. 1, January-June, 2025

PJSS PHILIPPINE JOURNAL OF SURGICAL SPECIALTIES

Familial Adenomatosis Polyposis Associated Papillary Thyroid Carcinoma- Cribriform Morular Variant: A Case Report

Jennifer A. Winter, MD; Michelle C. Payagen, MD, FPCS, FPSGS and Mathew B. Bawayan, MD

Cordillera Consortium General Surgery Training Program, Baguio City, Benguet, Philippines

Familial Adenomatous Polyposis (FAP) is a multi-tumoral syndrome that includes neoplasms in the duodenum, brain, pancreas and thyroid. The Cribriform Morular Variant (CMV) is a rare form of Papillary Thyroid Cancer seen in patients with FAP. Presented here is a 32 year old female who initially presented with an anterior neck mass followed years later by a rectal mass. She was diagnosed with FAP and colorectal adenocarcinoma and underwent total proctocolectomy with end ileostomy. She subsequently underwent a total thyroidectomy which revealed CMV Papillary Thyroid Carcinoma (CMV-PTC). Since FAP can have diverse presentations, a high index of suspicion is needed in order to make an earlier diagnosis to reduce potential morbidity and mortality. Papillary thyroid carcinoma can predate colonic polyposis. Identifying CMV-PTC early on can serve as an opportunity diagnose FAP early.

Key words: Familial adenomatous polyposis, papillary thyroid carcinoma, cribriform morular variant

Familial Adenomatous Polyposis (FAP) is an inherited autosomal dominant condition with varied levels of penetrance that is characterized and can be diagnosed clinically by the early onset of hundreds to thousands of polyps growth in the colon and rectum. FAP is the most common adenomatous polyposis syndrome and the second most prevalent inherited colorectal cancer condition, occurring in 1 in 1000 people.[1,2] FAP is a multi-tumoral syndrome that includes tumors in the duodenum, brain, pancreas and thyroid and can therefore offer a variety of presentations.[3] Papillary Thyroid Carcinoma (PTC) in FAP has an incidence of only 1 to 2% with predominance in the female population.[4] The Cribriform Morular Variant (CMV) seen on histopathology is a distinct variant that can be seen in those with FAP.[5]

The objective of this case report was to present a rare variant of thyroid cancer seen in patients with FAP which presented before colonic manifestations surfaced.

The Case

This is a case of a 32 years old female who presented with an anterior neck mass. 7 years prior to admission the patient palpated a 2 cm anterior neck mass associated with a pricking type of pain. No consult was sought at the time. Six years prior to admission, patient presented with hematochezia and noted a non-tender anal mass. Upon consult and further investigation, she was diagnosed with FAP and early stage colorectal adenocarcinoma. Patient underwent a total proctocolectomy with end ileostomy. The patient had no co-morbidities. There was no family history of cancer or FAP noted. Patient had 4 siblings who were all apparently well with no co-morbidities. During the same admission, the previously noted anterior neck mass was assessed. Thyroid nodules were demonstrated upon diagnostic ultrasound. A fine needle aspiration biopsy was performed. Cytopathology was interpreted as suspicious for papillary thyroid carcinoma. Patient was advised to have a thyroidectomy, to undergo surveillance for colorectal cancer and to subject family members for screening. The patient, however, opted to defer surgical intervention and was lost to follow up thereafter.

Over time, her thyroid tumor enlarged and this led to her current consult. The mass associated with odynophagia. There was no dysphagia or dyspnea. A cervical CT scan revealed a left thyroid mass displacing the upper trachea to the right. Nodularities were

demonstrated in the isthmus and right thyroid lobe. No cervical lymphadenopathies were detected.

Patient underwent a total thyroidectomy. The lobes of the thyroid were bilaterally enlarged with nodular firm components (Figure 1). No enlarged cervical lymph nodes were noted intraoperatively. There were no intra-operative or post-operative complications.

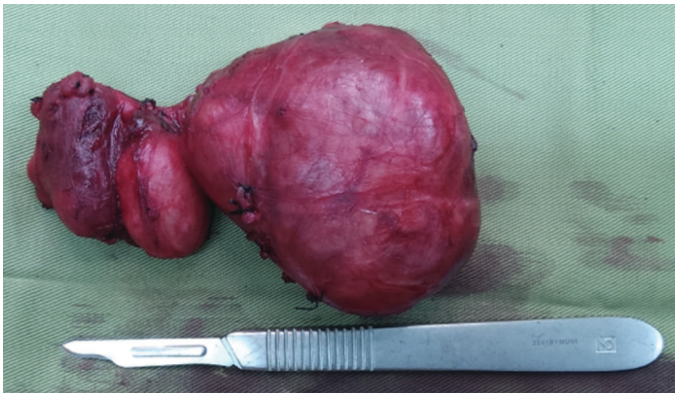

Figure 1. Image of gross total thyroidectomy specimen: The right and left thyroid lobe and isthmus measured 5.0 cm x 4.0 cm x 2.0 cm; 8.0 cm x 7.0 cm x 4.0 cm and 3.0 cm x 1.0 cm x 2.0 cm, respectively.

Final histopathology revealed papillary carcinoma. Sections of the right lobe and isthmus showed nodules measuring from 0.5 cm to 2.0 cm with whitish finely granular cut surfaces. Section of the left lobe showed a nodule measuring 6.0 cm x 5.0 cm with a thinned out capsule having light to brown whitish to cut surfaces. Microscopic sections (Figure 2A-C) revealed complex, branching and randomly oriented papillae with fibrovascular cores. The nuclei were optically clear with irregular nuclear contour, nuclear grooves and nuclear pseudoinclusions. Sections showed back to back follicles without colloid with hyperchromatic nuclei, with grooves and pseudoinclusions. Some spindle shaped tumor cells were seen scattered in between the follicles. Sections in Figure 2D to 2E demonstrate the classic morular architecture consistent with Cribriform Morular Variant Papillary Thyroid Carcinoma (CMV-PTC).

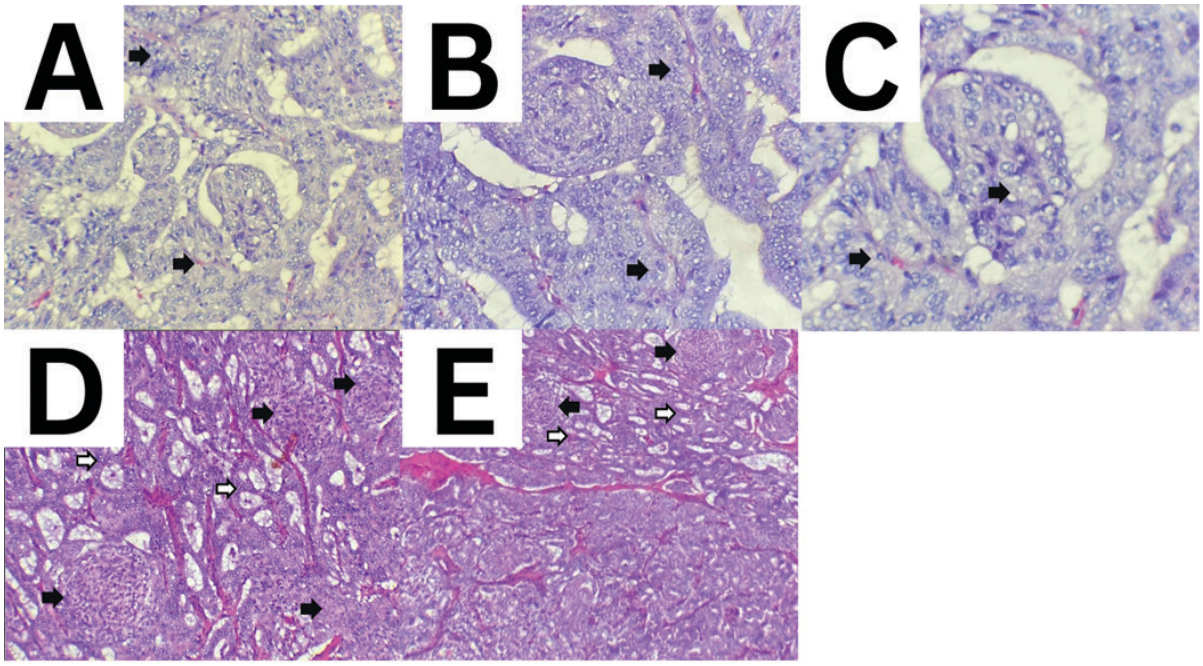

Figure 2. Microphotographs of speciment. A (LPO), B (MPO) & C (HPO): Sections reveal complex, branching and randomly oriented papillae with fibrovascular cores (black arrows). The nuclei are optically clear with irregular nuclear contour, nuclear grooves and nuclear pseudoinclusions. D (HPO) & E (MPO): Sections show back to back follicles without colloid with hyperchromatic nuclei, with grooves and pseudoinclusions. Some spindle shaped tumor cells are seen scattered in between the follicles. Sections show the classic morular variant. (black arrows: Morula; white arrows: back to back follicles)

Patient was referred to nuclear medicine for Radioactive Iodine therapy and was recommended further disease monitoring. Due to the high cost of genetic testing, the patient in this case was not able to test herself or any of her family members.

Discussion

Patients with FAP can have a variety of presentations. A diagnosis can be established clinically by extracting a family history along with clinical and colonoscopy findings suggestive of FAP. Since de novo mutations in the Adenomatous Polyposis Coli (APC) gene may arise in up to 15% of FAP patients and MUTYH-associated polyposis is recessively inherited, the absence of a family history of polyposis or colorectal cancer does not rule out the possibility of a polyposis syndrome.[3,6] The clinical diagnosis of FAP however, if feasible, should be confirmed via genetic testing for the APC mutation. A study by Grover, et al. on prevalence of phenotypes of APC and MUTYH mutations in patients with colorectal adenomas revealed that mutations were found in 82% of patients with more than 1000 polyps, 17% of patients with 20 to 99 polyps and 9% of individuals with 10 to 19 polyps. These results revealed that genetic testing alone may not detect all patients with polyposis syndromes. In those with no mutation detected, clinical criteria are necessary to diagnose such syndromes.[7]

Thyroid carcinoma that arises in a FAP patient is classified under Familial Non-Medullary Thyroid Carcinoma (FNMTC). FNMTC comprises 5-10% of all thyroid cancers with thyroid cancer arising in FAP at 1-2% and 80:1 female to male ratio.[3,10-11] FAP-associated Papillary Thyroid Carcinoma (PTC) is diagnosed prior to the usual diagnosis of colonic manifestations in 40% of cases.[8] This is similar to the patient in the present case who initially presented with a thyroid mass prior to the anal mass. In some studies, thyroid cancer diagnosis can occur before colorectal polyposis symptoms by four to twelve years in up to 30% of patients.[4] In 1968, Camiel, et al. initially proposed an association between FAP and thyroid carcinoma.[12] Harach, et al. in 1994, reported that patients with thyroid carcinoma in FAP exhibited a unique histologic characteristic that distinguished it from conventional papillary carcinoma. Although the CMV pattern could be found in sporadic thyroid carcinoma, authors have proposed that when a CMV pattern thyroid carcinoma is diagnosed, it would be imperative to investigate the possibility of a coexisting FAP.[5]

CMV is a distinct uncommon subtype of PTC associated with FAP. When this pattern is noted on histopathology, it gives the clinician a unique opportunity to diagnose FAP prior to the diagnosis of intestinal polyposis. CMV has an unusual pattern characterized by a prominent cribriform pattern of growth with interspersed cell clusters arranged in morule or squamoid islands. The follicular spaces are free of colloid, and the cribriform portions are made up of anastomosing bars and arches of cells without any intervening stroma. Morules are composed of solid regions where nest-like whorls of cell clusters are assembled. They primarily consist of oval and spindle-shaped tumor cells. These cells' nuclei have a distinctive pale staining that sets them apart from PTC's more common "Orphan Annie" appearance and intranuclear pseudo-inclusions.[13]

CMV-PTC is seen in 65% in Asians making it more common with this population as compared to populations in America where its prevalence is reported to be only 23%.[14] Harach, et al, reported 4 FAP associated PTC cases in 1994. They described the tumor as being multifocal, encapsulated and with patterns of cribriform, solid, spindling and whorls. It has been surmised that FAP associated PTC was significantly different from regular PTC.[10] A large case series of 33 CMV-PTC tumors published in 2021, confirmed that these lack definitive biomarkers of thyroid follicular cell differentiation.[9] Due to its distinct cytomorphology, immunohistochemical, and genetic features, they proposed that CMV-PTC be classified as a separate type of thyroid carcinoma.[9] Histologic characteristics that are compatible with CMV and present with multifocality are seen in 90% of patients with FAP and PTC. Even in the absence of genetic analysis, the mere presence of colonic polyposis and young age during presentation would strongly suggest FAP associated CMV-PTC.[14]

The treatment of CMV-PTC is similar to that of papillary thyroid cancer.[15] A total thyroidectomy is performed for tumors that are multifocal, multicentric or FAP-associated. Sporadic CMV-PTC can be treated with a lobectomy.[16] Due to multiple nodules and a large

left thyroid mass, a total thyroidectomy was performed in the present case. This surgical treatment was followed by radioactive iodine therapy.[15,17]

Lymph node metastases has been reported in only 10–20% of cases. Due to indolent nature of CMV-PTC, routine prophylactic lymph node dissection is not necessary. Patients with FAP-associated PTC have reported 5- and 20-year survival rates of 90 and 77%, respectively. The recurrence rate in CMV-PTC patients has been reported to be 8.5%, lower than that of other PTCs. While unusual, aggressive FAP-related CMV-PTC has been reported. Though there generally is little chance of distant metastases or recurrence, patients exhibiting histological evidence of vascular invasion should be closely monitored.[16]

Conclusion

FAP is an adenomatous polyposis syndrome that may initially present with tumors outside of the gastrointestinal tract. CMV-PTC is such a condition. The presence of CMV especially if multifocal should warrant investigation for possible underlying FAP.

References

1. Schulmann K, Pox C, Tannapfel A, Schmiegel W. The patient with multiple intestinal polyps. Best Pract Res Clin Gastroenterol 2007; 21(3): 409-26. doi: 10.1016/j.bpg.2006.11.003.
2. Kanth P, Grimmett J, Champine M, Burt R, Samadder NJ. Hereditary colorectal polyposis and cancer syndromes: A primer on diagnosis and management. Am J Gastroenterol 2017 Oct;112(10):1509-25. doi: 10.1038/ajg.2017.212.
3. Herzig D, Hardiman K, Weiser M, You N, Paquette I, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Inherited Polyposis Syndromes. Dis Col Rect 2017 Sep;60(9):881-94. doi: 10.1097/DCR.0000000000000912.
4. Dalal KM, Moraitis D, Iwamoto C, Shaha AR, Patel SG, Ghossein RA. Clinical curiosity: cribriform-morular variant of papillary thyroid carcinoma. Head Neck 2006 May;28(5):471-6. doi: 10.1002/hed.20383.
5. Harach HR, Williams GT, Williams ED. Familial adenomatous polyposis associated thyroid carcinoma: a distinct type of follicular cell neoplasm. Histopathology 1994 Dec;25(6):549-61. doi: 10.1111/j.1365-2559.1994.tb01374.x.
6. Aretz S, Uhlhaas S, Caspari R, Mangold E, Pagenstecher C, Propping P, Friedl W. Frequency and parental origin of de novo APC mutations in familial adenomatous polyposis. Eur J Hum Genet 2004 Jan;12(1):52-8. doi: 10.1038/sj.ejhg.5201088.
7. Grover S, Kastrinos F, Steyerberg EW, Cook EF, Dewanwala A, Burbidge LA, Wenstrup RJ, Syngal S. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA 2012 Aug 1;308(5):485-92. doi: 10.1001/jama.2012.8780.
8. Sharma KL, Singh RB, Fidda N, Lloyd RV. Cribriform-morular variant of papillary thyroid carcinoma with poorly differentiated features: Report of a case and review of the literature. Surg Exp Pathol 2022; 5(1). https://doi.org/10.1186/s42047-021-00103-5.
9. Boyraz B, Sadow PM, Asa SL, Dias-Santagata D, Nosé V, Mete O. Cribriform morular thyroid carcinoma is a distinct thyroid malignancy of uncertain cytogenesis. Endocr Pathol 2021 Sep;32(3):327-35. doi: 10.1007/s12022-021-09683-0.
10. Cetta F. FAP associated papillary thyroid carcinoma: A peculiar subtype of familial nonmedullary thyroid cancer. Pathol Res Int 2015;2015:309348. doi: 10.1155/2015/309348.
11. Uchino S, Ishikawa H, Miyauchi A, Hirokawa M, Noguchi S, Ushiama M, Yoshida T, Michikura M, Sugano K, Sakai T. Age- and gender-specific risk of thyroid cancer in patients with familial adenomatous polyposis. J Clin Endocrinol Metab 2016 Dec;101(12): 4611-7. doi: 10.1210/jc.2016-43.
12. Camiel MR, Mulé JE, Alexander LL, Benninghoff DL. Association of thyroid carcinoma with Gardner's syndrome in siblings. N Engl J Med 1968 May 9;278(19):1056-8. doi: 10.1056/NEJM196805092781908.
13. Liyanapathirana N, Seneviratne SA, Samarasekera DN. A distinct variant of papillary thyroid carcinoma indicating familial adenomatous polyposis (FAP): a case report and brief review. BMC Res Notes 2015 Dec 17;8:795. doi: 10.1186/s13104-015-1736-1.
14. Cameselle-Teijeiro JM, Sobrinho-Simões M. Cribriform-morular variant of thyroid carcinoma. Pathologica 2019 Mar;111(1):1–3. doi:10.32074/1591-951x-66-18
15. Giuffrida M, De Giorgi F, Rossini M, Bonati E, del Rio P. Cribiform-morular variant of papillary thyroid carcinoma and familial adenomatous polyposis: report of a case and literature review. Acta Biomed 2021 92(Suppl 1): e2021153; doi:10.23750/abm.v92iS1.9691
16. Akaishi J, Kondo T, Sugino K, et al. Cribriform-morular variant of papillary thyroid carcinoma: Clinical and pathological features of 30 cases. World J Surg 2018 Nov;42(11):3616-23. doi: 10.1007/s00268-018-4644-4.
17. Abdullah Suhaimi SN, Nazri N, Nani Harlina ML, Isa N, Muhammad R. Familial adenomatous polyposis-associated papillary thyroid cancer. Malays J Med Sci 2015 Jul-Aug;22(4):69-72.