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Case Report

Multiple concurrent unusual neoplasms presenting in a patient with familial adenomatous polyposis: A case report and review of the literature

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A B S T R A C T

We report the case of a 57-year-old woman with familial adenomatous polyposis (FAP) who presented with bilateral ovarian microcystic stromal tumors (MCSTs) and a cribriform-morular variant of papillary thyroid carcinoma, as well as concurrent noninvasive endometrial adenocarcinoma. The ovarian masses were confined to the ovaries. The tumor cells were positive for nuclear expression of β-catenin. The papillary thyroid carcinoma revealed the cribriform morular architecture associated with FAP, and immunohistochemistry also showed aberrant nuclear β-catenin. The endometrial adenocarcinoma, in contrast, showed an immunophenotype of negative nuclear β-catenin. Whole exome sequencing of blood was performed, and analysis revealed a rarely reported variant in the adenomatous polyposis coli (*APC*) gene, c.475dupT(pTyr159Leufs*9). The concurrence of these various neoplasms within one patient could provide insights into the pathogenesis of MCST, which has only recently been described, and underscores the importance of recognizing this rare entity in the setting of FAP.

1. Introduction

FAP is usually due to a germline mutation in the adenomatous polyposis coli (*APC*) gene. *APC* regulates the turnover of β-catenin, and inactivating *APC* mutations lead to aberrant accumulation of β-catenin in the nucleus, which in turn leads to dysregulated cellular proliferation. FAP-associated clinical syndromes include Gardner syndrome, which is characterized by the classical gastrointestinal involvement of FAP in addition to mesenchymal manifestations including desmoid tumors, osteomas, extranumerary teeth, epidermal cysts, and other soft tissue tumors; and Turcot syndrome, which involves familial desmoid tumors and central nervous system neoplasms. Additional associated extracolonic manifestations in FAP include congenital hypertrophy of the retinal pigment epithelium, hepatoblastomas, and papillary thyroid cancer, particularly the cribriform-morular type [1, 2].

Although FAP has not classically been associated with ovarian neoplasms, rare occurrences of microcystic stromal tumor (MCST) of the ovary have recently been described in patients with FAP [3, 4]. First recognized as a distinct entity in 2009, this benign tumor possesses striking histological features of islands of generally bland round cells, microcystic spaces, and intervening hyaline stromal bands. MCST generally lacks the inhibin and calretinin staining typical of other sex cord stromal tumors, and bears a unique immunohistochemical signature of positive staining for cyclin D1, WT-1, SF-1 and FOXL2 and aberrant nuclear positivity for β-catenin [4]. Although only 2 cases have been linked to FAP so far, a number of other cases with available molecular analysis contain exon 3 mutations in the *CTNNB1* gene encoding β-catenin [5–7].

Here we describe a patient with a strong family history of FAP with a previously unknown *APC* germline mutation, who presented with abdominal pain and was discovered to have concurrent bilateral ovarian MCST, papillary thyroid carcinoma of the cribriform morular variant, and a FIGO grade 1 endometrial carcinoma. The multiplicity and rarity of this patient's manifestations of FAP prompted an investigation for the specific mutation, and highlight the importance of persistent application of molecular diagnostics to better characterize the manifestations of particular genetic variants of FAP. The unique presentation of this patient underscores the importance of recognition of syndrome-associated entities at time of presentation, especially if specimens are sent for frozen section diagnosis. As the reported numbers of MCST accumulate in the literature, this unusual entity may increasingly be in the differential diagnosis in a patient presenting with a history of FAP and ovarian mass.

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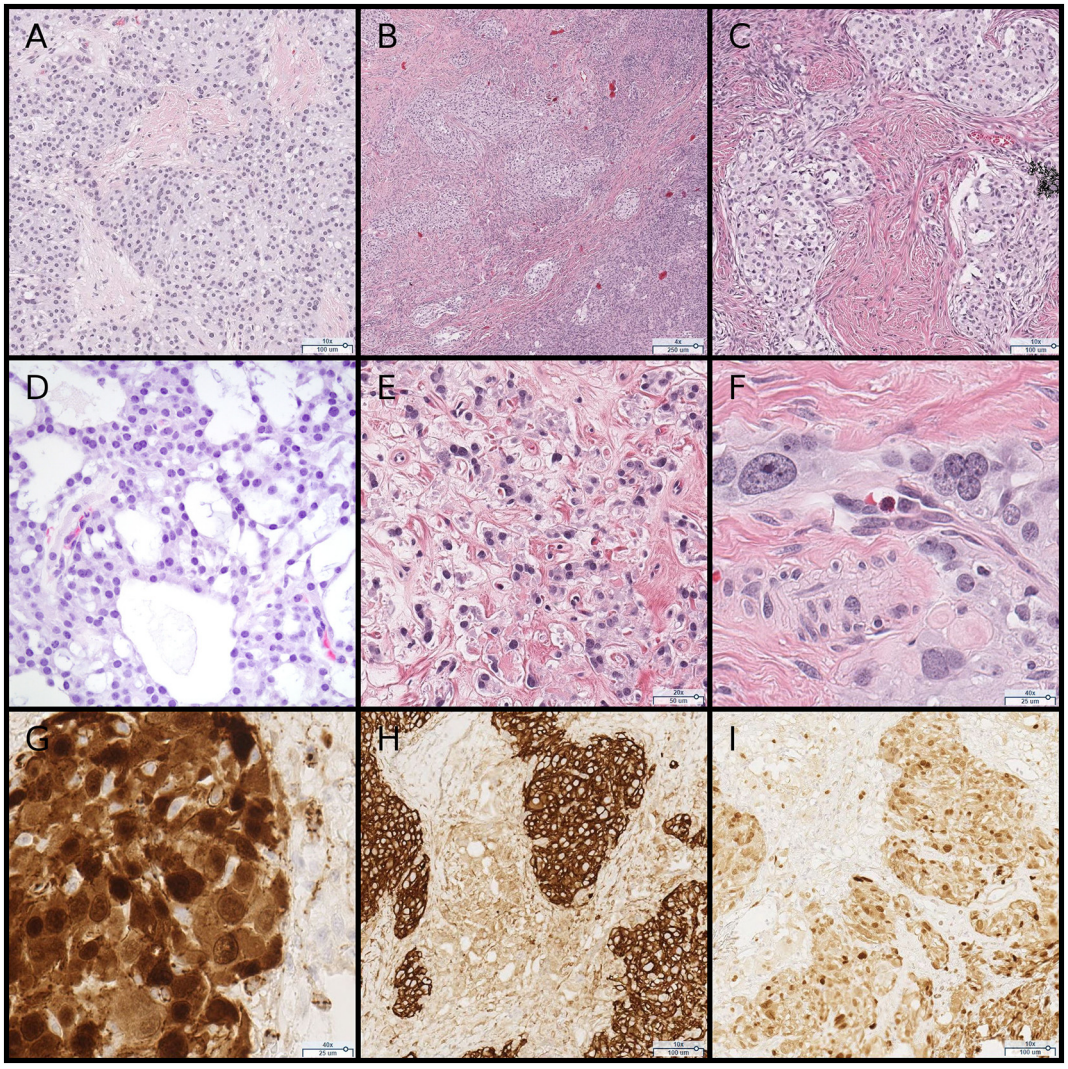

Fig. 1. Representative sections from the ovarian microcystic stromal tumors. (A) Low-power view of the right-sided tumor showing nests of tumor with bland round nuclei and slightly eosinophilic cytoplasm, with occasional interspersed microcysts. (B—F) Low- and high-power views of the heterogeneous morphology of the left-sided tumor, with areas of microcysts, dense hyalinized stroma, and occasional bizarre nuclei. Immunohistochemistry was positive for nuclear β-catenin (G), CD10 (H), and cyclin D1 (I).

2. Case presentation

A 57-year-old female with a clinical history of FAP and prior history of colectomy > 20 years ago, presented with abdominal pain and light post-menopausal bleeding. Her pain was initially thought to be due to an incisional hernia subsequent to her remote abdominal surgery. An endometrial biopsy at initial presentation was negative, but a CT scan showed a left adnexal mass and thickened endometrial stripe, with a non-obstructing ventral hernia. An MRI showed bilateral adnexal masses, as well as a 5 cm infiltrating soft tissue mass in the uterus, extending into the right uterine cornu. CA-125 level was low; however, an enlarged left common iliac node on MRI made the clinical picture concerning for both endometrial and ovarian cancer. The patient was consented for an exploratory laparotomy, hysterectomy, and bilateral salpingo-oophorectomy with frozen section result to dictate staging. On preoperative testing for this surgery, a chest x-ray revealed a superior mediastinal mass. A follow up CT scan revealed a large intrathoracic mass involving the left lobe of the thyroid and causing rightward deviation of the trachea.

The patient underwent an exploratory laparotomy, enterolysis, total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, and herniectomy as a combined procedure. Frozen section pathology favored a non-malignant sex cord stromal tumor of the bilateral ovaries and a grade 1 endometrioid adenocarcinoma of the uterus with no invasion. Permanent section histology and immunostaining confirmed bilateral ovarian MCSTs and FIGO grade 1 endometrioid endometrial adenocarcinoma. Following the initial surgery, the patient returned two months later and underwent a total thyroidectomy. Pathology from that surgery showed multifocal papillary thyroid carcinoma, cribriform-morular variant. The patient recovered well from both surgeries and remains well at her most recent follow-up.

This patient had a significant personal and family history of colonic polyps. Her own colectomy approximately 20 years prior to this presentation had revealed approximately 300 polyps, the sampled of which were dysplastic tubular adenomas, and the patient underwent regular endoscopy for monitoring and removal of gastric fundic polyps. The patient reported a history of familial polyposis first recognized in her family in the late 1970's, with 7 out of 8 of her mother's siblings known to be affected by polyposis. In addition to the patient, her mother, aunt (mother's twin sister), and cousin (daughter of the twin sister) had also undergone colectomies for polyposis. The patient had no children. One relative had undergone unspecified molecular testing, with reported negative results. The patient reported no knowledge of other family