Case report

Attenuated familial adenomatous polyposis (AFAP) in a patient associated with a novel mutation in APC

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SUMMARY

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome associated with mutation in the adenomatous polyposis coli (APC) gene, a tumour suppressor located on chromosome 5q21. Attenuated familial adenomatous polyposis (AFAP) is a variant associated with fewer and later onset of colon polyps. AFAP-associated APC mutations have largely been found before codon 157, in exon 9 or after codon 1595. We present the case of a 44-year-old man incidentally found to have numerous gastric polyps during bariatric surgery, with innumerable polyps in the remaining part of the stomach and the entire colon, with rectal sparing, consistent with AFAP phenotype. Genetic testing demonstrated the c.7682dup (p.Ser2562Lysfs*21) variant in exon 15 of APC. This represents a previously undescribed APC mutation. This mutation likely yields end-binding protein 1 and human disc large binding protein inactivation, causing cell cycle microtubule dysregulation and tumour suppressor inactivation. Through loss of these regulatory mechanisms, this mutation is associated with AFAP phenotype. The patient was treated surgically and is doing well.

BACKGROUND

Familial adenomatous polyposis (FAP) is an autosomal, dominant, inherited syndrome associated with mutation in the adenomatous polyposis coli (APC) gene, with resultant clinical phenotype of numerous adenomatous colonic polyps and near-certain eventual progression to colon cancer. Classic FAP phenotype is characterised by >100 colonic polyps primarily affecting the rectum and left colon, with early incidence of the disease starting around age 20 with progression to cancer by age 40.¹ Extracolonic intestinal manifestations include gastric fundic gland hyperplastic polyps and duodenal adenomas.² Extraintestinal manifestations include desmoid tumours, osteomas, congenital hypertrophy of the retinal pigment epithelium and thyroid, adrenal and hepatobiliary cancers.³ APC is a tumour suppressor gene located on chromosome 5q21 and its gene product affects cell signalling through its interactions with β -catenin/Tcf and the Wnt signalling pathway.⁴ APC codes for a 2843 aminoacid protein, with pathogenic mutations most often occurring between codons 168 and 1580 and greatest frequency at mutational hotspot codons 1061 and 1309.^{5,6} Most of these mutations are nonsense or frameshift mutations that yield a truncated protein product.⁷

Attenuated familial adenomatous polyposis (AFAP) is a recognised variant of this disease, associated with the following phenotypic features: fewer than 100 colonic polyps, right-sided colonic predominance and later onset of polyposis (usually age 35–45).⁸ Additionally, extracolonic and extraintestinal manifestations are rarer. AFAP-associated mutations in APC have largely been found before codon 157, in exon 9 or after codon 1595.^{6,7} The MutY homologue gene (MutYH) is responsible for base excision repair, and has known pathogenic mutations also associated with the AFAP phenotype.⁹

We present the case of a 44-year-old man incidentally found to have numerous gastric polyps during bariatric surgery, with subsequent workup demonstrating AFAP phenotype. After undergoing genetic testing, this patient was found to have a novel mutation in APC previously undescribed in literature and was treated surgically.

CASE PRESENTATION

A 44-year-old super-morbidly-obese man body mass index (BMI 63) underwent sleeve gastrectomy for weight loss and was found to have multiple adenomatous fundic gland polyps on final pathology (figure 1). Subsequent workup included esophagogastroduodenoscopy which revealed innumerable polyps of the remaining gastric fundus and body consistent with fundic gland polyps, normal duodenum without polyps, and Barrett's oesophagus (figure 2A). Colonoscopy was significant for innumerable polyps of varying sizes up to 1.5 cm throughout the colon, with relative rectal sparing (figure 2B). Biopsies were consistent with tubular adenoma and hyperplastic polyps. Thyroid ultrasound was within normal limits and abdominal CT was significant for left-sided 3.4 cm mesenteric mass representing scarring versus possible desmoid.

Family history was significant for colon cancer diagnosed in his maternal grandfather at age 72, paternal grandmother who died of metastatic cancer at age 50 with unknown primary and mother diagnosed with thyroid cancer at age 40. Physical examination was notable for morbid obesity (BMI 45), cardiopulmonary examination within normal limits and abdomen with well-healing surgical scars from prior sleeve gastrectomy.

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Figure 1 Sleeve gastrectomy surgical specimen with numerous polyps visible.

Figure 2 (A) Gastric polyps visualised on upper endoscopy, post-sleeve gastrectomy; (B) polyps visualised on colonoscopy throughout the colon, with relative rectal sparing.

INVESTIGATIONS

A genetic referral was made and genetic testing and analysis were performed by Quest Diagnostics, Nichols Institute (San Juan Capistrano, California, USA) and Myriad Genetics (Salt Lake City, Utah, USA). Thirty-four genes were analysed as part of an assay, including the APC and MutYH genes. The National Center for Biotechnology Information (NCBI) reference sequence NM 000038.5 was used as a reference for mutation assessment of the APC gene.¹⁰ The assay used selective enrichment of sheared DNA fragments representing the coding regions and splice junction sites of all relevant genes, with subsequent massively parallel nucleotide sequence analysis. Results were significant for one copy of the c.7682dup (p.Ser2562Lysfs*21) variant in exon 15 of the APC gene. This mutation is proximal to the last known pathogenic mutation in the gene and is predicted to cause premature termination of APC protein synthesis, suggesting that this mutation is likely pathogenic. From our search of the literature and known online databases including dbSNP, the Universal Mutation Database and the Leiden Open Variation Database / InSiGHT variant database, this mutation has not been previously reported.^{11–15}

TREATMENT

Given the clinical findings of innumerable colonic polyps not amenable to endoscopic resection with rectal sparing, and results of genetic testing, the patient was counselled and colectomy was recommended. He underwent an elective robotic subtotal colectomy with ilealrectal anastomosis. Pathology from surgery was significant for approximately 80 polyps ranging from 0.3 to 1.6 cm in size, with occasional focal high-grade dysplasia without invasive carcinoma, and all lymph nodes negative for metastatic carcinoma. Intraoperatively and on pathology, no desmoid was found.

OUTCOME AND FOLLOW-UP

The patient recovered well from surgery, and has been subsequently found at outpatient follow-up to be doing well. He is being monitored closely with upper gastrointestinal tract and rectal surveillance.

Learning points

- ▶ With wider institution of treatment options such as bariatric surgery, screening modalities such as upper and lower endoscopy and increased imaging such as abdominal CT, incidental findings such as intestinal polyps and desmoid tumours are becoming more commonplace and should alert the astute clinician to consider further workup.
- ▶ If intestinal polyps manifest with decreased severity or altered distribution than expected for a classic familial adenomatous polyposis (FAP) syndrome, the astute clinician should continue to keep in mind the attenuated familial adenomatous polyposis (AFAP) syndrome when proceeding with further diagnostic workup.
- ▶ When evaluating a patient for bariatric surgery, significant consideration should be given for performing a preoperative upper endoscopy, especially when revision in anatomy may make endoscopic screening or surveillance more difficult.
- ▶ Given a clinical suspicion for presence of FAP or AFAP syndrome, further diagnostic testing, including genetic testing for an adenomatous polyposis coli mutation, recognised in literature or otherwise, can help confirm the diagnosis.

The patient's clinical presentation and final colon pathology were consistent with AFAP with a previously undescribed APC mutation. The patient and his family members have been referred for genetic screening and counselling.

DISCUSSION

To the best of our knowledge, this mutation has not been previously described in association with AFAP phenotype. A thymine residue at index 7682 is duplicated, yielding a DNA coding sequence frameshift from 'GTA AGC ACT...' to 'GTT AAG CAC T...'. This frameshift results in mutation of amino acid 2562 in the resultant protein product from serine to lysine. Normally, the final protein would contain 281 additional amino acids prior to termination. However, with this frameshift mutation, only 19 more mutated amino acids are appended until a stop codon is reached.

Based on prior mapping of the APC protein, this mutation likely yields an incomplete or missing End-binding protein 1 (EB1) binding site and human disc large (HDLG) binding site.^{16 17} EB1 is involved in regulation of microtubule function during the cell cycle; loss of its binding domain on APC may be associated with indiscriminate microtubule binding.¹⁷ The HDLG protein is a tumour suppressor. The APC-HDLG complex appears to be responsible for halting progression of the cell cycle from G0/G1 to S phase; thus, absence or lack of function of the HDLG binding site on APC may result in decreased regulation of the cell cycle at this phase.¹⁷

With these proposed mechanisms, mutation c.7682dup (p.Ser2562Lysfs*21) in exon 15 of the APC gene, previously unreported in the literature and online databases, appears to be associated with an AFAP phenotype in our patient. Identification of this mutation in future patients should warrant a full workup and genetic testing and counselling of the affected patient and family members.

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