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Retrospective Study

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Clinical features and long-term outcomes of patients with colonic oligopolyposis of unknown etiology

Outcomes in CPUE

Abstract

BACKGROUND

¹Colonic adenomatous polyposis of unknown etiology (CPUE) is an adenomatous polyposis phenotype that resembles Familial Adenomatous Polyposis even though no germline pathogenic variant is identified.

AIM

¹We sought to better characterize the clinical features and outcomes in a cohort of CPUE patients.

METHODS

This is ²a retrospective case series of ¹patients 18 years old or older with adenomatous oligopolyposis (between 10-100 adenomas) and negative genetic testing, ²identified through the Hereditary Gastrointestinal Cancer Database at Massachusetts General Hospital, ⁶a tertiary academic referral center. A retrospective chart review was performed with a focus on demographics, alcohol and tobacco use, medication use, familial malignancy and polyp burden, genetic testing information, endoscopic surveillance data including the corresponding histopathology, colonic and extracolonic malignancies, mortality events, and their etiology. Spearman correlation and Pearson ¹⁰Chi-square test (or Fisher's exact test) were used for continuous and categorical variables respectively.

RESULTS

CPUE patients were primarily ¹male (69%) and ¹presented for genetic counseling at 63.7 years. Only 2 patients (2.9%) reported a first-degree relative with polyposis. During an average surveillance period of 12.3 years, 0.5 colonoscopies per year were performed. Patients developed 2.3 new adenomas per year. 4 (5.7%) ²were diagnosed with CRC at a mean age of 66 years, and 3 were diagnosed prior to the onset of oligopolyposis. ¹7 (10%) required colectomy due to advanced dysplasia or polyp burden. With respect to upper gastrointestinal ¹manifestations, 1 patient had a gastric adenoma,

but there were no cases of gastric or small bowel polyposis. During surveillance, 10 (14%) patients died at a mean age of 72, and none were due to CRC.

CONCLUSION

CPUE is distinct from FAP syndrome and the use of FAP surveillance guidelines may result in unnecessarily frequent upper and lower endoscopies.

Key Words: Colonic polyposis of unknown etiology; Multigene cancer panel; Colorectal cancer; Colectomy; Surveillance; Mortality.

⁴ Feldman D, Rodgers-Fouche L, Hicks S, MD DCC. Clinical features and long-term outcomes of patients with colonic oligopolyposis of unknown etiology. *World J Gastroenterol* 2022; In press

¹ **Core Tip:** Colonic adenomatous polyposis of unknown etiology (CPUE) resembles FAP syndrome, but no genetic alterations are identified. The optimal management of CPUE is uncertain. Patients with CPUE are typically older males that exhibit a low rate of new adenoma formation without upper gastrointestinal polyposis during long-term surveillance. 10% required colectomy for polyposis, and none died from colon cancer. The clinical behavior of CPUE is distinct from FAP, and the current application of FAP surveillance guidelines for CPUE may result in unnecessarily frequent upper and lower endoscopies.

³ INTRODUCTION

Colorectal cancer (CRC) is the 4th most frequently diagnosed cancer and the second leading cause of cancer death in the United States^[1,2]. Most CRCs are considered sporadic and the lifetime cumulative risk for CRC in the general risk population is estimated at 5%^[3]. Approximately 5% of CRCs are attributable to a hereditary CRC syndrome. These are broadly classified into polyposis and nonpolyposis syndromes.

Current clinical guidelines suggest a ⁵ minimal set of genes that should be tested in all patients suspected of hereditary CRC or polyposis, preferably by using a multigene panel because of ⁵ overlapping clinical phenotypes, inconsistent definitions for oligopolyposis, challenges with accurately classifying polyp histology, and variable modes of inheritance^[4,5]. Adenomatous polyposis syndromes are the most common polyposis syndromes and typically result from a germline mutation in *APC* or bi-allelic variants in *MUTYH*. Rarely, adenomatous polyposis that may be phenotypically indistinguishable from *APC*/*MUTYH*-related polyposis, can be observed secondary to germline mutations in *AXIN2*, *GREM1*, *NTHL1*, *POLE*, *POLD1*, or *MSH3*^[5-7]. Germline mutations in one of these genes are not always identified, and the term ⁹ “colonic adenomatous polyposis of unknown etiology (CPUE)” has been coined to describe cases of ¹ adenomatous polyposis in which no pathogenic variant is found in a polyposis gene. This occurs in as many as 30-50% of all polyposis cases^[8,9]. *APC* promoter 1B mutations^[10] and somatic mosaicism for *APC*^[11] are possible mechanisms, but this is likely to account for only a small fraction of these cases. Recent data also suggested that missed germline mutations can be potentially revealed by retesting^[12].

CPUE appears to be more common in those with lower polyp numbers. 48% of cases of polyposis with over 100 adenomas were explained by a germline mutation, most commonly in *APC* or *MUTYH*. However, only 13.6% of individuals with 20-99 adenomas and 6.4% of those with 10-19 adenomas exhibited a germline mutation in a polyposis gene. Thus, a diagnosis of CPUE is more common in individuals who exhibit oligopolyposis (10-99 adenomas)^[13].

The clinical features of individuals with adenomatous oligopolyposis of unknown etiology are not well-defined, and management recommendations are largely extrapolated from guidelines for FAP syndrome^[14]. Previous reports of CPUE are mostly small and heterogeneous. While some have described a benign course^[6], others found

duodenal adenomas and fundic gastric polyposis in addition to an approximately 30% risk of extracolonic malignancies including skin cancer, leukemia, breast, bladder, and prostate cancer^[9,15,16]. We sought to better describe the clinical characteristics and outcomes in a large cohort of CPUE patients.

MATERIALS AND METHODS

Study population

The study population of CPUE patients was identified through the Hereditary Gastrointestinal Cancer Database at Massachusetts General Hospital. Patients 18 years old or older who were documented to have at least 10 cumulative adenomas and less than 100 adenomas and completed sequencing of at least *APC* and the 2 common mutations (Y179C and G396D) of *MUTYH* without evidence of a pathogenic germline mutation were included.

Data collection

Patient charts were reviewed utilizing the EPIC Electronic Health Record from the first available endoscopic surveillance documentation through September 1, 2021. Data were retrospectively collected including demographics (age, gender, race, maternal and paternal ethnicities), self-reported tobacco and alcohol use, metabolic comorbidities (diabetes mellitus, obesity, metabolic syndrome), and medication usage (as documented at the time of genetic counseling) associated with possible chemoprevention effect (Statins, Aspirin, and Glucophage). Genetic data and relevant family history were collected and included the date and age at the time of genetic consultation, results of genetic testing, and family history of polyps and malignancy up to 3rd degree relatives.

Data from colonoscopies, sigmoidoscopies, esophagogastroduodenoscopies (EGD), and video capsule endoscopies (VCE) including indication, quality of bowel preparation, polyps, and other significant findings were recorded. Histopathology reports were

reviewed. Colonic and extra-colonic malignancies, mortality, and causes of death were also documented.

² A REDCAP platform (a secure, password-protected database) was utilized to store data, and these data were ³ later exported as Excel sheath files (saved on encrypted drives) for analysis.

Data analysis:

Categorical variables were described as frequencies and percentages. Pearson Chi-square test (or Fisher's exact test if > 20% of cells had expected count < 5) were used to test correlations of dichotomous and categorical variables. Continuous variables were described as a mean \pm standard deviation (SD), median, and range. ¹¹ Student's *t*-test and non-parametric Mann-Whitney U test were used to compare means or mean ranks across scale variables of two independent samples. ¹² A univariate logistic regression analysis was performed to assess the impact of a set of predictors on extra colonic malignancies (dependent variable). ⁷ Limited by the low number of cases observed we did not have the power to estimate their confounding effect using multiple regression. ⁸ All statistical tests were two-sided and $p < 0.05$ was considered as statistically significant. ¹⁴ SPSS software (IBM SPSS Statistics for Windows, ver. 28.0.1.0(142)) was utilized for statistical analysis. A statistical review of the study was performed by a biomedical statistician.

³ This study was approved by the institutional review board and was carried out in accordance with the ethical principles as described in the Helsinki Declaration.

RESULTS

Patient demographics

70 patients met the inclusion criteria and comprised our cohort of CPUE patients with oligopolyposis. The last clinical surveillance was documented ² at a mean age of 69.3 (range

30.6-85.5, median 70.6). 48 (69%) patients were male and 62 (89%) were Caucasian, predominantly represented by Irish and English ancestry. 29 patients (41.4%) were diagnosed with any metabolic comorbidity. 34 patients (49%) reported any history of alcohol usage. 7 patients (21.2%) were documented to consume more than 1 alcoholic beverage per day. 14 of these patients (42.4%) consumed between 1-7 drinks per week. 41 patients (58.6%) reported any smoking history. Data concerning current use of tobacco could be retrieved in 39 patients, and 15 of these patients (38.4%) were reported as active smokers. 17/41 (41.4%) patients who smoked had reported a mean of 30.1 packs/year (range 0.5-100 packs/year, median 25) (Table 1).

Genetic test results

All 70 CPUE patients had genetic counseling and testing at a mean age of 63.7 years (Range 27-83, median 65.5). Each patient had documentation of at least 10 adenomas as an indication for counseling, and most presented with a cumulative polyp burden of 10-20 polyps (36 patients; 51.4%), followed by 21-30 polyps (18 patients; 25.7%), 31-50 polyps (12 patients; 17.1%) and 4 patients (5.7%) with 51-100 polyps.

All patients had sequencing of the *APC* (full) and *MUTYH* gene (24% had sequencing of the 2 common mutations Y179C and G396D, 76% had full sequencing). 26 patients (37%) had sequencing of only these 2 genes, 5 patients (7%) had 4-7 additional genes analyzed (including *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*), and the majority (39 patients, 56%) had multi-gene panels with a mean of 35.2 (+/-3.6) genes tested (Range 12-91; Median 28). The CRC-related genes that were sequenced are described in Table 2 (full list in Supplementary Table 1).

None of the patients carried a pathogenic *APC* or *MUTYH* mutation, and no other polyposis-related gene mutations were identified when tested as part of a multi-gene panel. 2 patients were identified as carriers of a non-polyposis associated pathogenic

variant (*APC* I1307K and *CFTR* (TG)11-5T). 5 patients (7.1%) carried a VUS (in *RAD 50*, *ATM*, *BARD1* or *APC*).

Family history of cancer and polyps

At the time of initial genetic consultation, 54 patients (77.1%) reported a family history of any malignancy in a first-degree relative (FDR). There was a total of 113 cases of malignancy in FDRs in our cohort. Of these, the most prevalent were CRC (25 cases, 22.1%), breast (20 cases, 17.7%), and prostate (14 cases, 12.4%) cancer (Table 3). 14 patients (20%) had at least 1 FDR with CRC and 6 patients (8.6%) had at least 1 FDR and 1 s degree relative (SDR) with CRC. The mean age of CRC diagnosis in an FDR was 66 (range 44-97, median 66). Most of these patients (30) had only 1 FDR (55.6%) with any cancer. With respect to SDRs, 94 cases of any malignancy were found in our cohort, mostly represented by 17 cases of CRC (18%) and 11 cases (11%) of breast cancer.

22 patients (31.4%) were reported to have an FDR with any colon polyp, and most of these patients were reported to have 1 or 2 FDR (36% and 41%, respectively) with any colonic polyp. Only 2 patients (2.9%) were reported to have a family history of multiple polyps in a FDR. In one patient, the father required a partial colectomy for multiple polyps.

Polyp and adenoma burden during colonoscopy surveillance

Among the 70 patients, 430 colonoscopy reports were reviewed, resulting in a calculated mean of 6.1 \pm 3.4 colonoscopies (range 1-15; median 6) performed per patient. The first documented colonoscopy was in March 1992 and the last one was documented in November 2021. Among the 63 patients who had more than one colonoscopy performed over more than one year of surveillance, 418 colonoscopies were documented, with a calculated mean of 6.6 \pm 3.2 colonoscopies (range 2-16, median 6) per patient, during a mean surveillance period of 12.3 \pm 6.2 years (range 1.3-24.8, median 11.8 years). The calculated average frequency of colonoscopy surveillance among this group was 0.5 colonoscopies/year.

For these 63 patients, there was a total of 2547 documented polyps in 408 colonoscopies and 1826 documented adenomas in 394 colonoscopies, with a mean total cumulative burden of 39 ± 24.7 polyps (range 10-111; median 29) and 29.0 ± 18.9 adenomas (range 10-102; median 24). Over the entire surveillance period, this translates to a mean of 3.2 polyps diagnosed per year and 2.3 adenomas/year.

With respect to the distribution of polyps and adenomas in the colon, the right colon was the most prevalent location (75% and 54%, respectively), followed next by the transverse colon (49.7% and 38.8%, respectively). For polyps in general, the next most prevalent locations were the sigmoid colon (41.6%), left colon (39.0%), and rectum (26.6%), while for adenomatous polyps the locations and prevalence were left colon (31.1%), sigmoid colon (22.4%) and the rectum (10.5%).

The most prevalent adenoma histology found was tubular adenoma with low-grade dysplasia (90%). High-grade dysplasia in a tubular adenoma or tubulovillous adenoma was seen in 11 exams (3.2%) (Supplementary Table 2). In 142 of the 428 colonoscopies (33%), at least one non-adenomatous polyp was reported. Except for one colonoscopy in which only an inflammatory polyp was described, serrated polyps were reported in 141 of these 142 colonoscopies (99%), and these included hyperplastic polyps (74%), sessile serrated polyps/adenomas (24%) and traditional serrated adenoma (1.3%). Most of the serrated polyps were located in the sigmoid colon (33.3%) followed by the right colon (22.5%), rectum (20%), transverse colon (13.3%), and left colon (10.7%). No hamartomas were reported.

Incidence of invasive colorectal cancer

Four patients were diagnosed with invasive CRC (5.7%; mean age 66). Three underwent colectomy and one had a malignant polyp that was resected endoscopically. Among these four cases, three patients were diagnosed with CRC prior to the development of

oligopolyposis. The first was a male diagnosed with rectal carcinoma at the age of 63 along with 4 adenomas; this patient later developed 23 more adenomas over 17 years of surveillance. The second patient was a male diagnosed at the age of 70 with a malignant polyp (T1N0M0, well-differentiated adenocarcinoma) in the sigmoid colon that was completely resected at colonoscopy. He presented with a polyp burden of only 6 adenomas over a 15-year period prior to the diagnosis of CRC. The third patient was a female diagnosed with a sigmoid colon CRC at the age of 71 at her first colonoscopy with a polyp burden at that time of 5 adenomas. This patient later developed 33 adenomas over 4.5 years of surveillance. The fourth patient was a female diagnosed with transverse colon CRC at the age of 69, one year after her first colonoscopy with a cumulative burden of approximately 30 adenomas. Immunohistochemical stains for DNA mismatch repair proteins were available for two of these patients, and both demonstrated preserved expression of all proteins (hMLH1, hMSH2, hMSH6, and hPMS2).

Rates of colectomy for ¹high polyp burden or advanced dysplasia

Four additional ¹patients (5.7%, mean age 64) underwent colectomy due to high polyp burden without cancer. Two had a subtotal colectomy for multiple tubular and tubulovillous adenomas, some of which were large and unresectable endoscopically. Another had a subtotal colectomy due to a cumulative burden of approximately 50 adenomas as well as recurrent diverticulitis. One had a total proctocolectomy due to a cumulative burden of more than 80 adenomas in addition to adenomatous polyps with high-grade dysplasia. These patient characteristics are summarized in Table 4. Three patients (4.3%, mean age 52) were diagnosed with intramucosal carcinoma during colonoscopy, and all underwent colectomy.

When comparing these 11 patients who had a significant clinical outcome (intramucosal cancer, invasive cancer, or risk-reducing colectomy for polyposis) to the rest of the cohort (59 patients), no difference was found in any clinical parameters including gender,

tobacco use, metabolic comorbidities, familial malignancy burden, personal malignancy burden or duration of colonoscopy surveillance (Supplementary Table 3).

Extracolonic findings

With respect to upper gastrointestinal findings, 39 patients (55.7%) had at least 1 upper endoscopy performed (first exam at mean age 62.3, range 22-83, median 65). 10 patients (14%) were found to have any gastric polyp. In 11 gastroscopies, there were up to 5 polyps documented and none was above 1 cm. Among cases in which histologic sampling was performed, the most common histology was fundic gland polyp without dysplasia (72%) followed by hyperplastic polyp (22%), and there was one case of 1 gastric adenoma that also exhibited high-grade dysplasia (6%). This patient also had low-grade dysplasia that arose in a background of chronic gastritis and intestinal metaplasia secondary to *H. pylori*.

No duodenal adenomas were detected. 4 patients (5.7%) had a formal ⁶ small bowel evaluation with video capsule endoscopy (VCE), and no small bowel polyps were identified.

A total of 49 extra colonic malignancies (ECM) were documented in 35 patients (50%), and 9 patients (20%) had more than 1 ECM. The mean age of first ECM diagnosis was 60 (range 23-82, median 62) with ¹ non-melanoma skin cancer (51%) and prostate cancer (12%) as the most common. (Table 5). Gender, age, and cumulative adenoma burden were evaluated by univariate analysis logistic regression for their potential contribution to the development of an ECM. Age was found to have a correlation with breast cancer and melanoma occurrence ¹⁶ with an odds ratio of 0.8 ($p=0.01$) and 0.9 ($p=0.01$). Otherwise, cumulative adenoma burden was not found to be a predictor. (Supplementary Table 4). No correlation was found between the cumulative adenoma burden and the total number of extra colonic malignancies reported ($p=0.18$).

Mortality

10 patients (14%) ²⁰ died during follow-up. The mean age of death was 72 (range 61-78, median 73.5). 5 patients (50%) died of malignancy, but none was from CRC. The mean age of death from cancer was 74.4 (range 71-77, median 75) and 5 patients (50%) died from non-malignancy causes at a mean age of 69.6 (range 61-78, median 69). None of these causes were directly related to the underlying polyposis (i.e., complications from colonoscopy or colectomy) (Table 6).

DISCUSSION

CPUE is a colonic ¹ adenomatous polyposis syndrome in which no germline mutation is detected. Our relatively large CPUE cohort is comprised primarily of older white males ¹ without a family history of polyposis but a modest ¹ family history of colon cancer and personal history of tobacco use. The adenoma burden is modest and is characterized by a relatively low rate of adenoma growth (average of 2.3 adenomas/year). However, 15.7% were considered to have a significant outcome, which included colectomy due to polyp burden, advanced polyp histology of intramucosal carcinoma, or a diagnosis of CRC. There were no deaths related to CRC or polyposis.

Interestingly, three patients had a CRC diagnosis before developing at least ten cumulative adenomas, However, all did exhibit colonic adenomas either prior to or at the time of CRC diagnosis, demonstrating that a predisposition to polyp formation was present at the same time. These findings reveal the heterogeneity of disease presentation associated with CPUE.

Although CPUE is often considered an attenuated variant of FAP, our findings in a large CPUE cohort over an extended period of surveillance (12.3 +/-6.2 years) suggest that CPUE is quite dissimilar from FAP given the gender distribution, age of onset, absence of family history, low rate of colon adenoma growth, and absence of upper GI and other extra-colonic manifestations. Others have described CPUE cohorts to have higher rates

of colon polyp formation, family history of polyposis and CRC, and upper GI polyposis. For example, CRC was observed in 19.3% of a different CPUE cohort. However, more comprehensive multi-gene panel testing was not performed. A low rate of upper GI findings in CPUE was also observed^[17], consistent with our findings. The relatively high rates of metabolic co-morbidities as well as alcohol and tobacco use in our cohort suggest that there may be significant environmental and lifestyle contributors in patients with CPUE.

Because data are limited with respect to clinical features and outcomes in CPUE, it has been difficult to formulate definitive management recommendations. The NCCN describes CPUE as a potential attenuated subgroup of familial adenomatous polyposis with possible FAP-related extra colonic manifestations. In addition to recommending short colonoscopy intervals (every 1-2 years), consideration is given to the evaluation of the upper GI tract, with specific attention to the duodenum and the ampullary area^[5]. Our findings suggest that most with CPUE do not exhibit features suggestive of a FAP-related syndrome. Annual colonoscopy and routine upper GI surveillance may therefore not be required.

¹⁸ Our study has some limitations. Due to its retrospective nature, complete endoscopic and pathology data in some patients could not be retrieved, and not all endoscopy reports reliably quantified polyp burden. Thus, our results might reflect an underestimation of the cumulative polyp burden. In addition, approximately 40% had only *APC* and *MUTYH* genes sequenced, so alternative genetic etiologies for polyposis may not have been recognized. However, the frequency with which mutations in these other novel intermediate-risk genes are identified is very low^[13,18], and it is unlikely that a significant number of these cases would be explained by one of these mutations. Finally, our cohort was comprised mostly of Caucasian men of Irish and English descent and may not be representative of the broader CPUE population. This may result in a selection bias that

could be attributable to lower rates of referrals for genetic counseling and testing in non-White populations^[19-20].

CONCLUSION

Most individuals with CPUE in our cohort exhibited ¹ a relatively benign course, characterized by a generally modest colonic adenoma burden, dominance of non-advanced histology, low rates of CRC during surveillance, negligible upper GI involvement, and low rates of mortality due to polyposis or CRC. We suggest that colonoscopy surveillance intervals could be extended, and that ¹ routine upper GI screening may not be required.

ARTICLE HIGHLIGHTS

Research background

Colonic polyposis syndromes typically result from germline mutations in the *APC* or *MUTYH* genes and less commonly from other low/intermediate-risk genes. When no pathogenic variant is identified, a diagnosis of colonic polyposis of unknown etiology (CPUE) is made.

Research motivation

The existing literature on CPUE is limited, and the precise clinical features and long-term outcomes are not well-defined.

Research objectives

To characterize the natural history of CPUE by defining the malignancy risk, long-term colonic adenoma burden, and risk of extra-colonic tumors over an extended period of surveillance.

Research ⁶ethods

We performed a retrospective detailed chart review of demographic, lifestyle habits, endoscopic, genetic, and clinical data of patients aged 18 years old or older meeting the criteria for CPUE in the Hereditary Gastrointestinal Cancer Database at Massachusetts General Hospital.

Research results

70 patients met the inclusion criteria and were predominantly Caucasian males. During an extended surveillance period, a very low cumulative colonic adenoma burden was observed, with no evidence for duodenal adenomas. 4 patients were diagnosed with CRC, but none had extra-colonic malignancies that are typically seen in FAP syndrome (i.e., gastric, duodenal, or thyroid cancer). There was no mortality attributable to CRC.

Research conclusions

Individuals with CPUE exhibited a relatively mild course with respect to polyp burden and cancer risk, which differs significantly from the FAP syndrome. The modest colonic burden implies colonoscopy surveillance intervals could be extended, and regular gastroscopic exams may not be necessary.

Research perspectives

CPUE is an underdiagnosed and heterogeneous clinical entity. The current findings should be validated in large-scale multi-center prospective studies, with greater representation of non-Caucasian populations in order to better define this unique condition in an evidence-based approach.

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SIMILARITY INDEX

PRIMARY SOURCES

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