Rapidly progressive adenomatous polyposis in a patient with germline mutations in both the APC and MLH1 genes: the worst of two worlds

R Scheenstra, F E M Rijcken, J J Koornstra, H Hollema, R Fodde, F H Menko, R H Sijmons, C M A Bijleveld, J H Kleibeuker

CASE REPORT

The two most common inherited forms of colorectal cancer are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer. Simultaneous inheritance of both an APC gene mutation and a mismatch repair gene (for example, MLH1) mutation has never been described. In the present case report, we report rapidly progressive adenomatous polyposis in a 10 year old boy with a germline frame shift mutation in the APC gene and a germline splice site mutation in the MLH1 gene. Immunohistochemical investigations showed abnormal expression of β-catenin in early adenomas with low grade dysplasia, attributed to the APC gene mutation. Subsequent loss of function of the MLH1 gene, as shown by absent immunostaining of its protein in adenomas with high grade dysplasia, may well have caused the rapid progression to high grade dysplasia in many of the adenomas.

In this report, a case is presented of a patient manifesting a severe phenotype who had inherited germline mutations in both the APC gene and the MMR gene MLH1.

CASE REPORT

A 10 year old boy attended the outpatient clinic for evaluation of slimy and bloody stools. His mother had previously been diagnosed with FAP. At the age of 27 years, she underwent prophyllactic colectomy. Due to the development of extensive abdominal fi bromatosis (desmoid tumour), she died at the age of 32 years. Genetic analysis had revealed a germline de novo frame shift mutation in the MLH1 gene. Immunohistochemical examinations showed abnormal expression of β-catenin in early adenomas with low grade dysplasia. Genetic analysis revealed a germline de novo frame shift mutation in the APC gene and a germline splice site mutation in the MLH1 gene. Immunohistochemical investigations showed abnormal expression of β-catenin in early adenomas with low grade dysplasia, attributed to the APC gene mutation. Subsequent loss of function of the MLH1 gene, as shown by absent immunostaining of its protein in adenomas with high grade dysplasia, may well have caused the rapid progression to high grade dysplasia in many of the adenomas.

The two most common inherited forms of colorectal cancer are familial adenomatous polyposis (FAP), caused by germline mutations in the APC (adenomatous polyposis coli) tumour suppressor gene, and hereditary non-polyposis colorectal cancer (HNPCC), caused by germline mutations in one of the DNA mismatch repair (MMR) genes. Together, FAP and HNPCC account for approximately 2% of colorectal cancer cases. In this report, a case is presented of a patient manifesting a severe phenotype who had inherited germline mutations in both the APC gene and the MMR gene MLH1.

Abbreviations: FAP, familial adenomatous polyposis; APC, adenomatous polyposis coli; HNPCC, hereditary non-polyposis colorectal cancer; MMR, mismatch repair.
Adenomatous polyposis with germline mutations in \textit{APC} and \textit{MLH1} genes

Figure 1 Normal colonic mucosa and areas of adenomatous epithelium with low grade dysplasia (A–C) and adenomatous epithelium with high grade dysplasia (D–F). Serial haematoxylin-eosin staining (A, D) and immunohistochemical (brown) staining of \(\beta\)-catenin (B, E) and MLH1 protein (C, F). In the adenomatous areas with low grade dysplasia, \(\beta\)-catenin staining is normal [membranous] in normal mucosa, in contrast with abnormal [cytoplasmic and nuclear] staining in adenomatous areas; MLH1 protein is expressed in both normal mucosa and adenomatous epithelium. In the adenomatous epithelium with high grade dysplasia, \(\beta\)-catenin staining is similar to the adenomatous areas with low grade dysplasia, whereas MLH1 protein expression is seen in normal mucosa but lost in areas with high grade dysplasia (magnification 100×).

background.\textsuperscript{1,4} In mice carrying both \textit{APC} and \textit{MLH1} mutations, the incidence of intestinal adenomas was markedly increased compared with mice carrying only one of these mutations.\textsuperscript{8} Alternatively, the severe phenotype in our patient may in fact reflect the marked heterogeneity which is known to exist in both FAP and HNPCC.\textsuperscript{1,4}

Our patient probably has a higher risk of developing cancer at other sites than average FAP or HNPCC mutation carriers. Intensive follow up and surveillance are therefore warranted.

In conclusion, our case represents the first report of a patient with adenomatous polyposis who carried both a pathogenic \textit{APC} and \textit{MLH1} germline mutation. The early adenoma onset and the rapid tumour progression in this patient illustrate that the multistep process of colorectal carcinogenesis in this setting was markedly accelerated.

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