A Rare Case of FAP in Kashmir Valley

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Abstract Familial adenomatous polyposis (FAP) is the commonest form of inherited form of CRC. It comprises of about 5% of all the colorectal cancers (CRCs). FAP patients have a family history of CRC that suggests a genetic contribution, common exposures among family members, or a combination of both. This case report gives a glimpse of the phenotypic manifestation of FAP and the underlying molecular mechanism which leads to FAP, in addition it also sheds a light on the management of FAP in early stages of life.

Keywords Colorectal cancer · FAP · Kashmir · APC · PCR-SSCP

Introduction

Colorectal cancer (CRC) is the third most common cause of cancer-related death in the western world. It is a commonly diagnosed cancer in both sexes [1]. CRC arises as the cumulative effect of multiple mutations within the cell, allowing it to escape growth and regulatory control mechanisms [2–4]. While the majority (75%) of cases of CRC are sporadic, a significant minority (25%) occur as a result of an inherited genetic mutation. Among inherited cases of CRC Familial adenomatous

polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) account for about 5% [5].

Case Report

A male patient of 40 years—residing from south Kashmir & farmer by profession, visited our Institute with the chief complaints of severe constipation and profuse bleeding per rectum for the last 5 months. Other clinical complaints were nausea, vomiting, anemia, anorexia, loss of appetite and rampant abdominal cramps. The patient was also a high user of tobacco, *noon-chai* (Salt tea), meat and pickles. Medical history of the patient revealed a familial predisposition to cancer, as patient's father, Uncle and his Grandfather suffered from cancer's of GIT (Fig. 1). The patient's sigmoidoscopy in Oncology Department revealed multiple (Hundreds) of sessile polyps present on the luminal surface of entire colon—from rectum upto the caecum (Figs. 2, 3). Hence oncologists gave a provisional diagnosis of familial adenomatous polyposis (FAP). The examination also revealed a rosette shaped ulcerative lesion located at the transverse section of the colon—whose histopathological examination revealed it to be Poorly Differentiated Adenocarcinoma. The stage of the tumor was (later) found to be T2N2M1 (Fig. 4). Following the provisional diagnosis, the patient was referred to the Department of General Surgery, where he underwent total proctocolectomy with ileal pouch anal anastomosis using stapling technique. The margins of the excised tissue were found to be free of the tumor but there was histological evidence of metastasis into the nearby lymph nodes. The post operative period was uneventful. The treatment was completed with 2 cycles of chemother-

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Fig. 1 Pedigree of patient belonging to FAP family. All of his immediate relatives died of CRC in their early 40's. But his aunt was alive when he reported in our institute

apy. However the patient died 4 months after the surgery, the cause of death was not known as he died at home.

Discussion

Familial adenomatous polyposis was first identified as the dominantly inherited condition by Lockhart-Mummery in 1925 [6]. The major clinical trait of FAP is the presence of thousands of sessile colonic polyps on the luminal surface of the colon and rectum that usually appear by the third decade of life. FAP patients have a 100% life-time risk of developing CRC, although the

Fig. 2 Image showing the entire colon of the third generation FAP patient, which was removed by APR surgery

Fig. 3 Image showing the inner lining of the colon, notice hundreds of polyps all over the surface of the colon and a rosette shaped malignant tumor at transverse section of the colon

transition to cancer is low, the vast numbers of polyps virtually assure CRC development at a young age [5]. The overall incidence of the FAP is about 1 in 8000 [7]. Debinski et al has showed that the relative risk of development of CRC in FAP patients depends significantly on the number of polyps [8].

The foremost phenotypic feature which helps the clinicians in identification of FAP patients is the presence

Fig. 4 A closeup of the rosette shaped malignancy of the colon. The tumor was classified as T4N2M1. Histopathology revealed the tumor to be Poorly Differentiated Adenocarcinoma

of large number of polyps on the luminal surface of the intestines. Second being the presence of cancer in immediate relative. Blair et al has also shown the presence of Congenital hypertrophy of the retinal pigment epithelium (CHRPE) in about 60% of FAP patients [9].

The molecular basis of FAP is the mutation of one of the most important genes of the Wnt signaling pathway—adenomatous polyposis coli (*APC*) gene. *APC* gene located in 5q21 comprises of 15 exons coding for 310 kDa multidomain protein. *APC* is a classical tumour suppressor protein which indirectly regulates transcription of a number of critical cell proliferation genes, through its interaction with β -catenin. Almost 75% of the coding sequence of *APC* gene comprises of exon 15 which is the most common target for both somatic and germline mutation. The coding sequence between 1286 and 1513 codons is the most frequent target of about 60% of somatic mutations, this region is termed as the mutation cluster region (MCR) of *APC* gene [10, 11]. Germline mutations in the *APC* gene have been demonstrated in most FAP patients. The vast majority (95%) of *APC* mutations are nonsense or frameshift mutations that result in a truncated protein product with abnormal function [12]. Up to one-third of all FAP-causing mutations occur at *APC* codons 1061 and especially 1309 [13].

For the better management of the FAP families/patients better diagnostic systems is needed. Earlier patients or kindred of high risk FAP families were regularly screened using either colonoscopy or sigmoidoscopy coupled with followup annually. However nowadays, a best diagnostic tool available is the genetic test which enables the early detection of the FAP predisposition even before the appearance of polyps on the colonic lumen. These genetic tests involves the isolation of the genomic DNA from the tissue/ blood of the potential high risk patients which is then subjected to analysis of *APC* gene mutations using PCR-SSCP technique [14, 15].

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