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Familial Adenomatous Polyposis: Review of Current Diagnosis, Screening and Management

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Abstract

The management of familial adenomatous polyposis (FAP) has been enhanced due to our improved understanding of genetics, screening protocols, registries, and advancement in surgical techniques. In this review, we will examine the current diagnosis criteria, screening, and management of FAP.

Keywords: FAP, diagnosis criteria, screening, management

Introduction

According to the Global Cancer Observatory (GCO) published by the World Health Organization, colorectal cancer (CRC) is the 3rd and 2nd most common cancer in males and females respectively.[1]

It is estimated that approximately 5-10% of all CRC can be attributed to inherited genetic mutation, with familial adenomatous polyposis (FAP) being the most commonly identified.[2] Our improved understanding of hereditary CRC syndromes has led to creation of patient registries, modified screening protocols, and prophylactic colon resection, all of which have translated into decreased cancer incidence in this population and improved overall patient survival.[3] In this review, we will be focusing our discussion on the presentation, screening, and treatment of FAP.

Genetics

One of the most prominent studied familial colorectal cancer syndrome is familial adenomatous polyposis (FAP). This is due to a germline mutation in the APC (adenomatous polyposis coli) gene, with an autosomal dominant inheritance. Depending on the variation of mutation, presentation varies and can be categorized as familial adenomatous polyposis (FAP), attenuated FAP (AFAP), and MUTYH-associated polyposis. All 3 syndromes are manifested by the onset of multiple colorectal adenomas at an early age with different, but increased, potential for the development of colorectal cancer.

Classic FAP occurs in 1:8,300 live births and affects genders and races equally.[4] Although largely an inherited condition, approximately 25-30% of FAP syndromes reported are due to de novo mutation. This syndrome is

caused by an autosomal dominant mutation in the APC tumor suppressor gene located on the 5q21 chromosome.[5] There have been over 600 germline mutations of the APC gene that have been identified with one third found between codon 1061 and 1309.[6] Most commonly, the mutation in the APC gene creates a premature stop codon, leading to a truncated APC protein.[6] Clinically, FAP presents as having 100 -1000 colorectal polyps during adolescence and these adenomatous polyps invariably develop into cancer before the age of 40.

However, when the mutation occurs at the flanking ends of the APC gene, generally at 5' part of codon 168 or the 3' part of codon 1580, this leads to the development of AFAP. These patients develop a decreased number of adenomatous polyps (<100) at an older age (30-40 years old), and the rectum is usually spared. In this review, we will be focusing on the presentation and management of classic FAP.

Presentation

The presentation of FAP can be divided into colonic, extracolonic intestinal and extraintestinal manifestations.

The defining feature of FAP is the large number of colonic polyps that develop early in the patient's lifetime. These polyps are not present at birth. However, 50% of patients will have detectable polyps by age 15, and 95% by age 35.[7] Without intervention, 100% of these patients will develop malignancy by age 40.[8] These polyps are more commonly found in the rectum and left colon. [8]

Extracolonic intestinal manifestations include gastric polyps, duodenal polyps, and small bowel polyps. Gastric fundic gland polyps occur in approximately 50% of FAP patients. These polyps are nonneoplastic and carry no malignant potential.[9] However, there have been specific genetic mutations linked to an increased development of gastric adenocarcinoma.[10]

Approximately 90% of FAP patients will also develop duodenal adenomas. Despite the high incidence of adenomas, only 5-10% of patients develop periampullary cancer. The lifetime risk of developing duodenal cancer is 3-5%. These generally develop 10-15 years after the onset of colonic polyps. Most commonly, they are located at the ampulla of vater at the second portion of the duodenum.[11] Recent reports have also noted the increased incidence of polyps in the remaining small bowel. Nonetheless, the rate of occurrence and malignant potential has yet to be elucidated.[12]

Extraintestinal manifestations include desmoid tumors, thyroid cancer and several other rare tumors. Desmoid tumors affect approximately 5-15% of patients with FAP. These tumors are most commonly found within the abdomen either along the mesentery or within the abdominal wall.[13,14] The pathophysiology is unclear. Observational studies show there is a predominance for women and pregnancy, speculated to be due to the increased estrogen that act as growth factor for desmoid tumors.[13,14] It is also observed that the majority of desmoid tumors occur after the surgical intervention of FAP, leading to speculation that desmoid tumor development is stimulated secondary to an inflammatory response.[13,14] Desmoid tumors most commonly develop in the 4th decade of life, and present with obstructive symptoms.[14]

FAP patients also have an increased risk of developing both benign and malignant thyroid disease.[15,16] It is estimated that these patients are at 5 times the risk of the normal population for developing thyroid cancer, with papillary thyroid cancer being the most commonly identified pathology.[15,16,17] These tumors develop in the 4th decade of life and are generally not palpable by physical examination.[16,17]

Other rare extracolonic malignant tumors that have been reported in association with FAP include pancreatic adenocarcinoma in adults and hepatoblastoma in children.[18,19]

In addition to the neoplastic manifestation of FAP, there are several benign clinical characteristics that can aid in the diagnosis of the syndrome. The most common is congenital hypertrophy of the retinal pigment epithelium (CHRPE), which is found in 90% of FAP patients. This describes well circumscribed pigmented spots seen with a fundoscopic exam within the retina. Development of CHRPE is believed to be directly related to APC gene mutation, and develops in the 2nd to 3rd decade of life and is often the first extracolonic manifestation of FAP.[20] Fundoscopic exam for CHRPE has a sensitivity of 70% and specificity of 90% for FAP.[21]

Diagnosis

The diagnosis of FAP is performed clinically, followed by genetic confirmation of APC mutation. The autosomal dominant inheritance pattern and the distinct clinical manifestations are seen in FAP guides clinical suspicion for diagnosis. Patients with more than 100 polyps or fewer than 100 polyps with a family history of FAP

are clinically diagnosed with FAP. These individuals are offered genetic testing for APC mutation. Some experts recommend genetic panel testing including other polyposis mutations such as MUTYH.[22]

Keeping in mind not all FAP will have an identifiable APC mutation, all patients diagnosed with FAP both genetically and clinically should be enrolled into a screening program.[23] If germline mutation of the APC gene is identified in an index patient, genetic counseling should be offered to the patient, and genetic testing should be extended to all first-degree relatives.[24] Index patients without APC mutation should have 1st degree relatives screened clinically for FAP.

Screening

The stepwise progression of adenomatous polyp to CRC in FAP makes this disease process an ideal candidate for screening and prevention with prophylactic resection. The benefits of CRC reduction and mortality have been repeatedly demonstrated in multiple registries.[25,26,27]

Current FAP screening guidelines for CRC recommend an initial screening at the onset of puberty (10-12 years old).[8,22] This is based on the review of registries that found CRC to be exceedingly rare in patients under 20.[28] The endoscopic technique recommended for screening initiation is flexible sigmoidoscopy since the rectum is always affected in FAP.[22] If polyps are detected, this is then followed by a full colonoscopy.

If no prophylactic surgery is planned at this time, follow up colonoscopy should occur at 1 year intervals if polyps were detected and at 2 year intervals if no polyps were detected for the remainder of the patient's lifetime. This screening protocol can be increased to 3-5 years in patients without identifiable APC mutation at age 40 and revert to the screening protocol of the general population at age 50.[22]

Current FAP screening guidelines for upper gastrointestinal tumors recommend initial EGD to be performed at the onset of colonic polyposis, or at age 25-30.[8] The Korean and Japanese populations are at risk for developing gastric cancer in FAP.[30] Although, in the western population, the risk of gastric cancer is traditionally believed to be similar to the general population.[29] Nevertheless, new registry data appears to show a sudden increase since 2005.[31, 32] Gastric cancers develop approximately 25 years following colectomy.[32] It is speculated that the improved management of FAP patients are now unmasking the risk of gastric cancer in old age. More data is needed to provide screening risk stratification for gastric cancer in the future.

Currently, the frequency of follow up endoscopy will be based on the Spigelman staging system, which stratifies the risk of developing duodenal carcinoma based on number, size, histology, and dysplasia of polyps.[33] The 10-year risk of developing duodenal cancer in stage II, III and IV reported 2.3%, 2.4% and 36%, respectively (34). Screening intervals for stage 0, I, II, III, and IV are 4 years, 2-3 years, 1-2 years, 6 -12 months and resection, respectively.[8]

FAP patients should also undergo annual thyroid ultrasound screening due to the increased prevalence of papillary thyroid cancer. All nodules 1cm or above should undergo fine needle aspiration.[8,16]

Despite the prevalence of desmoid tumors found in FAP, there are currently no screening recommendations for desmoid tumors.[8]

Infants identified with APC gene mutation should have hepatoblastoma screening with alpha-fetoprotein and liver ultrasound every 6 months.[8]

Treatment of Colonic Lesions

A defining feature of FAP is early onset CRC. Current guidelines recommend immediate surgical resection for FAP patients presenting with proven or suspected cancer, or patients with significant symptoms related to colonic polyps.[8] Nevertheless, there is no consensus in the timing of prophylactic colonic resection. An appropriately timed resection must focus on balancing the improved CRC risk reduction of an early reaction with the improved quality of life and achievement of life goals of a late resection.

The risk of CRC in FAP increases with age, with an average age of cancer diagnosis at 39 years old. Contemporary and classic registry data puts the risk of CRC rate in this population at <1%, 10%, 25%, 87% and 93% at ages 10, 28, 32, 45 and 50, respectively.[35,36] Given the significant risk of CRC following teenage years, prophylactic surgery is generally offered to FAP patients in the 2/3rd decade of life in predominantly English-speaking countries.[8] This allows for the development of physical and mental maturity prior to undergoing major abdominal surgery. In young women with FAP, additional consideration should be given to family planning. Surgical resection is associated with a significant impact on future ability to bear children; therefore, it is advised

that teenage females wishing to have children in the future can further delay surgery until after giving birth.[37] Asymptomatic patients with a family history of desmoid tumors may also elect to have their surgeries delayed, given desmoid tumors usually form after surgical resection. Earlier surgery should be considered in patients with known risk factors of CRC progression, including polyps >10 diameter, significant interval increase in colonic polyps, adenoma with high grade dysplasia, and inability to adequately survey the colon.[8]

Surgical Techniques

There are several surgical procedures described for prophylactic colorectal resection. Similar to timing, the selection surgical procedure is a balance between CRC reduction and impact on quality of life.

Prophylactic resection can include the rectum in total proctocolectomy (TPC). An end ileostomy or a continent ileostomy can be constructed, or a restorative proctocolectomy with a pouch may be created. Total colectomy (TC) with ileorectal anastomosis can be performed in a low-risk population for FAP (IRA). TPC with IPAA is a complex and challenging procedure. It has been associated with increased morbidity including urinary dysfunction,[38] sexual dysfunction,[38] decreased fecundity,[37] and reduced quality of life.[39] The creation of IPAA also leads to more frequent bowel movement and higher incontinence rates when compared to TC with IRA.[42] The increased morbidity in TPC with IPAA is balanced with a more complete reduction of CRC, with one meta-analysis showing 0% and 5.5% CRC in TPC with IPAA and TC with IRA, respectively. [43]

Good candidates for TC with IRA include young patients who desire to preserve fertility. However, they should be followed with close surveillance of the remaining rectum. Patients with low polyp burden are also good candidates for TC. An observational study demonstrated FAP patients with <1000 colonic and <20 rectal adenomas at presentation, none of which required reoperative proctectomy.[40]

Good candidates for TPC with IPAA include high-risk genotypes such as mutations in codon 1309 and 1328 of the APC gene, which is associated with increased rectal cancer risk.[41]

In FAP patients that present with CRC, the management differs from the average population. The operation of choice for FAP patients presenting with colon cancer is TC due to increased cancer risk in the remaining colon. TPC is not recommended in these cases, as it increases the risks of complications and may lead to a delay in adjuvant chemotherapy.

However, if the tumor is in the rectum, the operation of choice is a total proctocolectomy with IPAA. Neoadjuvant radiation therapy is advised as postoperative radiation therapy for patients that undergo IPAA and are associated with toxicity and loss of the ileal pouch. If IPAA is not performed, radiation can be given post operatively. In this case, an omental sling or pelvic mesh should be considered to exclude the small bowel from the pelvis.

Two anastomotic techniques have been described for IPAA: mucosectomy with hand-sewn anastomosis and double stapled anastomosis. Mucosectomy with hand-sewn anastomosis aims to remove all mucosa at risk of neoplasia. However, this is a technically challenging procedure.

One study found 21% of patients who underwent mucosectomy with hand-sewn anastomosis still had residual rectal mucosa.[44] There is also the risk of inverting the rectal mucosa during anastomosis, leaving it outside the lumen of the gut when constructing the anastomosis, thus making detection of recurrent cancer during surveillance impossible. Despite these drawbacks, most clinicians still advocate for mucosectomy with hand-sewn anastomosis. A recent study from Cleveland Clinic showed that patients who underwent mucosectomy and hand-sewn anastomosis had 1/2 as many recurrent neoplasia compared to stapled anastomosis. However, this must be balanced with the findings of worse and higher incontinence rates.[45]

Management of Duodenal Lesions

Another major source of morbidity in FAP is duodenal adenoma. Similar to colonic polyps, duodenal polyps have been observed to undergo predictable malignant transformation, although at a much slower rate. In one observational study, 11% and 1% of adenomas were found to have undergone histologic dysplasia and malignant transformation, respectively after 7 years.[46]

The Spigelman staging system is used to risk stratify patients based on size, number, histology, and metaplasia of polyps found in the duodenum. The overall lifetime risk of duodenal cancer in FAP is 5%; Spigelman grade IV lesions have much higher risk at 36%.[36,47]

Interventions for this high-risk population include endoscopic resection of polyps > 1cm or in those with

high-grade dysplasia.[48] Traditional endoscopic techniques such as snare, thermal, and argon have not been very effective, with >50% recurrence and 17% complication rate.[49] Novel endoscopic techniques including submucosal dissection and mucosal resection have yet to be evaluated in this setting and have the potential to make a large impact on treatment. These techniques provide a method to resect polyps that were not possible using traditional techniques, allowing the patient to avoid the morbidity associated with a major surgical resection involving the duodenum.

Current indications for surgical resection include Spigelman stage IV, duodenal adenocarcinoma, and persistent and recurrent high-grade dysplasia. Surgical procedures include Whipple or pancreas preserving duodenectomy.

Management of Desmoid Tumors

Desmoid tumors are a common extracolonic manifestation of FAP. These tumors have the potential to grow rapidly, thus causing mass effect with associated local complications. They are more common in women after the age of 30 years and develop a few years after surgery. The pathogenesis of desmoid tumors is not well understood. However, tissue trauma appears to have a correlation with the development of desmoid tumors. Observational studies have found that proctocolectomy performed laparoscopically has been associated with decreased incidence of desmoid compared to open surgery.[50]

Traditionally, these tumors have been treated with aggressive resection with 1cm margins. However, observational studies have demonstrated that up to 50-60% of desmoid tumors stabilize or regress after a period of rapid growth.[51-53] As these are benign tumors, the new guidelines currently recommend active surveillance or medical management as a first line treatment.[54] Currently, surgical indications are limited to mechanical complications such as mass effect causing obstruction, perforation, and mesenteric ischemia.[55] Even in these cases, it is recommended that the tumor be left in place when possible, and the obstruction addressed by passing the involved segment.[54]

Medical therapy with NSAIDS, hormone therapies such as Tamoxifen, tyrosine kinase inhibitors such as Gleevec, or chemotherapeutic agents have been shown to result in desmoid shrinkage or stabilization in some patients. Medical management of desmoids in women includes discontinuation of OCP and the delay of pregnancy for at least 1 year. Surveillance imaging is recommended at 3 or 6 months intervals.[54]

In the event of failure of medical therapy, local treatment options include radiation therapy, cryotherapy, and local resection. Radiation therapy has been shown to be effective in up to 80% of patients.[56] However, the complications of the radiated field such as fibrosis, radiation induced sarcoma, fractures, or radiation enteritis limits its use. Clinical trials are currently investigating the effectiveness of cryotherapy.[57]

Conclusion

Although we have made great advancement in the treatment of FAP, there is still much to be learned.

Conflict of Interest Disclosure Statement

Authors listed do not have any financial or personal conflict of interest to disclose.

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