Polyp-Cancer Sequence

Colorectal cancer is the third most common cancer affecting the human being. It can be called as polyp-cancer sequence. Colorectal cancer is believed to occur secondary to the transformation of the mucosal epithelial cells characterized by rapid turnover. The mucosal cells protrude into the lumen as polyps which might transform into a dysplastic and invasive lesion. Adenomatous polyps are the most common colon polyps associated with malignant transformation. Herein, we will discuss the different types of colon polyps and genetic basis for colorectal cancer transformation and overview of the management strategies.

Introduction

Colorectal cancer is represented by the development of polyps in lumen that arise from mucous layer of colon. It starts with formation of benign tumor such as polyps. Colorectal cancer can be sporadic, familial or inherited. The inherited disease is associated with a genetic mutation leading to either polyposis or non-polyposis colorectal cancer. Hereditary polyposis colorectal cancer includes familial adenomatous polyposis, juvenile polyposis syndrome, Peutz-Jeghers Syndrome, while hereditary nonpolyposis colorectal cancer includes Lynch Syndrome.

Adenomatous polyps are most commonly associated with cellular dysplasia into colorectal carcinoma which takes up to 7 – 10 years for cancer to develop. Mucosal
epithelial cells are renewed continuously from the crypt cells towards the lumen due to continuous shedding and turnover of the epithelium into the lumen. Dysplastic cells acquire invasive potential and transform into malignant carcinoma.

Histologic Types of Colonic Polyps

Colonic polyps are mucosal or sub-mucosal projections into the colonic lumen. They can manifest with bleeding, intestinal obstruction and sometimes they transform into malignant tumors. Colonic polyps can be classified into neoplastic, non-neoplastic, hamartomas, serrated and sub-mucosal. Non-neoplastic polyps include; hyperplastic, mucosal, sub-mucosal, inflammatory and hamartomas. Neoplastic polyps are adenomatous polyps.

Non neoplastic polyps:

1. Serrated polyps can be hyperplastic polyps which are the most common non-neoplastic colonic polyps, A heterogenous group of polyps are called sessile serrated adenoma. They develop at the right colon. They are more common in women than males they show characteristic flat and irregular growth that extent to the crypt base. Serrated polyposis syndrome is characterized by large > 10 mm polyps that are usually located proximal to the sigmoid colon.
2. Juvenile polyps or hamartomatous polyps consists mainly of connective tissue covered by epithelium. They appear as pedunculated, cherry red smooth polyps. 75% of them develop in children below 10 years, so they are termed as juvenile polyps. They are highly vascular, so they tend to cause bleeding. Intussusception and obstruction may be another happenings with the polyp.

Juvenile polyps and juvenile polyposis coli are usually hamartomas that have the potential risk of colorectal and gastric cancer. Juvenile polyposis coli (JPC) is the presence of 10 or more juvenile polyps along the GI tract and is usually associated with the SMAD4 mutation. Mutation of SK11 is also associated with another hamartomatous polyp in Peutz-Jeghers syndrome. The risk of polyp transformation into colon cancer is high along with other malignancies all over the body, e.g., pancreas, stomach, and breast.

1. Inflammatory polyps are pseudo polyps most commonly occur in patients with inflammatory bowel disease and ulcerative colitis. The polyps are formed as a result of accumulation of inflammatory infiltrations with disturbed mucosa.
2. Submucosal colorectal polyps are not truly colorectal polyps, they are lesions inside the submucosal layer of colon of benign or malignant character.

Neoplastic polyps:

Adenomatous polyps are the most common neoplastic polyps in the colon. Most colon cancers arise from adenomatous polyps and within a 7 - 10 years period.

Morphologically, adenomas can be sessile, pedunculated or non-polypoid flat or depressed lesions. Pathologically, they are divided into villous, tubular and tubulovillous adenomas.

Tubular adenomas are the most common with branching epithelium, while villous are less common with straight adenomatous glands. Advanced adenomas are large adenomas > 10 mm with high-grade dysplasia. Synchronous adenomas are diagnosed at the same time as the colorectal neoplastic lesion. Metachronous adenoma is the one diagnosed after 6 months from a previous one.
Risk Factors

Risk factors for adenoma transformation are villous histology, high-grade dysplasia, and large adenomas. Adenomas larger than 10 mm in size are more susceptible to develop carcinoma. High-grade dysplasia is more associated with invasive carcinoma and metachronous carcinomas, especially with large polyps. Villous histology is also associated with more transformation into colorectal cancer and metachronous carcinoma.

**Transformation of epithelium into adenoma then carcinoma can be explained by several pieces of evidence including:**

- Presence of both adenoma and carcinoma at the same time.
- Metachronous adenoma occurs after resection of carcinoma in about 30% of cases.
- Synchronous adenoma occurs in about 30% of patients with carcinoma.
- Large adenomas have a high risk of dysplasia.

Several theories have been introduced to explain the molecular basis for a polyp-cancer sequence including hypermethylation, activation of oncogenes and deactivation of tumor suppressor genes. The first step in epithelial transformation is **hyperproliferation of the epithelium to form aberrant crypt foci than low-grade dysplasia**, followed by high-grade dysplasia and eventually carcinoma.

The chromosomal instability is a gain of function mutation due to either over-activation of oncogenes or de-activation of tumor suppressor genes leading to uncontrolled cellular overgrowth. Chromosomal instability can lead to the alteration in chromosomal number, molecular changes in **chromosome 5q, 18q and 17p and APC & K-RAS mutations**.

![Diagram of Tumor Initiation](image)
Microsatellite instability or the mutator phenotype/mismatch repair pathway: mutations of DNA mismatch repair enzymes leads to the transformation of polyps into carcinoma, especially with Lynch syndrome and sporadic cases. The mismatch repair mutation leads to an accumulation of microsatellites within the DNA. Hereditary non-polyposis colorectal cancer is a result of a germline mutation of mismatch repair genes, while methylation of hMLH1 mismatch repair gene leads to sporadic disease.

Hypermethylation phenotype pathway: Hypermethylation of certain genes leads to silencing of their expression.

Oncogenes are normal cellular genes that promote cellular growth and multiplication. Activating mutation of one of the cellular oncogenes leads to gain of function mutation and uncontrolled cellular growth and multiplication. RAS, SRC, MYC, and HER2 are all examples of cellular oncogenes.

RAS oncogene signals via G protein coupling to transmit growth factor signals to the nucleus. RAS mutation prevents lysis of activated GTP with continuous signaling and proliferation. RAS mutation is associated with resistance to treatment against growth factors receptors, e.g., anti-epidermal growth factor receptor (EGFR) chemotherapy.

Tumor suppressor genes act to control cell division and proliferation. Loss of function mutations in both genes alleles leads to the loss of inhibitory control over cell division and proliferation. Retinoblastoma (RB) tumor suppressor gene is an example of tumor suppressor genes with either 2 somatic mutations in both alleles, or one somatic mutation in a single cell with an inherited mutation of the other allele. Examples of tumor suppressor gene mutation include: APC gene, P53, DCC, SMAD2, and SMAD4. P53 chromosome 17p mutation is the most common gene mutation in colorectal cancer. P53 gene is responsible for the cellular arrest of the division during times of stress via activation of several genes and proteins which promote cell cycle arrest and apoptosis.

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APC mutation is present in most cases of sporadic colorectal cancer and cases of familial adenomatous polyposis. APC gene acts through the Wnt pathway by phosphorylation and degradation of beta-catenin inside the nucleus. Mutations of the APC gene leads to
the loss of the regulatory effect and accumulation of the beta-catenin which, in turn, activates transcription factor Tcf-4. Activation of this pathway prevents the arrest of division, differentiation, and apoptosis. Following APC mutation is the Gastrin/cholecystokinin receptors activation which leads to inhibition of apoptosis and promotes cellular proliferation. SMAD4 mutation is associated with juvenile polyposis and sporadic cases of colorectal cancer. The gene acts through TGF beta pathway.

Germline mutation in the base excision repair gene mutY homolog MUTYH is also associated with FAP, known as MUTYH associated polyposis.

Cyclooxygenase inhibitors including aspirin and sulindac are linked to protective effect from the progression of adenomatous polyps to colorectal cancer. Sulindac in part is helpful in patients with familial adenomatous polyposis with evidence of regression of polyps’ growth.

Management of Colonic Polypi

Colonoscopy remains the screening modality of choice for the detection of colonic polyp. Its sensitivity increases with size > 5 mm and with left side colon polyps more than the right side. It also has a therapeutic advantage in case of polyp removal and biopsy rather than CT colonography and capsule colonoscopy.

Excision of the adenomas is the main cure in management except if they present in large numbers. Various biopsies from multiple lesions should be performed to exclude any metaplasia. Large adenomas > 2 cm are excited with follow-up colonoscopy after 3 months to ensure the absence of residual lesion or metachronous adenomas. Follow-up colonoscopy after resection should vary according to each adenoma. Follow-up colonoscopy should be performed after 10 years in case of no adenoma in the first colonoscopy.

If one or two small tubular adenomas were found < 10 mm in size, colonoscopy should be repeated in 5 years. Patients with more than 3 adenoma or advanced adenomas which are villous, large in size with high-grade metaplasia should have a repeat colonoscopy in 3 years. Small serrated polyps with no dysplasia should undergo colonoscopy in 5 years; unless they are larger than 10 mm and show signs of dysplasia, they should undergo colonoscopy in 3 years.
Prevention of Colonic Polypi and Colorectal Cancer

A high fiber diet rich in fresh fruits and vegetables with less alcohol and smoking has a major protective role against colorectal cancer. Aspirin also has a proven protective role against metachronous adenomas and colon cancer. COX2 agents, e.g., celecoxib have been tried with success in prevention of colorectal cancer, but with an increased risk of cerebrovascular accidents and heart attacks limiting their use in high dosage.

References

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