Lecture 5[2hrs]

Lymphoma

Non-Hodgkin's lymphoma may involve the gastrointestinal tract as part of the more generalized disease or may rarely arise in the gut. These are B-Cell lymphoma .lymphoma may complicate coeliac disease these are usually T cells lymphoma. Lesions may be annular, ulcerating, multiple, or occasionally diffuse.

Clinical Presentation

*Obstruction most commonly
*Hemorrhage
*Perforation.
*Weight loss.
*Failure to respond to gluten withdrawal in coeliac disease may indicate the development of T cell lymphoma.
*Abdominal mass may be palpable
*Malabsorption when there is diffuse bowel involvement.
*Hepato-Splenomegaly is rare.

Diagnosis

-Abdominal CT scan.
-Small bowel radiology.
-Small bowel biopsy.
-Staging is performed by thoracoabdominal CT scan, bone marrow, and section biopsy at Laparotomy.

Treatment

*Surgical resection where possible is the treatment of choice
*Radiotherapy and combination chemotherapy reserved for those with advanced disease.

Immunoproliferative Small intestinal Disease (IPSID)

[**Alpha heavy chain disease**]

This rare condition occurs mainly in the Mediterranean, the Middle East, and North America. There are proliferation IgA-producing small bowel cells (in response to chronic bacterial antigen stimulation). these tumors may be benign or malignant. The small intestinal mucosa is diffusely infiltrated by a dense lympho-plasmacytic cell with mesenteric lymph nodes enlargement.

Presentation

Most patients are adults presented with
Diarrhea, Malabsorption, clubbing, weight loss, and fever.

differential diagnosis

Crohn's and Whipple's disease.

Investigation

Presence of alpha heavy chains by Serum electrophoresis.
Hypogammaglobulinemia.
Staging by Laparotomy is recommended.

Treatment

Prolonged remissions can be obtained with long-term antibiotic therapy [tetracycline 500mg four times daily for > 6 months].
Chemotherapy is required for those who fail to respond or who have aggressive disease.

Intestinal Ischemia

The blood supply of the foregut by the coeliac artery and midgut by superior mesenteric artery and hind-gut by the inferior mesenteric artery. The 'watershed' area [splenic flexure of the

colon] between the supply of the superior and inferior mesenteric artery is the most vulnerable area for ischemia.
Intestinal ischemia may be acute or chronic, occlusive or non-occlusive

Causes of acute small bowel ischemia include.

*****Systemic emboli causes are [atrial thrombus, bacterial endocarditis].
*Non-occlusive causes are [cardiac failure, septicemia, trauma, anaphylaxis],
*Thrombosis causes are [polycythemia,sickle cell, oral contraceptive, antithrombin III deficiency, protein C deficiency, antiphospholipid antibodies].
*Vasculitis causes are [rheumatoid arthritis, polyarteritis nodosum, systemic lupus, Behcet's disease].
*Other causes include aortic dissection, infiltration by the tumor, intestinal volvulus**.**

Acute Small Bowel Ischemia.

The superior mesenteric artery supplies the intestine to the mid-transverse colon. Decrease of blood supply leads to a spectrum of pathological changes ranges from a transient alteration of bowel function to trans mural hemorrhagic necrosis and gangrene.

Clinical Features and investigations include

*Tachycardia,fever ,hypotension
* Severe Abdominal pain with minimal physical signs in the elderly patient with [generalized atherosclerosis, atrial fibrillation, vasculitis].
*Abdominal distension and reduced bowel sounds are early singing.
*Rectal bleeding, perforation, and Peritonitis are late signs.
*Epigastric bruits are diagnostic

Investigations

*Leukocytosis, metabolic acidosis, hyperphosphatemia, and hyperamylasaemia.
*Plain abdominal radiographs show ‘thumb-printing’ due to mucosal edema.
*CT abdomen may show thickening, dilatation abnormal bowel wall enhancement
*Mesenteric angiography reveals an occluded or narrowed major artery with a spasm of arterial arcades.

Treatment

*Resuscitation.
*intravenous antibiotic therapy, followed by Laparotomy at which embolectomy, thrombectomy, and resection of non-viable bowel.
A 'second look’ Laparotomy 24-48 hours later to resect any further necrotic intestine. The results of therapy are dependent upon early intervention. Patients treated at a late stage have a 75% mortality rate.

Non-occlusive vascular disease

Colonic ischemia

The condition can involve any portion of the large intestine but usually affects the splenic flexure and descending [watershed’ areas] ‘A spectrum of injury ranging from transient colitis to colonic stricture, gangrene, and fulminant colitis.
Causes include - Arterial thromboembolism, colonic ischemia can also occur following [severe hypotension, colonic volvulus, Strangulated hernia, systemic vasculitis, and hypercoagulable states].

Clinical features

*Sudden onset of cramping left-sided lower abdominal pain and rectal bleeding. In the majority of cases, symptoms resolve spontaneously over 24-48 hours and healing occurs within 2 weeks. Some are left with a residual fibrous stricture or a segment of colitis.
A minority develops gangrene and peritonitis.

Diagnosis

*Plain abdominal X-ray is important to rule out other diagnoses but may show abnormal segment usually at the splenic flexure, with mucosal edema [thumb printing].
*Colonoscopy .may shows hemorrhage.
*CT scan.

Management

*Intravenous fluids to maintain intravascular volume.

*Blood transfusion. *Surgical resection for complications.
*Endoscopical dilatation for stricture.

Chronic Intestinal ischemia[abdominal angina].

This results from atherosclerotic stenosis of mesenteric arteries involving at least 2 or all major visceral arteries [celiac axis, superior mesenteric artery, inferior mesenteric artery]. the postprandial blood flow is not sufficient to meet the increased energy demands of the intestine during digestion.

Presentation

*The patient develops mid- or upper abdominal pain approximately 30 minutes after eating lasting 1-4 h this is called mesenteric angina. *Anorexia and weight loss due to meal-related pain.

Physical examination

* Patients appear cachectic in advanced disease.
*Evidence of generalized arterial disease *An abdominal bruit is sometimes audible but not diagnostic.

Investigation

*Duplex ultrasound of the CA, SMA.
*Mesenteric angiography confirms at least two affected mesenteric arteries.
CT scan. Magnetic resonance angiography.

Treatment

*****Angioplasty or Vascular reconstructive surgery for patients whose angiogram shows occlusive involvement at least 2 of the 3 major arteries.
*Small frequent meals**.**

Focal intestinal ischemia

Causes include

Trauma, radiation, vasculitis, strangulated hernia, or drugs [enteric –coated potassium, slow-release anti-inflammatory drugs].

Presentations include

features of Intestinal Obstruction, bleeding, or perforation**.**

Diagnosis

*Small bowel enema or Enteroscopy.

Management

*Surgery

Disorders of the colon and rectum

Polyps

Polyps are mucosal projections into the lumen of the gastrointestinal tract. polyps may be single or multiple and vary in size from a few millimeters to several centimeters. macroscopically cannot differentiate between benign and malignant polyps.so polypectomy and histology are always indicated. Polyps maybe

*Neoplastic [adenoma] or *Non-neoplastic [Metaplastic, inflammatory, Hamartomatous]

According to the shape, polyps maybe

*Sessile-raised protuberance with a broad base and less than 5 mm in diameter.
*Pedunculated- attached to the bowel wall by a stalk that is narrower than the body of the polyp.
*Flat-completely flat or slightly raised or depressed.

According to the size, polyps maybe

Diminutive <5 mm, large >1 cm

According to histopathology polyps can be

1-Metaplastic [hyperplastic].

The commonest type of polyps usually multiple, sessile

2-Inflammatory

Occur after severe colitis of any cause may be sessile or finger-like appearance.

3-Hamartomatous is the proliferation of normal tissues arranged in an abnormal and disorganized fashion.

4-Adenomas

They are more common in the rectum and distal colon may be pedunculated or sessile.50% of people over 60 years of age have adenomas and in half of these the polyps are multiple. The majority of cancers arise from adenomas ('adenoma-carcinoma sequence") over 5-10 years. Adenomatous polyps can be classified according to the glandular architecture to [tubular, villous, Tubulo-villous, serrated].

Clinical Presentation

Maybe asymptomatic and discovered incidentally some patients presented with bleeding and anemia, abdominal pain Or Diarrhea, and hypokalemia because Villous adenomas sometimes secrete large amounts of mucus.

Risk factors for malignant change in colonic polyps include

1-Large size (>2 cm)
2-Multiple polyps
Villous architecture
4-Dysplasia

Management

*Discovery of a polyp at Sigmoidoscopy is an indication for colonoscopy because proximal polyps are present in 40-50% of such patients.
*Polypectomy should be done.
*Very large or sessile polyps which cannot be removed endoscopically should be removed by surgery.
*All polyps must be examined histologically because 10 - 20% of polyps show histological evidence of malignancy.
*Polyps recur in 30-40 % of patients so surveillance is appropriate by colonoscopy at 3-5 year intervals.

Classification of GI Polyposis Syndromes

Inherited Polyposis Syndromes

1-Adenomatous Polyposis Syndromes

A*Familial adenomatous polyposis (FAP). autosomal dominant disorder. Caused by a mutation in the APC [tumor suppressor] gene on the long arm of chromosome 5. The incidence is about (1 in 8000-14000) in live births.
*1/3 of cases have no family history.
*Characterized by multiple hundred to thousands of adenomatous colonic polyps.
*Polyps will develop in 50% of patients by age 16 and 90% of those will develop colorectal cancer by the age of 45 years.
Adenomatous polyps are also frequently found in the stomach and duodenum around the ampulla of Vater and may undergo malignant transformation to adenocarcinoma. Papillary carcinoma is the most common thyroid carcinoma associated with familial adenomatous polyposis.

Extraintestinal features of FAP include

*Subcutaneous epidermoid cysts(extremities, face, scalp)
*Lipomas
*Desmoids tumors[diffuse mesenteric fibromatosis complicating adenomatosis polyposis syndromes. may cause obstruction of bowel, vessels, or ureters.
*Dental abnormalities (15-20%).
*Congenital hypertrophy of the retinal pigment epithelium (CHRPE).

B*Gardner's syndrome. Characterized by the presence of colonic polyposis and Benign osteomas, especially the skull and angle of the mandible.

C*Turcots syndrome. Characterized by the presence of colonic polyposis and medulloblastoma.

D*Attenuated FAP', in which fewer polyps are found and cancer development is delayed.

Diagnosis and management
Early diagnosis usually is done by the screening of family members.
*Flexible Sigmoidoscopy starting at 10-12 years of age and repeated every 1-2 years until the age of 40.
*Genetic testing.
Once the diagnosis is made
Affected individuals After school or college education has been completed should undergo proctocolectomy with permanent ileostomy or ileo-anal pouch anastomosis.
Periodic upper gastrointestinal endoscopy is recommended to detect duodenal adenomas.
2-Hamartomatous Polyposis Syndromes
1-Peutz-jeghers syndrome.Autosomal dominant
Characterized by mucocutaneous melanin pigmentation of the lips, mouth, digits, and Multiple Hamartomatous polyps in the small intestine, colon, and stomach.
Presentation
May be
*Asymptomatic or
* GIT bleeding.
* intestinal obstruction or Intussusceptions.
There is an increased risk of cancer of small bowel adenocarcinoma, pancreas, ovary, breast, and endometrium.
Treatment
Screening by colonoscopy and small bowel imaging by age 8 years and repeated every 2 years.
Endoscopic Polypectomy or surgery
2-Juvenile polyposis.
*Tens to hundreds of mucus-filled Hamartomatous polyps are found in the colon, stomach, and rectum. *One –third of cases are inherited in an autosomal dominant manner and up to 20% of patients develop colorectal cancer before the age of 40.
Screening
Colonoscopy and OGD usually begin after 15 years of age. If symptoms have not occurred already.
Asymptomatic relatives also should be screened
Treatment is with endoscopic polypectomy to prevent bleeding and obstruction.
3-Cronkite- Canada syndrome
Characterized by the presence of colonic, Esophageal, small intestine and gastric polyps with extraintestinal features like
*hair loss, nail dystrophy, and Malabsorption.
4-Cowden's disease
Autosomal dominant inheritance. Characterized by the presence of colonic, Esophageal, small intestine, and gastric polyps with extraintestinal features like congenital anomalies, oral, cutaneous hamartomatous, thyroid and breast tumors.

Colorectal Cancer

Colorectal cancer is the second most common internal malignancy and the second leading cause of cancer deaths. increasingly after the age of 50. And 90% is Adenocarcinoma.
Etiology
Important factors in the development of colorectal cancer include
Environmental factors include.
Dietary with Increased risk of colorectal cancer include
Red meat and saturated animal fat. Probably because [carcinogenic amines formed during cooking, High fecal bile acid, and fatty acid levels May affect colonic prostaglandin turnover].
Dietary with decreased risk of colorectal cancer include
*Dietary fiber.[probably because-Shortened transit time. - binding of bile acids and- Effect on bacterial flora].
*Fruit and vegetables .because contain anticarcinogens.

*Calcium. Binds and precipitates fecal bile acids.
*Folic acid. Reverses DNA hypomethylation**.**

Non-dietary risk factors in colorectal cancer

*Colorectal adenomas, Long-standing extensive ulcerative colitis, Acromegaly and Pelvic radiotherapy*Obesity and sedentary lifestyle-may be related to dietary factors
*Alcohol and tobacco (weak association)

Genetic factors

important hereditary forms of colon cancer include
*Hereditary non-polyposis colon cancer.
*Family history of colorectal cancer.
*Familial adenomatous polyposis (FAP).

Hereditary Non-Polyposis Colon Cancer [HNPCC] also known as[Lynch syndrome] is an autosomal dominant disorder. These patients have mutations in genes (MSH2, MLH1, PMS1, and PMS2) involved in the repair of errors that normally occur during DNA replication.

Criteria for the diagnosis of hereditary non-polyposis colon cancer include

1-Three or more relatives with colon cancer (at least one first-degree)
2-Colorectal cancer in two or more generations.
3-At least one member affected under 50 years of age
4-Familial adenomatous polyposis (FAP) excluded.

The lifetime risk of colorectal cancer in affected individuals is 80%. The mean age of cancer development is 45 years, and two-thirds of tumors occur in the right colon. There is also an increased incidence of extracolonic cancers like [endometrium, urinary tract, stomach, and pancreas].

Those who fulfill the criteria for diagnosis should be referred for genetic testing and colonoscopy. This should begin around 25 years of age or 5-10 years earlier than the youngest case of cancer in the family. Colonoscopy needs to be repeated every 1-2 years.

Pathology of colorectal carcinoma.

Most tumors arise from malignant transformation of a benign adenomatous polyp. Adenocarcinoma almost always arises from preexisting adenomatous polyps except in UC or Crohn's colitis. Over 50% of colorectal cancer occurs in the rectosigmoid and synchronous tumors are present in 2-5% of patients. Macroscopically colorectal cancer may be[polypoidal, 'fungating', annular or constricting]. Dissemination occurs through the bowel wall. , Lymphatic invasion, and both portal and systemic circulations to reach the liver and the lungs.

Clinical presentations

Right colonic tumor

*Patient presented with symptoms of iron deficiency anemia*Anorexia, weight loss
*Palpable mass
*Obstruction uncommon because of the larger diameter of the cecum and ascending colon.

Left colonic tumor

*Colicky abdominal pain occurs in 2/3 of the patient due to partial obstruction, spasm or invasion
*****Fresh bleeding per rectum, mucus discharge, or feeling of incomplete evacuation.
*Altered bowel habit more common in distal tumors
*Emergency presentation including [obstruction, perforation leading to peritonitis, localized abscess or fistula formation].

Examination

1-There may be a palpable mass,
2-Signs of anemia or weight loss
3-Hepatomegaly due to metastases.
4-Low rectal tumors may be palpable on digital examination.

Investigations

***Blood test**

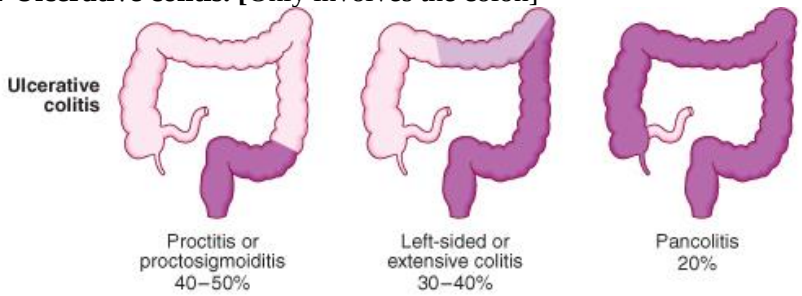
-Anemia may be the only feature of caecal tumors.
-Raised ALP may e due to hepatic metastases.
* Elevated Serum carcinoembryonic antigen (CEA) concentration.

***Colonoscopy** is the investigation of choice because it is more sensitive and specific than barium enema. Because lesions can be biopsied and polyps removed
***Barium enema** .features of cancer include strictures with shouldering or irregular filling defect in the bowel
***CT Colonography** [virtual colonoscopy] noninvasive technique for diagnosing tumors and large polyps. **Investigations for staging include**
*** the Abdominal US.**
***EUS**.
***Pelvic MRI** for rectal tumor staging
***Computed tomography** is valuable for detecting hepatic metastases.
***CXR**
Dukes staging of colorectal cancer.
Stage A-Tumor confined within the bowel wall.
Stage B-Tumor Extension through the bowel wall. But there is no lymph node involvement.
Stage C-Extension through bowel wall With lymph node involvement.
Stage D-Tumor has spread outside the colon such as the liver or the lung**.**
5 year survival depend on the stage **.** Stage A >90%, Stage B 65 %, Stage C 30-35 %, Stage D <5 %.
Management
Surgery
The tumor is removed with adequate resection margins and pericolic lymph nodes. Continuity is restored by direct anastomosis wherever possible.
Carcinomas within 5 cm of the anal verge may require abdomeno-perineal resection and formation of a colostomy.
Solitary hepatic metastases are sometimes resected at a later stage.
After surgery patients should undergo colonoscopy after 6-12 months and periodically to search for local recurrence or development of new lesions.
Adjuvant therapy
*Adjuvant chemotherapy with 5-fluorouracil and folinic acid (to reduce toxicity) or radiotherapy in patients with advanced but locally confined colorectal cancer.
*In patients with dukes B or C rectal tumors, post-operative radiotherapy in combination with 5-fluorouracil reduces local recurrence and mortality.
Screening For Colorectal Cancer
Aims to detect cancer at the treatable stage
Screening methods after the age of 50 years Include
*Annual FOB, Fecal DNA, fecal immunochemical test (FIT).
*Flexible Sigmoidoscopy. It is recommended every 3-5 years.
*Colonoscopy remains the gold standard method ever 10 y.
*Computed tomographic (CT) colonography every 5 years
*Screening by molecular genetic analysis.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an idiopathic and chronic intestinal inflammation, which characterized by relapsing and remitting courses usually extending over the years. Ulcerative colitis (UC) and Crohn's disease (CD) are the two major types of IBD. The diseases have many similarities and it is sometimes impossible to differentiate between them.
Ulcerative colitis is an idiopathic chronic inflammatory disorder of the colonic mucosa with the potential for extra-intestinal inflammation. The disease extends proximally from the anal verge in an uninterrupted pattern to involve all or part of the colon.
Crohn's disease is an idiopathic chronic inflammatory disorder of the
the full thickness of the intestine, most commonly in the ileum and the colon, with the potential to involve the gastrointestinal tract at any level from the mouth to the anus and perianal region. There is also the potential for extra-intestinal inflammation. Typically, there is a patchy disease in the gastrointestinal tract, with intervening areas of normal mucosa

Epidemiology
Prevalence of UC about 10 per 100.000 and Crohn's disease about The incidence rates of UC and CD about 5- 7 per 100.000.
Age-The peak age of onset of UC and CD is between 15 and 30 years. A second peak occurs between the ages of 60 and 80.
Sex-The male to female ratio for UC is 1:1 and for CD is 1.1 to 1.8:1.
Race-IBD more common among Jews.
Pathogenesis.
Both genetic and environmental factors are implicated
Genetic factors include.
*More common in Jews
*10% have a first-degree relative or at least one close relative with IBD.
*High concordance between identical twins
*Associated with autoimmune thyroiditis and SLE.
*HLA-DR103 associated with severe UC.
*UC and CD patient with HLA-B27 commonly develop ankylosing spondylitis.
Environmental factors include.
*UC-more common in non-smoker or ex-smokers
*CD-most patients are smokers.
*Associated with low-residue, high refined sugar diet.
*Appendectomy protects against UC.
Pathophysiology of IBD is related to the inappropriate host response to commensal bacteria in genetically susceptible individuals Dietary or bacterial antigen either are taken up by M cells or pass between epithelial cells or enter through ulcerated mucosa Macrophage within the payer's patches process the antigen and then secrete cytokines like TNF, IL1, IL8.
T-cell activation and differentiation results in a Th_1 T cell-mediated cytokine response
*TNF- Regulate adhesion molecules these are localized on the vascular endothelium and causing circulating neutrophils to adhere to the endothelium and then pass through into the bowel wall.TNF also cause s anorexia, malaise, fever, and metabolic bone disease.
*IL1 activate CD4 Lymphocytes which secrete IL3, IL4 these interleukins activate mast and plasma cells --activated mast cells secrete PAF and leukotrienes which produce inflammations.
-activated plasma cells secrete IgG, Ig E.
In Crohn's disease IL1 lead to activation of fibroblast. activated fibroblast secretes TGFB, IGFI these stimulate collagen metabolism, fibrosis, stricture formation.
*IL8-secreted by activated macrophage activate and degranulates neutrophils. The end result of these processes is the production of toxic proteases, and reactive oxygen species these are toxic and cause ulceration.
The regulatory IL10 and transforming growth factor-B[TGF] produced by macrophages and mature T lymphocytes down-regulate these inflammatory processes in a normal individual exposed to an inflammatory insult. In genetically predisposed person dysregulation of these steps leads to chronic IBD.
PATHOLOGY
1-Ulcerative colitis. [Only involves the colon]



Ulcerative colitis is characterized by diffuse mucosal inflammation limited to the colon invariably involve the rectum. Disease extent can be broadly divided into a distal and more extensive disease. *Proctitis- refers to colitis confined to the rectum

*Procto- sigmoiditis -- refers to colitis confined to rectum and sigmoid colon. *left-sided colitis- More extensive disease' (up to the splenic flexure),
*Extensive colitis'' (up to the hepatic flexure)
*Pancolitis (affecting the whole colon).
When the whole colon is involved the inflammation extends 1 to 2 cm into the terminal ileum This is called backwash ileitis and has little clinical significance
Histological. UC is limited to the mucosa and superficial submucosa with deeper layers unaffected except in fulminant disease. Both acute and chronic inflammatory cells infiltrate the lamina propria, the crypts [cryptitis], and crypt abscesses are typical. Goblet cells lose their mucus and in long-standing glands become distorted. Dysplasia may herald the development of colonic cancer.

Clinical features of Ulcerative colitis include

The first attack is usually the most severe and thereafter the disease is followed by relapses and remissions
The severity of symptoms correlates with the size and activity of the disease. Emotional stress, intercurrent infection, gastroenteritis, AB, and NSAID therapy may provoke a relapse.
Patients With Proctitis usually complain of rectal bleeding, mucous discharge, and tenesmus patient may present with constipation.
When the disease extends beyond the rectum, the presentation includes
*bloody diarrhea, anorexia, nausea, vomiting, fever, and weight loss.
*lower abdominal pain before a bowel movement and temporarily relieved by defecations.
Disease severity assessment in ulcerative colitis include

	Mild disease	Severe disease
Bowel frequency/day	less than 4	more than 6
Blood in stool	+-	+++
Pulse	<90 b.p.m	>90 b.p.m
Temperature	normal	37.8[2days out of 4].
Sigmoidoscopy	diffuse erythema	intense inflammation
	Loss of vascular pattern	purulent exudates
	Contact bleeding	discrete ulcer
Abdominal radiograph	normal	dilated bowel, mucosal island
Hb	normal	< 100
ESR	< 20mm/hr	> 30mm/hr
Albumin gr/L	> 35	< 30