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Editorial

Festered and Amassed - Crohn's Disease

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Crohn's disease is an idiopathic, chronic, relapsing inflammatory disorder of gastrointestinal tract which incriminates upper and lower bowel segments in discontinuity and engenders transmural inflammation. Additionally designated as terminal ileitis, granulomatous enterocolitis or regional enteritis, segmental, patchy bowel inflammation is commonly confined to ileum, colon or upper gastrointestinal tract. Characteristically, chronic or active colitis is associated with non caseating granulomas, transmural lymphoid aggregates and fissuring ulcers.

Crohn's disease can be appropriately discerned with cogent clinical features combined with haematological or faecal parameters, endoscopic manifestations of upper and lower gastrointestinal tract, radiological imaging and histological assessment. Precise detection aids in disease segregation and categorization of disease severity.

Adult onset Crohn's disease exhibits a mild female predominance. Disease onset is common between 20 years to 40 years or within fifth decade to sixth decade. Disease incidence and prevalence is elevated in individuals of enhanced socio-economic status [1,2].

Crohn's disease commonly incriminates small bowel or ileo-colonic segment of gastrointestinal tract. Alternatively, small bowel or colon may be singularly implicated in the absence of rectal involvement. Crohn's disease of colon commonly incriminates ileum and vice versa. Implication of right colon is frequent as compared to left colon whereas pancolitis is relatively infrequent [1,2].

Perianal complications as fissures and fistulas may occur. Complications of upper gastrointestinal tract may appear in children and adolescents. Few instances of isolated perianal, extra-intestinal or upper gastrointestinal tract complications can be encountered [1,2].

Of undetermined pathophysiology, Crohn's disease is posited to arise due to various factors as

- Immuno-biology comprised of impaired function of gastrointestinal barrier with dysregulation of innate and adaptive immune mechanisms and altered gut microbiota.

Impaired mucus biofilm barrier is associated with decimated expression of mucin secretion genes as MUC1, MUC19 and PTGER4 confined to terminal ileum [1,2].

Altered permeability of intestinal epithelium is accompanied by altered expression of tight junction proteins as claudin.

Dysfunction of Paneth cells is observed. Autophagy of invasive microbial organisms appears defective.

Proportion of effector T cells and natural, regulatory T cells is deranged.

Recruitment and retention of leukocytes remains unpredictable [1,2].

- Dysbiosis is comprised of perpetual alterations within intestinal microbiota with consequent clustering and decimated diversity of Firmicutes and Bacteroidetes phyla. Declining quantification of Faecalibacterium prausnnitzii enhances reoccurrence of postoperative ileal Crohn's disease.

- Genetic factors are associated with enhanced possible disease emergence in individuals with distinct family history. Disease concordance within monozygotic twins is augmented, in contrast to dizygotic twins. Genome association studies exhibits ~200 genetic loci concordant to Crohn's disease which can moderately amplify proportionate disease occurrence. Genetic variants as NOD2, ATG16L1 or IL23R may confer certain inheritable factors concurrent to disease emergence [1,2].
- Environmental factors as cigarette smoking, decimated dietary fibre, ingestion of nonsteroidal anti-inflammatory drugs, oral contraceptives, aspirin or antibiotic therapy within paediatric population augments possible occurrence of Crohn's disease. Breastfeeding emerges as a protective factor towards emergence of Crohn's disease [1,2].

Clinically, idiopathic Crohn's disease demonstrates symptoms such as abdominal pain, diarrhoea, fatigue or weight loss.

Incrimination of diverse sites within gastrointestinal tract manifests painful oral aphthous ulcers, odynophagia or dysphagia, postprandial nausea and vomiting or features of malabsorption as diarrhoea, steatorrhea and associated nutritional deficiencies [1,2].

Crohn's disease denominates distinctive phenotypic and clinical subtypes as

- Inflammatory phenotype is comprised of inflammation of gastrointestinal tract in the absence of fistula or bowel stenosis along with classic disease symptoms.
- Stricture phenotype delineates progressive intestinal inflammation which engenders fibrosis and stenosis. Clinical symptoms of bowel obstruction as nausea, vomiting or loss of intestinal motility may be observed.
- Fistula phenotype exhibits persistent transmural inflammation which configures a sinus tract with consequent fistulas emerging between gastrointestinal tract and adjacent organs as vagina or urinary bladder [1,2].

Extra-intestinal manifestations of Crohn's disease are denominated as ~musculoskeletal features as arthritis, arthropathy or osteoporosis.

- Ocular features as uveitis, iritis or episcleritis.
- Cutaneous features as erythema nodosum or pyoderma gangrenosum.
- Hepatobiliary features as primary sclerosing cholangitis or pyogenic liver abscess.
- Renal features as secondary amyloidosis with consequent renal parenchymal disease or renal calculi composed of calcium oxalate and uric acid.
- Pulmonary features as bronchiectasis, chronic bronchitis, interstitial lung disease, bronchiolitis obliterans with organizing pneumonia or sarcoidosis [1,2].

Upon gross examination, segmental involvement of gastrointestinal tract is observed. Transmural inflammation depicts aggregates of 'creeping' adipose tissue. Intestinal walls appear thickened and fibrotic with configuration of strictures [1,2].

Mucosal aphthous ulcers appear circumscribed by zones of hyperaemia which engenders a 'cobblestone' countenance to superimposed mucosa. Inflammatory pseudo-polyps appear adherent to mucosal surface. Fissures, sinuses, fistulous tracts and intestinal abscesses may emerge as eventual complications. Exceptionally, perforation of gastrointestinal tract may ensue [1,2].

Upon microscopy, chronic Crohn's disease demonstrates architectural distortion of crypts, inflammatory exudate expanding the lamina propria and aggregates of lymphoid and plasma cells confined to basal segment of crypts. Metaplasia or hyperplasia of Paneth cells may occur. Segments of small bowel and right colon exhibit pyloric gland metaplasia [1,2].

Typically, untreated Crohn's disease demonstrates features of active, chronic colitis [1,2].

Active Crohn's disease delineates acute bowel inflammation with neutrophilic infiltration and cryptitis, mucosal ulceration and configuration of crypt abscess. Intestinal inflammation and mucosal ulceration is patchy and segmental with articulation of 'skip' lesions [1,2].

'Aphthous' ulcers, deep seated fissures and ulcers may ensue. Well formed, sarcoid-like, epithelioid cell granulomas are characteristically discerned in ~50% of Crohn's disease. However, poorly configured granulomas consisting of giant cells may be discerned. Segregation from granulomas engendered due to crypt rupture may be necessitated.

Transmural inflammation is associated with lymphoid aggregates confined to sub-serosal adipose tissue. Eventually, sinus tracts or fistulas may be configured within gastrointestinal tract.

Lesions of extended duration depict metamorphosis and dysplasia of mucosal epithelium of gastrointestinal tract [1,2].

Mucosal lesions of Crohn's disease appear immune non reactive to CMV [1,2].

Disease activity is graded as

- **Inactive Disease:** Absence of neutrophilic infiltration
- **Mild Disease:** Inflammatory activity incriminating < 50% of mucosa
- **Moderate Disease:** Inflammatory activity incriminating > 50% of mucosa with frequent emergence of crypt abscess.
- **Severe Disease:** Occurrence of superficial mucosal ulceration or epithelial erosion [1,2].

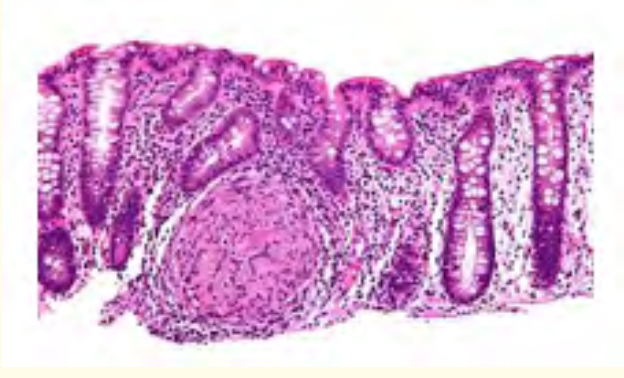

Figure 1: Crohn's disease depicting a non caseous epithelioid cell granuloma interspersed with focal mucosal ulceration and inflamed lamina propria [5].

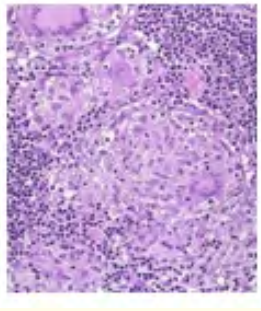

Figure 2: Crohn's disease delineating epithelioid granulomas intermixed with an abundant lymphocytic infiltrate confined to the lamina propria [6].

Crohn's disease requires segregation from conditions such as ulcerative colitis, indeterminate colitis, infectious colitis, infection with Yersinia, Salmonella, Campylobacter or Mycobacterium tuberculosis, segmental colitis associated with diverticulitis, amoebiasis, Behcet's disease, coeliac disease, intestinal carcinoid tumour, intestinal tuberculosis or mesenteric ischemia [3,4].

Surgical tissue samples may be inadequate in evaluating depth and distribution of inflammation. Appropriate disease discernment can be obtained with concurrence of clinical symptoms with assessment of surgical resection specimen. Clinical scoring systems as Crohn's disease activity index or Harvey-Bradshaw index can be adopted to appropriately categorize Crohn's disease into 'low risk' and 'high risk' subtypes [3,4].

Additionally, biochemical markers as C reactive protein, anti-Saccharomyces cerevisiae antibodies (ASCA), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) or faecal calprotectin can be beneficially evaluated [3,4].

Classically, ileo-colonoscopy is a recommended diagnostic manoeuver.

Features discernible upon endoscopy emerge as

- Mucosal ulceration with configuration of miniature aphthous ulcers < 5 millimetre magnitude along with transmural ulcers.
- Cobblestone appearance of mucosa denominating linear and serpiginous ulcers with intervening non-ulcerated mucosal epithelium.
- Skip lesions exhibiting discontinuous ulcerative lesions circumscribed by adjacent normal mucosal epithelium [3,4].

Infrequently discerned manifestations are denominated as

- Normal rectal mucosa
- Inflammation of terminal ileum with absence of colonic inflammation.

Imaging techniques are frequently employed to assess small bowel disease. Ultrasonography, computerized tomography (CT) and magnetic resonance imaging (MRI) appear advantageous in assessing extent of disease and emergence of complications [3,4].

Upon imaging, Crohn's disease of small bowel exhibits an asymmetrical, segmental, mural hyper-enhancement. Also, wall

thickening, intramural oedema, strictures and ulcers can be discerned. Pelvic MRI is beneficial in assessing perianal fistulous tracts [3,4].

Cogent medical therapy is an optimal, recommended strategy which may adequately ascertain clinical, endoscopic and histologic disease remission as enunciated with complete mucosal healing [3,4].

Contingent to stage, severity and disease localization, cogent therapeutic manoeuvers are denominated as

- Low risk instances which are subjected to 'step up' therapy with initial employment of minimally potent medication with mild adverse effects whereas potent medication is adopted in subjects unresponsive to initial therapeutic approach.
- High risk instances managed with 'top down' strategy comprised of therapeutic commencement of potent drugs as biologics and immuno-modulators within preliminary disease in order to circumvent disease complications [3,4].

Medical therapy is achieved with corticosteroids, thiopurines, methotrexate or anti-TNF agents [3,4].

Surgical intervention is necessitated in ~ 50% instances of Crohn's disease associated with disease complications [3,4].

Gastrointestinal tract strictures appear irreversible when treated with medical therapy. Also, gastrointestinal tract obstruction can be suitably managed with surgical manoeuvers [3,4].

Surgical intervention is mandated for fistulas occurring within gastrointestinal tract as entero-vesicular, entero-vaginal or entero-cutaneous fistula or sinus tract and configuration of abscess or perianal disease with articulation of perianal fistula or perianal abscess.

Crohn's disease depicts minimally enhanced disease associated mortality. Crohn's disease reoccurs in a majority (~95%) of incriminated subjects following 10 years of disease detection and generally manifests as ileo-colonic disease [3,4].

Postoperative disease reappearance is contingent to disease location as ~isolated ileal disease demonstrates reoccurrence proximal to anastomosis

- Ileo-colitis with disease re-emergence is frequently discerned proximal and distal to intestinal anastomosis [3,4].

Crohn's disease exhibits enhanced proportion of surgical intervention, re-emergence or associated complications, especially with initial disease representation in young subjects < 40 years, cigarette smoking, extensive disease of prolonged duration, perianal disease with strictures or incrimination of upper gastrointestinal tract which may be treated with corticosteroids during initial disease flare [3,4].

Deep seated ulcers may concur with absence of epithelial healing following clinical remission [3,4].

Surgical tissue specimens may depict epithelioid cell granulomas. Crohn's disease exemplifies elevated C reactive protein, ASCA and faecal calprotectin levels along with anaemia and decimated serum albumin [3,4].

Enhanced proportionate occurrence of small bowel carcinoma or colorectal carcinoma with malignancy associated mortality is observed. Besides, anal squamous cell carcinoma or lymphoproliferative disorders may ensue [3,4].

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5. Image 1 Courtesy: Libre Pathology.
6. Image 2 Courtesy: Radiopaedia.com.