pathoprofile.

crohn's disease

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal (GI) tract that falls under the umbrella of inflammatory bowel disease (IBD).[1] A 2023 impact report estimated that approximately 4.1 in 1000 Canadians live with CD.[2] CD is characterized by discontinuous and patchy 'skip lesions' and transmural inflammation. The former may impact any part of the GI tract from the mouth to the anus, while the latter extends across the entire thickness of the bowel wall.[3] Symptoms are variable and may include diarrhea, abdominal pain, and weight loss, among other potential complications.[3] Patients with CD experience a poorer quality of life due to unpredictable bouts of remission, relapse, and no known cure.[1]

RISK FACTORS & DIAGNOSIS

Although the exact pathogenesis of CD is unknown, studies have shown that dysregulated immune responses, genetic factors, gut microbiota, and other environmental factors can modulate disease risk.[3] Currently, there is ample evidence to postulate a link between the gut microbiome and IBD. Clinical and animal trials have suggested that gut bacteria trigger and perpetuate colitis and IBD.[4] In one study, researchers deduced that individuals with GI infections from *Salmonella* or *Campylobacter* have an increased risk of developing IBD within the first year of illness.[3] Early antibiotic exposure and gut microbiome disruption, most prominently from ages 0 to 5, also correlate with an increased risk of CD. Among other environmental factors, emerging evidence suggests that diet may be a potential risk factor for CD. For instance, Narula et al. discovered that a high intake of ultra-processed food was positively associated with a higher risk of IBD.[5] Although genetic risk factors are still being elucidated, over 200 genes are found to be associated with IBD development. For instance, homozygotic mutations at the NOD2 locus of chromosome 16 may result in fibrostenotic–or narrowing–disease of the GI tract and altered interactions between ileal microbiota and mucosal immunity; affected individuals are 20 to 40 times more likely to develop CD.[3,6,7]

CD diagnoses are made based on clinical evaluation, diagnostic imaging, and laboratory tests. Generally, CD is suspected when a patient presents with GI symptoms such as inflammation or obstruction, abdominal pain and bloating, persistent diarrhea, perianal fistulas or abscesses, and malnutrition and malabsorption of nutrients, particularly vitamin D or B12.[3,8] Using a combination of computed tomography and magnetic resonance scans as well as upper and lower endoscopy imaging, physicians can recognize the internal markers of CD: bowel wall thickening, narrowing of the intestines (stricturing), ulceration, and a "cobblestone" pattern of inflammation on the intestinal lumen.[8,9] While imaging is typically required to confirm CD, blood and stool laboratory testing can also be helpful in diagnosis, monitoring inflammation, and ruling out other digestive disorders (e.g., GI infection, Celiac disease, malignancy, irritable bowel syndrome, etc.).[8,9]

DISEASE PATHOPHYSIOLOGY & COMPLICATIONS

For research and treatment purposes, CD is categorized into three phenotypes: inflammatory, stricturing, or fistulizing CD.[3,8] Inflammatory CD may evolve into either of the two latter phenotypes of CD and is characterized by transmural inflammation of the GI tract. This begins with inflammation and small focal ulceration, which may develop into deep longitudinal or transverse GI ulcers.[8] These mucosal lesions produce edema, creating a characteristic "cobblestoned" appearance in the bowel of individuals with CD.[8]

In the stricturing phenotype of CD, excessive inflammation may result in hypertrophy of the muscular mucosa of the intestine, intestinal fibrosis, and stricture formation.[8] Strictures refer to areas of stenosis and luminal narrowing in the GI tract, which could cause a bowel obstruction. These fibrostenotic changes are irreversible, aside from surgical correction.[3]

Prolonged transmural inflammation may also produce a sinus/fistulous tract, which is characteristic of the fistulizing phenotype of CD. Fistulas are abnormal tunnels that can form between the bowel and adjacent organs.[3] CD fistulas result from an epithelial defect related to chronic inflammation—epithelial-to-mesenchymal transition (EMT). In EMT, intestinal epithelial cells (IECs) lose their epithelial phenotype to undergo mesenchymal differentiation. The epithelial phenotype is characterized by strong intercellular junctions and cell polarity, whereas the mesenchymal phenotype results in a fibroblast-like morphology, which involves reduced intracellular contact.[10] Due to this, IECs gradually migrate and tunnel into deeper layers of the gut wall, causing tissue damage and fistulous tract formation.[10] If this tract does not reach an adjacent organ, an abscess—a painful collection of pus, typically caused by infection—is likely to develop. Fistulas and abscesses can induce systemic pain, fever, and other infections related to their location on the GI tract.[3,8]

While CD is not fatal, it may increase the risk of life-threatening complications, such as sepsis, colorectal cancer, malnutrition, and peritonitis.[11] Fistulas may also tunnel to the skin's outer surface, forming an enterocutaneous fistula.[11] Moreover, chronic inflammation, fistulas, abscesses, and strictures can weaken points of the intestinal wall, tearing or perforating the colon to allow for subsequent leakage of GI substances into the abdomen.[11]

TREATMENTS

Currently, there are no available curative treatments for CD or preventative therapies to correct a potential underlying genetic factor for disease onset.[12] The course of management is often individualized depending on a range of factors, including age, comorbidities, symptoms, severity of inflammation, and location of disease.[13] CD management involves two primary goals: treating inflammation and complications, and minimizing symptoms.[13] Treatments induce mucosal healing, resulting in sustained clinical and endoscopic remission.[12] Patients with mucosal healing consistently demonstrate improved outcomes such as lower relapse rates and improved quality of life.[14]

In the intestine, macrophages, neutrophils, and T cells promote pro-inflammatory mediators like tumour necrosis factor (TNF)-α. Intestinal inflammation in CD dominantly presents with a T-helper 1 and 17 cell-mediated response.[1] At present, anti-TNF therapy is an established biologic that may be effective on some CD patients.[14] Human TNF is a family of proteins and receptors involved in immune regulation.[15] TNF is strongly associated with CD as its biological effects include increased inflammatory cytokine production and inhibition of inflammatory cell apoptosis.[15] Therapeutic uses of anti-TNF antibodies result in anti-inflammatory effects, including TNF neutralization, depletion of TNF overexpression, and cytokine suppression via reverse signalling processes.[15] These effects allow anti-TNF therapy to be effective in inducing and maintaining remission in moderate to severe CD.[3] Anti-TNF therapy is often prescribed alongside immunosuppressants (e.g., thiopurine, methotrexate) to decrease immunogenicity rates and increase anti-TNF drug concentration.[3,14] Other potential treatments include enteral nutrition and corticosteroids.[10] Combination therapies play a substantial role in symptom improvement, mucosal healing, and remission maintenance, with complete remission being the ultimate goal.[3,12]

RECENT ADVANCEMENTS

Novelly, the Genetic, Environmental, Microbial (GEM) project, an international research study dedicated to determining possible causes for CD, has recently discovered that the gut bacteria composition of individuals who develop CD differs from healthy individuals up to five years before disease development.[16] By establishing a model to evaluate the microbiome risk score (MRS), researchers could classify individuals who later developed CD or not, providing insight into microbial determinants of CD pathogenesis. Notably, *Ruminococcus torques* and *Blautia* were positively correlated with the MRS, whereas *Faecalibacterium* and *Lachnospira*, which produce anti-inflammatory protective metabolites, were negatively correlated with the MRS.[17]

The role of nutrition, which is suggested to be a significant environmental factor for CD, is an ongoing area of investigation.[18] A recent 2024 prospective observational study comparing nutrient intake and blood values of CD patients undergoing anti-TNF therapy suggests potential new nutritional biomarkers capable of predicting therapeutic responses.[18] Blood analysis conducted before anti-TNF therapy showed that patients who did not respond to treatment also had significantly decreased levels of taurine and iron.[18] Additionally, there was an observable trend of decreased vitamin B12 levels in those who could not achieve clinical remission upon biological therapy.[18] Within the realm of CD management, the lack of therapeutic response is a common problem, calling for optimized treatment and predictions for patients. Rizzello et al. suggests iron and taurine blood levels may be connected to CD patients' therapeutic outcomes, and has the potential to be used in association with validated biomarkers to assist in therapeutic decision-making.[18]

Colonic lesions in CD also have characteristically high levels of pro-inflammatory cytokines, like interferon-γ, interleukin (IL)-2, IL-12, and IL-18.[1] A breakthrough study in May 2023 introduced the first oral medication, upadacitinib, successful in treating moderate-to-severe CD.[19] Upadacitinib is a novel Janus kinase (JAK) inhibitor and a promising therapeutic candidate for treating inflammatory disorders, including CD.[20] The mechanistic ability to modulate the JAK pathway, which is key to CD pathogenesis, demonstrates potential in achieving remission and improving quality of life, especially for patients with suboptimal responses to existing treatments.[20] JAK inhibition results in decreased production of pro-inflammatory cytokines, significantly diminishing immune events inciting and perpetuating the chronic inflammation characteristic of CD.[20] A Phase 3 trial conducted for upadacitinib has demonstrated that patients with moderate-to-severe CD responded favourably compared to a placebo, garnering US Food and Drug Administration approval.[21] However, safety profiles show consistent reports of adverse events following upadacitinib use, urging careful monitoring of treatment continuation.[20] Further investigation has persisted into the efficacy of dual-targeted therapy (DTT), in which the amalgamation of different inflammatory cascades can lead to a synergistic therapeutic effect in select CD cases.[21] One study explores the concurrent use of upadacitinib and ustekinumad, a monoclonal antibody to the p40 subunit of ILs. Ultimately, combining the two drugs was effective and well tolerated for patients with medically-wresistant CD.[21] However, the long-term safety profile of DTT remains scarce and limited, given the novelty of upadacintinib.[21]

Though a permanent cure for CD has not been developed, exciting strides in prognosis and treatment set the stage for continued progress and evolution.

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