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Crohn Disease: Pathophysiology, Diagnosis and Management

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Abstract: Crohn's Disease is a chronic idiopathic inflammatory bowel condition, characterized by lesion, that can affect the entire gastroinstestinal tract from the mouth to the anus. The annual incidence of Crohn's Disease is 3 to 20 cases per 100.000 with an average age of 30 years. The pathophysiology of Crohn's Disease is based on tissue inflammation by an uncontrollable immune response to bacterial antigens. Computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography are the standard diagnosis of Crohn's Disease. The prognosis of Crohn's Disease depends on the compilation that arise such as fistula, bowel obstruction and the remission condition of the patient or the level of response of each patient to treatment. So that in treating Crohn's Disease is to treat active inflammatory conditions to quickly go into remission and maintain it as long as possible.

Keywords: Crohn's Disease; Pathophysiology; Diagnosis; Management; Prognosis

Introduction

Crohn's disease (CD) is a chronic inflammatory condition affecting the gastrointestinal tract that often leads to extraintestinal complications (Veauthier & Hornecker, 2018). Crohn's disease, which usually presents asymptomatically, will present as an acute toxic disease. The annual incidence of Crohn's disease reaches 3 to 20 cases per 100,000 with an average age range of 20 - 40 years (Fatahi et al., 2018; Feuerstein & Cheifetz, 2017). Crohn's disease is related to genetic factors where the risk of disease will increase if there is a family history of the disease. Men and women have an equal chance of developing Crohn's disease. However, smokers are three times more at risk of developing Crohn's disease (Medina & Lubis, 2017).

Crohn's disease is also known as granulomatous colitis, regional enteritis, and terminal ileitis which is an autoimmune disease involving many areas of the gastrointestinal tract ranging from the esophagus, stomach, small intestine, large intestine, rectum, to the anus. Swelling that extends to the inner wall lining of the involved organs will cause abdominal pain and often intestinal emptying which triggers nausea accompanied by weight loss and diarrhea (Medina & Lubis, 2017; National Digestive Diseases Information Clearinghouse, 2018). Crohn's disease occurs gradually and may worsen over time, can have periods of remission when symptoms disappear for weeks or years in the majority of individuals (National Digestive Diseases Information Clearinghouse, 2018).

Definition

Crohn's disease is a chronic, ongoing inflammatory condition that affects the gastrointestinal tract in all parts from the mouth to the anus. This chronic inflammation results from inappropriate activity of the mucosal system due to the presence of normal intralumenal flora involving any part of the

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gastrointestinal tract such as the lower part of the small intestine, the upper part of the large intestine, or both. However, Crohn's disease most commonly occurs in the ileocaecum (Greuter et al., 2018). It is also part of the chronic inflammatory bowel disease (Chronic Inflammatory Bowel Disease) which consists of Crohn's disease, ulcerative colitis and mixed type (undeterminate) (Siwy & Gosal, 2020). The characteristic symptoms of Crohn's disease are abdominal pain flare ups, recurrent, subsiding and chronic (Medina & Lubis, 2017).

Epidemioloy

Crohn's disease is an inflammatory bowel disease (IBD) of idiopathic etiology and chronic nature that was first described by Dr. Burrill B. Crohn, Ginzburg and Opperheimer in a case series at the annual meeting of the American Medical Association in 1932 (Petagna et al., 2020). Recent reports indicate that 1.3% (3 million individuals) of the US population has a diagnosis of IBD. The annual incidence of Crohn's disease reaches 3 to 20 cases per 100,000 with an average age of 30 years with the first peak in the age range of 20 to 30 years and a smaller peak around the age of 50 years (Fatahi et al., 2018; Feuerstein & Cheifetz, 2017). The prevalence and incidence of Crohn's disease is higher in developed countries of the world such as North America and Western Europe when compared to developing countries such as South America and Asia (Fatahi et al., 2018). Data regarding Crohn's disease in Indonesia is minimal and the prevalence based on preliminary endoscopy data in 2008, in all hospitals in Indonesia ranged from 1 to 3.3% (Siwy & Gosal, 2020).

Pathophysiology

Crohn's disease is based on tissue inflammation by an uncontrollable immune response to bacterial antigens (Petagna et al., 2020). Inflammation is initiated when pathogens, such as mycobacterium paratuberculosis, pseudomonas, or listeria, enter the body's immune system. Crohn's disease is influenced by innate immunity in terms of mucus production by the Mut2 and FUT2 genes and adaptive immunity influenced by TH1 lymphocytic and TREG cell responses mediated by TNF-α, IL-12, IL-34, and IL-23 (Figure 1). Increased migration to the site of inflammation is also determined by extracellular matrix remodeling via metalloproteins (MMP-1 and MMP-3) and increased adhesion molecules MACCAM-1 and integrin 4β4 (Figure 1) (Petagna et al., 2020).

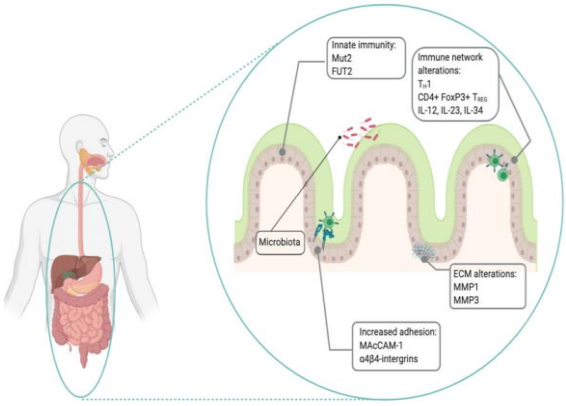

Figure 1. Immune System-Mediated Pathogenesis of Crohn's Disease
Attached figure in article Petagna, L. et al. (2020)

Metalloproteins (MMPs) consisting of MMP-1 and MMP-3 are elevated in the granule network in areas of inflammation to function as leukocyte activation; In the mucosa of Crohn's disease patients, there is dysregulation of various immune systems such as T cell hyperactivity with excessive cytokine production including IL-12, IFN-ɣ, TNF-α production which increases the number of CD4 cells, FoxP3, TREG especially in the mucosa of children diagnosed with Crohn's disease (Figure 2) (Petagna et al., 2020; Yeshi et al., 2020). Interleukins associated with the pathogenesis of Crohn's disease, IL-12 and IL-23, have the potential to increase the risk of infection, specific blockade of immunological targets, and induce alternative signaling or homing pathways (Figure 3). TNF-α causes a decrease in IL-34 expression which is implicated in the differentiation of monocytes and macrophages (Petagna et al., 2020).

Immune cells such as CD4 T cells, CD8 T cells, B cells, CD14 monocytes and natural killers when moving to the site of invasion will release cytokines to transmit intercellular messages, namely IFN-ɣ which activates macrophages (Figure 3). Activated macrophages will release more inflammatory compounds such as free radicals, proteases, and platelet activating factor that contribute to inflammation (Petagna et al., 2020). In Crohn's disease there are dysfunctional normal stages that lead to uncontrolled inflammation (Figure 3). Therefore many proteases and platelet activating factors are released around the gastrointestinal tract resulting in the destruction of healthy cell tissue (Petagna et al., 2020).

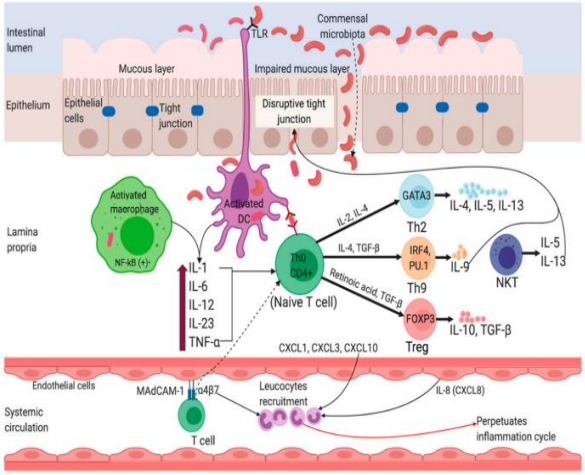

Figure 2. Immune System Dysregulation
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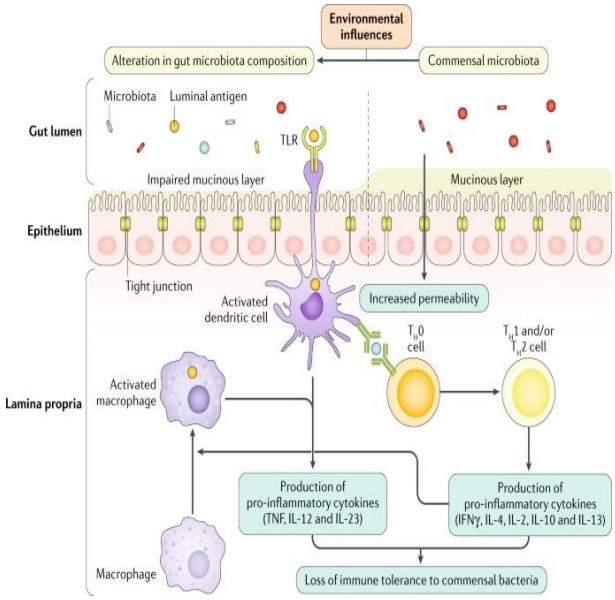

Figure 3. Inflammatory Process in Crohn's Disease
Attached figure in article Khalili, H., Chan, S. S.. and Lochhead, P. (2018)

There are many grooves in the intestinal wall, which consists of several layers: mucosa, submucosa, muscle, and serosa. Under normal circumstances, pathogens cannot directly penetrate the intestinal wall. However, in Crohn's disease, the epithelium is more easily bypassed by pathogens (Fatahi et al., 2018; Petagna et al., 2020). When it has entered past the epithelium, the pathogen will stimulate an immune response and cause uncontrolled inflammation. Immune cells invade inward to form granulomas to surround the foreign pathogen by the body. This causes cellular damage to the intestinal wall which is seen in the formation of ulcers. In Crohn's disease, damage and inflammation that is more extensive and deep reaching the serosa layer is called transmural inflammation (attacking all layers) (Figure 3) (Petagna et al., 2020).

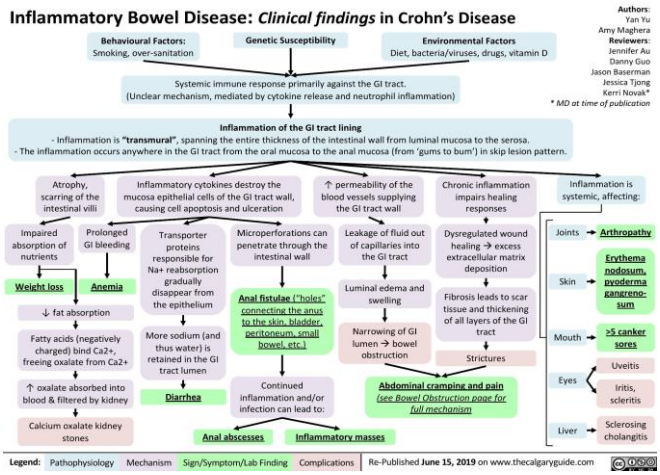

Figure 4. Pathophysiology, Mechanisms, Symptoms, and Complications of Crohn's Disease
Attached figure in article Yu, Y. and Maghera, A. (2022)

Diagnosis

In Crohn's disease all layers of the intestinal wall may be involved. The differential diagnosis of celiac disease, chronic pancreatitis, colorectal cancer, diverticulitis, ischemic colitis (bowel stroke), ulcerative colitis, tuberculosis, and sarcoidosis (Figure 4) (Wilkins et al., 2011). In establishing the diagnosis of Crohn's disease, it is important to perform history taking, physical examination and also supporting examination. Patients will usually complain of symptoms such as diarrhea, abdominal pain, rectal bleeding, fever, weight loss, and fatigue (Veauthier & Hornecker, 2018). A history of Crohn's disease is taken to identify alternative diagnoses such as food intolerance; travel; medications including antibiotic exposure; family history of inflammatory bowel disease; smoking status, and joint, eye, or skin symptoms. Physical examination is also important in order to identify patients who are unstable and need immediate help. Physical examinations that should be performed include pulse, temperature, respiratory rate, blood pressure, weight, and an abdominal examination that may include tenderness, distension, mass, or enlargement of the liver (National Digestive Diseases Information Clearinghouse, 2018; Veauthier & Hornecker, 2018).

Then there are several supporting examinations that can be done as follows:

a. Laboratory examination Cross-sectional imaging techniques namely, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography standardize the diagnosis of Crohn's disease. All these techniques can provide equal accuracy to make an initial diagnosis, monitor disease activity, and identify complications e.g. fistula, abscess. Computed tomography (CT) technique may provide the most consistent results but has the downside of radiation exposure (Veauthier & Hornecker, 2018).
b. Blood tests are done to check albumin levels. In Crohn's disease patients, it is synonymous with decreased albumin or hypoalbuminemia and decreased serum iron levels or iron deficiency. This test can also determine the decrease in the patient's Hb level or anemia which is indicated by bleeding in the intestine (National Digestive Diseases Information Clearinghouse, 2018).
c. Upper gastrointestinal series examination is performed to see the small intestine. The patient is given a barium enema that will coat the wall lining of the small intestine before the X-ray is taken; Barium that shows white marks on the X-ray film indicates inflammation or other abnormalities in the intestine (National Digestive Diseases Information Clearinghouse, 2018).

Management

The principle of management in managing patients with Crohn's disease is to treat the active inflammatory condition until it quickly goes into remission and maintain it as long as possible to prevent recurrent inflammation, as well as treat and prevent complications (Siwy & Gosal, 2020). Management for this disease depends on the severity of the disease and the clinical symptoms of the patient, because each person experiences different levels of severity. It is also important to consider the complications that may arise and the prognosis of the disease in the future (Lichtenstein et al., 2018).

Management of Crohn's disease is individualized, which means that the response of the therapy given is according to the symptoms and also the tolerance of each individual to medical intervention. The patient's response to the initial therapy must remain under the evaluation of medical staff for several weeks. In particular, any side effects that may occur should be closely monitored during the treatment period (Lichtenstein et al., 2018). Treatment for Crohn's disease works by suppressing the active intestinal immune system. The treatment consists of two levels, namely induction and maintenance. Induction includes medications in the initial weeks to months to induce a rapid reduction in the patient's clinical symptoms (remission) (Feuerstein & Cheifetz, 2017; Veauthier & Hornecker, 2018). Once the patient has achieved remission, maintenance therapy should be considered. Patients with continued symptoms should be treated with alternative therapies for mild to moderate disease, and the dose of drugs administered adjusted to optimize therapy. For moderate to severe disease, progress to treatment appropriate to their clinical status (Lichtenstein et al., 2018).

- Pharmacological Therapy

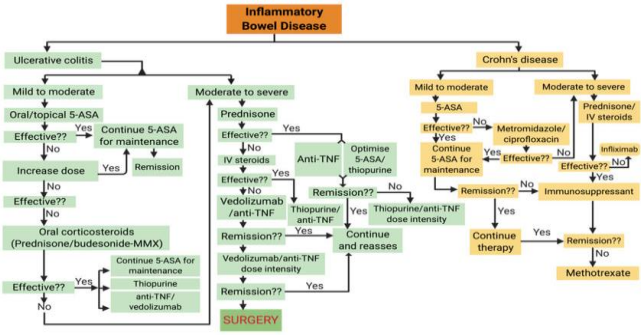

Figure 5. Management of Crohn's Disease
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Crohn's disease cannot be cured. However, the symptoms of the disease can be reduced. The goal of pharmacological therapy for Crohn's disease is to induce and maintain remission, and optimize one's quality of life to normal. Things that should be considered in providing drug therapy for patients with Crohn's disease are age, onset and penetrating complications, treatment with steroids, monoclonal antibodies, immunomodulators, comorbidities, symptoms, inflammatory status, location and extent of lesions, and the risk of more severe disease (Veauthier & Hornecker, 2018).

There are many options available for pharmacologic therapy of Crohn's disease. Some of the medications used for Crohn's disease include (National Digestive Diseases Information Clearinghouse, 2018):

1. Aminosalicylates

Aminosalicylates are drugs that contain 5-aminosalicylic acid (5-ASA). This medicine helps control inflammation. They are usually used to treat

newly diagnosed people with mild symptoms of Crohn's disease. The drugs included are balsalazide, mesalamine, olsalazine, and sulfasalazine which is a combination of sulfapiridine and 5-ASA.

In some studies it is said that mesalamine is not effective in the treatment of Crohn's disease and should not be used. However, mesalamine is still one of the drugs often prescribed to patients with mild colonic Crohn's disease whose cases appear similar to UC. Sulfasalazine is effective in inducing remission in colonic Crohn's disease, but has not been proven to maintain remission. If the medication is working well, then symptoms should start to improve within 2 - 4 weeks. However, if after several weeks of use it is not effective, another therapy should be started immediately (Feuerstein & Cheifetz, 2017).

2. Corticosteroids

Corticosteroids, also known as steroids, are used to help reduce immune activity and reduce inflammation. They are prescribed for patients with moderate to severe symptoms. Corticosteroid medications include budesonide, hydrocortisone, methylprednisolone and prednisone.

Steroids have little role in maintaining disease remission, but they have a rapid onset of action and are generally effective in inducing remission in Crohn's disease. However, steroids are said to be ineffective for treating perianal Crohn's disease. Long-term administration of steroids to Crohn's disease patients should be avoided. Patients prescribed systemic steroids should be switched to drugs that have been shown to maintain remission in Crohn's disease (Feuerstein & Cheifetz, 2017).

When the disease is located in or spreads to the colon, patients are more often given prednisone. However, budesonide may also be an option for disease affecting the ileum and or proximal colon due to its more area-specific breakdown. Generally, corticosteroid use will achieve remission within 8 - 12 weeks. A prednisone tapering off plan will be recommended based on the severity of the disease (Siwy & Gosal, 2020). Before tappering off, the response and remission rate will be assessed, and the dose will be gradually reduced until it is discontinued (Veauthier & Hornecker, 2018).

Corticosteroids are often used to treat temporary relapses of symptoms while patients are transitioning to more effective therapies as they do not maintain remission and have higher perforation complications. Some of the side effects that can arise after taking steroid drugs include adrenal insufficiency, obesity, cataracts, hypertension, and diabetes. It can also cause acne, high blood glucose, mood swings (Feuerstein & Cheifetz, 2017).

3. Immunomodulators or immunosuppressants

Immunomodulators work by reducing the activity of the immune system, and cause less inflammation in the gastrointestinal tract. Immunomodulators may be used if corticosteroids are not working. To start working, these medications can be taken from a few weeks to 3 months. Immunomodulators include azathioprine, thiopurines, 6-mecaptopurine, cyclosporine and methotrexate. These medications have been used for many years to treat Crohn's disease. Immunomodulators are usually used to maintain remission due to their slow onset of action, but are often used as an adjunct for steroid-sparing effects.

Usually, patients with Crohn's disease will be prescribed immunomodulators to help those in remission or for people who do not respond to other treatments. Healthcare professionals most often prescribe cyclosporine for patients with severe Crohn's disease due to serious drug side effects 8. For moderate to high risk patients, azathioprine in combination with anti-tumor necrosis factor (TNF) agents are usually prescribed. This combination will reduce exposure to corticosteroids, cause fewer side effects, and reduce the level of immunogenicity to anti-TNF agents.

4. Biological therapy

Biologic therapies are drugs that work by targeting proteins produced by the immune system to neutralize inflammation in the gut. They work quickly to produce remission, especially in people who do not respond to other treatments. Some of the monoclonal antibodies that have been approved for treatment of Crohn's disease are anti-TNF agents, anti-integrin agents and anti-IL-12/23 p40 antibody therapy.

Currently, anti-TNF therapy is the most effective therapy for moderate to severe Crohn's disease. It can also be used alone or in combination with immunomodulators to induce and maintain remission. There are 3 types of anti-TNF agents approved by the Food and Drugs Administration (FDA) for moderate to severe Crohn's disease, including infliximab, certolizumab and adalimumab (Feuerstein & Cheifetz, 2017). All 3 drugs induce and

maintain remission in moderate to high-risk patients, or in patients who do not respond to immunomodulators. When administered, onset of action and changes in the patient's clinical condition will be seen within 2 weeks of therapy, and the overall effect of these anti-TNF agents will be seen within 2 years of disease onset (Veauthier & Hornecker, 2018).

Anti-IL-12/23p40 antibody therapy, ustekinumab, is a treatment option for patients when standard therapy is ineffective. The use of ustekinumab was approved by the United States FDA in 2016. Ustekinumab is said to have an onset of action and response that will usually be seen within 6 weeks (Feuerstein & Cheifetz, 2017; Veauthier & Hornecker, 2018). The above 3 anti-TNF agents have similar safety profiles. The most common side effects are injection or infusion site reactions and an increased risk of infection. Although there is a slightly increased risk of melanoma with anti-TNF use, it is not yet clear that there is a risk of other malignancies. A recent meta-analysis suggested that patients are more likely to continue treatment with biologic therapy rather than immunomodulators due to their perceived higher efficacy and tolerability (Feuerstein & Cheifetz, 2017; Petagna et al., 2020; Veauthier & Hornecker, 2018).

Another treatment that can be used in the management of Crohn's disease is the administration of antibiotics. Antibiotics are used to prevent and/or treat infections and fistulas. However, the use of these antibiotics has not been proven effective for inducing and maintaining remission in active Crohn's disease. The use of antibiotics is best used in combination with anti-TNF for perianal Crohn's disease. Commonly used antibiotics are ciprofloxacin and metronidazole. Side effects and resistance to antibiotics arising in long-term use are a barrier to use (Feuerstein & Cheifetz, 2017).

In addition, the first-line therapy used to induce remission in children is enteral nutrition. A small study suggests that there are benefits of enteral nutrition for maintenance therapy in adults. So that later, when a drug is contraindicated or refused, it can be considered (Veauthier & Hornecker, 2018).

- Bowel Rest

When the symptoms of Crohn's disease become severe, bowel rest may be used by patients to recover their clinical condition. Bowel rest is carried out by resting the body, especially intestines, for several days to weeks. Nutrition will be administered intravenously with a special catheter as bowel rest includes only water, and no oral intake (National Digestive Diseases Information Clearinghouse, 2018).

- Diet

Some studies have shown that dietary therapy, including elemental diets, semielemental diets and specific diets may be effective for some Crohn's disease patients. Dietary therapy is considered an adjunctive therapy to induction therapy because however, the benefits of this therapy are not long-lasting. Especially with symptoms and active inflammation that may reoccur after the start of an unrestricted diet. Patients who are considered to be at a low risk for disease progression can be treated but should remain under supervision (Lichtenstein et al., 2018).

- Surgery

As many as 20% of people with a case of Crohn's disease will require surgery to treat their disease; Whereas in a journal written by Brian et al said that 57% of patients needed at least one surgery. Although this surgery cannot cure Crohn's disease, it can treat complications that will or have occurred and improve clinical symptoms. Surgical therapy is given if pharmacological treatment is unsuccessful and there are complications such as fistula, perforation, abscess, uncontrolled bleeding, intestinal obstruction, stricture (narrowing of the urethra), dysplasia, side effects of life-threatening drugs, and no improvement in clinical condition (National Digestive Diseases Information Clearinghouse, 2018; Veauthier & Hornecker, 2018).

Some types of surgery to treat Crohn's disease include small bowel resection, subtotal colectomy, proctocolectomy and ileostomy. Most patients after surgery will remain in hospital for 3 - 7 days, and complete recovery for 4 - 6 weeks (National Digestive Diseases Information Clearinghouse, 2018).

Prognosis

The prognosis of Crohn's disease depends on the complications that arise and the remission state of the patient, or the response rate of each patient to conservative treatment (Siwy & Gosal, 2020). Despite optimal therapy, most patients have a poor quality of life. Life expectancy decreases slightly with the progression of disease malignancy and biliary tract complications. Most patients with complicated Crohn's disease require surgery. Some even require multiple procedures as the disease progresses (Ranasinghe & Hsu, 2023).

Complication

1. Bowel obstruction

Crohn's disease can cause thickening of the intestinal wall, which over time causes the area of the intestine to narrow and thus obstruct the intestine. Partial or complete obstruction (blockage of the intestine), can prevent the movement of food or stool through the intestines. Total intestinal obstruction can be life-threatening and requires immediate medical action, such as surgery (National Digestive Diseases Information Clearinghouse, 2018).

2. Fistula

Fistula is the term for the condition of an abnormal tunnel or channel forming, connecting between two organs, or between an organ and the outside of the body. Treatment of a fistula depends on its type and severity, with some people, fistulas resolve with medication and dietary changes, while others require surgery (National Digestive Diseases Information Clearinghouse, 2018).

3. Fissure ani

An anal fissure is a small wound in the anus that may cause itching, pain or bleeding. Most anal fissures can heal with medical treatment, including the use of ointments, warm baths, and dietary changes (National Digestive Diseases Information Clearinghouse, 2018).

4. Ulcer

Inflammation along the gastrointestinal tract can cause ulcers or open wounds in the mouth, intestines, anus, and perineum. In most cases, the treatment prescribed for Crohn's disease can also simultaneously treat ulcers (National Digestive Diseases Information Clearinghouse, 2018).

Conclusion

Crohn's disease (CD) as one of the Idiopathic Inflammatory Bowel Disease (IBD) also known as granulomatous colitis, regional enteritis and terminal ileitis, is an autoimmune disease that involves many areas of the gastrointestinal tract from the esophagus to the anus, but mostly involves the small intestine (ileum terminalis) and colon, usually multifocal. The characteristic symptoms of Crohn's disease are abdominal pain that flares up, recurs, subsides and is chronic. Crohn's disease is based on tissue inflammation by an uncontrollable immune response to bacterial antigens initiated when pathogens such as mycobacterium paratuberculosis, pseudomonas, or listeria enter. The intestinal wall has many indentations consisting of several layers: mucosa, submucosa, muscle, and serosa. Under normal circumstances, pathogens cannot directly penetrate the intestinal wall. However, in Crohn's disease, the epithelium is more easily passed by pathogens which will then stimulate an immune response and cause uncontrolled inflammation. The immune cells invade inward to form granulomas to surround the pathogens foreign to the body. This causes cellular damage to the intestinal wall which is seen in the formation of ulcers. In Crohn's disease the damage and inflammation that is more extensive and deep reaching the serosa layer is called transmural inflammation (attacking all layers). The differential diagnosis of this disease is celiac disease, chronic pancreatitis, colorectal cancer, diverticulitis, ischemic colitis, ulcerative colitis, tuberculosis and sarcoidosis. In establishing the diagnosis of Crohn's disease, it is important to conduct a history, physical examination and also supporting examinations such as laboratory examinations of cross-sectional imaging techniques, blood tests, and upper gastrointestinal serial examinations performed to view the small intestine. The principle of management in dealing with Crohn's disease patients is to treat active inflammatory conditions to quickly go into remission and maintain it as long as possible to prevent recurrent inflammation, as well as treat and prevent complications. Management that can be done includes pharmacological therapy, bowel rest, and surgery.

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