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Inflammatory Bowel Disease in a Pemphigus Vulgaris Survivor

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ABSTRACT:
Inflammatory bowel disease (IBD) includes Crohn's disease and ulcerative colitis, caused by an abnormal immune response to gut bacteria in genetically predisposed individuals. The complex pathogenesis involves genetic, environmental, and immunological factors, leading to chronic inflammation of the gastrointestinal tract, which manifests as abdominal pain, diarrhea, weight loss, and fatigue, potentially resulting in complications like strictures and colorectal cancer. Advances in genetic and microbiome research are crucial for understanding IBD's mechanisms and developing targeted therapies, offering hope for personalized treatments. Globally, the incidence and prevalence of IBD are rising, making it a significant health concern. Additionally, patients with IBD have an increased risk of other autoimmune diseases, such as Pemphigus vulgaris, highlighting the need for comprehensive patient histories and vigilant monitoring. This research utilized the case report method to detail the clinical journey of a 70-year-old male from Surabaya, East Java, whose diagnosis of inflammatory bowel disease (IBD) was followed by the onset of Pemphigus vulgaris (PV) 11 years later. The patient's medical history, including symptoms, diagnostic procedures, treatments, and outcomes, was meticulously documented through medical record reviews and patient interviews, highlighting the intersection of IBD and PV and offering valuable insights into the coexistence of multiple autoimmune diseases. This research found that a 70-year-old man from Surabaya, East Java, who had survived Pemphigus Vulgaris diagnosed 11 years earlier, later developed Inflammatory Bowel Disease (IBD). He presented with gastrointestinal symptoms leading to a colonoscopy, which revealed a cobblestone appearance throughout the colon, caecum, and ileocaecal junction, confirmed by biopsy findings of ulcers, cryptitis, and crypt abscesses. The patient was treated with oral mesalazine and methylprednisolone, which significantly improved his symptoms, prompting his request for discharge. This case highlights the importance of vigilant long-term monitoring and comprehensive care for survivors of chronic autoimmune diseases, underscoring the need for timely and appropriate therapeutic interventions to manage IBD effectively.

Keywords: Inflammatory Bowel Disease (IBD), Pemphigus Vulgaris (PV), Autoimmune Disease.

1. Introduction

Inflammatory bowel disease (IBD) is an immune-mediated inflammatory condition that encompasses both Crohn's disease and ulcerative colitis. These diseases are hypothesized to result from an abnormal immune response to enteric bacteria in individuals who are genetically predisposed. The pathogenesis of IBD is complex and multifactorial, involving a combination of genetic, environmental, and immunological factors (Vuyyuru et al., 2022). Research indicates that in genetically susceptible individuals, the immune system mistakenly targets the gut microbiota, leading to chronic inflammation. This inappropriate immune response causes recurrent and destructive inflammation of the gastrointestinal tract, which is a hallmark of both Crohn's disease and ulcerative colitis (Shaheen et al., 2022).

The clinical manifestations of IBD vary widely but typically include abdominal pain, diarrhea, weight loss, and fatigue. These symptoms can significantly impair the quality of life and often require long-term medical management. The destructive nature of the inflammation in IBD can lead to complications such as strictures, fistulas, and increased risk of colorectal cancer (Rogler et al., 2021). Understanding the precise mechanisms underlying the abnormal immune response in IBD is crucial for developing targeted therapies. Advances in genetic research and microbiome studies continue to shed light on the etiopathogenesis of IBD, offering hope for more effective and personalized treatment approaches. The ongoing research efforts aim to identify specific genetic markers and microbial profiles associated with IBD, which could revolutionize the diagnosis and management of this debilitating disease (Lu et al., 2022).

The comprehensive review conducted in 2012 analyzed 167 population-based studies from Europe (1930–2008), 52 from Asia and the Middle East (1950–2008), and 27 from North America (1920–2004), providing insights into the incidence and prevalence of inflammatory bowel disease (IBD). The review highlighted a statistically significant increase ($P < 0.05$) in 75% of Crohn's disease (CD) studies and 60% of ulcerative colitis (UC) studies over time. Notably, the review did not include data from South America, where CD incidence averaged 1–3 per 100,000, rising to 3–4 per 100,000 in more developed urban areas of Brazil. Although data from developing nations are limited, the global trend shows a rising incidence and prevalence of IBD. A recent comparative study across Asia revealed varying IBD incidence rates, ranging from 0.54 per 100,000 to 3.44 per 100,000 individuals in different populations.

There is an elevated risk of autoimmune disease among individuals with inflammatory bowel disease (IBD). Despite increasing evidence indicating a connection between IBD and other autoimmune conditions, few population-based studies have thoroughly investigated this association (Bezzio et al., 2022). Pemphigus vulgaris (PV), a type of bullous autoimmune disease, is among those that may co-occur with other autoimmune disorders such as systemic lupus erythematosus, myasthenia gravis, and IBD (Fang et al., 2020). However, in medical literature, the simultaneous occurrence of IBD and PV is rarely documented, making such cases noteworthy for clinicians and researchers alike. Herein, we present a unique case of a 70-year-old man from Surabaya, East Java, whose diagnosis of IBD preceded the manifestation of PV by 11 years. This case illustrates the complexity and potential interrelation of autoimmune diseases, emphasizing the necessity for comprehensive patient histories and vigilant monitoring.

2. Literature Review

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by chronic inflammation, causing pain and swelling in the intestines. This term encompasses two types of diseases: ulcerative colitis and Crohn's disease (Yeshi et al., 2020). Ulcerative colitis involves persistent inflammation leading

to ulcers (sores) in the lining of the colon and rectum, whereas Crohn's disease is marked by inflammation that extends deeply and widely into the digestive tract wall. Both conditions can significantly disrupt health and may become life-threatening if not effectively managed (Antunes et al., 2021).

The cause of inflammatory bowel disease itself is still unknown. Several factors, such as diet and stress, are believed to be some of the factors that worsen the symptoms of this disease. Even so, this is not the cause of this disease. One possible cause is due to a malfunction or abnormality of the immune system. This happens when a person's immune system, which should fight bacteria and viruses, actually attacks the lining of the sufferer's intestines and interferes with the functioning of the intestines (Bertani et al., 2021).

Several risk factors that are believed to increase a person's risk of developing this disease include:

a. Age. Most people diagnosed with inflammatory bowel disease are 30 years old.
b. Certain races and ethnicities. White people are at higher risk for inflammatory bowel disease, but the disease can occur in people of any race.
c. Family history of the disease. A person is at higher risk if they have a close relative, such as a parent or sibling, who has inflammatory bowel disease.
d. Smoking. This is a risk factor for Crohn's disease.
e. Taking certain medications. Examples include excessive use of non-steroidal anti-inflammatory drugs, such as ibuprofen, naproxen sodium, diclofenac sodium, and others (Tosca et al., 2020).

Intestinal inflammation typically manifests as a chronic condition with symptoms that fluctuate over time. The severity of these symptoms varies based on the location of the inflammation. Common symptoms include:

a. Pain or discomfort in the abdomen.
b. Weight loss.
c. Loss of appetite.
d. Blood-tinged diarrhea that recurs.
e. Feeling very tired.
f. Nausea and fever (Gusev & Zhuravleva, 2022).

It's crucial to note that symptoms of intestinal inflammation can vary widely among individuals and may fluctuate over extended periods. Recurrences can range from mild to severe. Diagnosis of intestinal inflammation typically involves a thorough examination of signs and symptoms by a doctor, followed by a series of tests to confirm the condition (Ladds et al., 2020). The following tests may be necessary:

a. Blood tests are conducted to detect signs of anemia, bacterial or viral infections, and to examine stool samples for blood.
b. Endoscopic procedures allow doctors to visualize the interior of the digestive system and obtain tissue samples for laboratory analysis.
c. Imaging tests, including X-rays, CT scans, MRIs, and imaging of the digestive system, may also be performed (Brittenham et al., 2023).

Currently, there is no cure for colitis. Treatment focuses on managing symptoms and preventing their recurrence. Mild symptoms may resolve on their own within a few days, and treatment may not be necessary in such cases. Alongside symptom relief, treatment aims to minimize the risk of complications. Options include medication, therapy, or surgery as outlined in recent research (Cai et al., 2021).

The drugs that will be given to treat intestinal inflammation are:

a. Non-steroidal anti-inflammatory drugs (NSAIDs), such as aminosalicylates and corticosteroids, are often prescribed initially to reduce intestinal inflammation.
b. Immunosuppressant drugs like azathioprine, cyclosporine, and infliximab are used to suppress the immune system's harmful activity and reduce inflammation. Combinations of these drugs may be more effective for some individuals.
c. Antibiotics, such as metronidazole and ciprofloxacin, may be added to the treatment regimen, especially if there is an accompanying infection in ulcerative colitis patients.
d. Other medications can address symptoms related to intestinal inflammation beyond inflammation itself. It's advisable to consult a doctor before using over-the-counter drugs purchased from a pharmacy (Tai & McAlindon, 2021).

Anti-diarrheal medications, pain relievers, iron supplements, vitamin supplements, and calcium may be prescribed based on the specific symptoms and condition of the patient. If drug treatments aimed at alleviating symptoms of intestinal inflammation prove ineffective, surgery may be necessary (Meineri et al., 2022). Individuals with severe symptoms of ulcerative colitis often do not respond adequately to drug therapy. Surgery involves removing the severely inflamed portion of the colon. For Crohn's disease patients, surgery may entail removing the damaged segment of the digestive tract and reconnecting the healthy portions. Following surgery, ongoing medication is typically required to prevent recurrence (Segal et al., 2021).

Pemphigus Vulgaris

Pemphigus is a collection of chronic autoimmune blistering skin diseases, affecting the skin and mucous membranes, which are histologically characterized by intraepidermal blisters due to the process of acantholysis (separation of epidermal cells from each other) and immunopathologically antibodies are found against desmosome components on the surface of IgG type keratinocytes, which are bound or circulate in the blood circulation (Di Lernia et al., 2020). There are 4 main types of pemphigus, namely pemphigus vulgaris, pemphigus erythematosus, pemphigus foliaceus, and pemphigus vegetans, where all of these diseases give typical symptoms, namely:

a. Formation of loose blisters on the skin that generally look normal and are easily broken
b. When pressed, the blisters expand (positive Nikolsky sign)
c. Acantholysis is always positive
d. The presence of IgG type antibodies against intercellular antigens in the epidermis that can be found in serum (Sciuca et al., 2022).

Pemphigus is classified into two main types based on its location: suprabasal (including pemphigus vulgaris and its variant pemphigus vegetans) and granulosum (comprising pemphigus foliaceus and its variant pemphigus erythematosus). Pemphigus vulgaris is an autoimmune condition characterized by vesicles or bullae on the skin or mucous membranes. It arises from autoantibodies targeting desmoglein 1 and 3 proteins in the suprabasal layer of the epidermis (Chu et al., 2022).

Pemphigus vulgaris represents the most prevalent form among all pemphigus cases, accounting for 80% of occurrences. Its reported annual incidence ranges from 0.1 to 0.5 per 100,000 individuals. Pemphigus vulgaris typically manifests between the ages of 40 and 60 years, though it can also affect children. Demographically, individuals in regions such as India, Southeastern Europe, and the Middle East face the highest risk for developing pemphigus vulgaris. The prevalence of PV is similar among men and women (Timóteo et al., 2024).

Pemphigus vulgaris when divided based on the age group of sufferers can be divided into childhood pemphigus vulgaris if it affects children under 12 years old and juvenile pemphigus

vulgaris if it affects children aged 12-18 years. The mortality rate of pemphigus vulgaris cases reaches 75% in the first year (Lins Filho et al., 2021).

The cause of pemphigus vulgaris is antibodies that attack desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3) which are transmembrane glycoproteins with molecular weights of 160 and 130 kD, respectively. They are integral parts of the desmosomes of the cadherin family, which are responsible for adhesion between squamous epithelial cells. The basic pathophysiology of pemphigus is the inhibition of the adhesive function of desmoglein by autoantibodies, leading to blister formation. Desmoglein is a protein that plays a role in cell adhesion, especially in the epidermis and mucous membranes (Deyrup et al., 2022).

The diagnosis of pemphigus vulgaris is typically confirmed through positive findings on clinical examination, histological examination, and immunological tests, or the presence of two diagnostic signs along with immunological evidence. A key clinical indicator is the Nikolsky sign, which involves applying pressure to the skin near a lesion; a positive sign occurs if the skin peels away, indicating separation within the epidermis's superficial layers (Nili et al., 2021). Another diagnostic sign is the Asboe-Hansen sign, where pressure at the edge of a bulla causes it to extend outward. The histological picture of a biopsy of pemphigus vulgaris lesions is a picture of suprabasilar bulla with acantholysis. The layer between the stratum basale of the epidermis and the other more superficial parts of the epidermis appears to be loose and forms a bulla. Sometimes keratinocyte cells are seen coming off into the bulla. The superficial part of the epidermis looks intact (Leiferman et al., 2022).

Immunological examinations are crucial in diagnosing pemphigus vulgaris. Both direct and indirect immunofluorescence tests on serum antibodies and skin lesions play significant roles. Testing antibodies in skin lesions is particularly sensitive and specific compared to serum tests (Talagrand-Reboul et al., 2020). Enzyme-linked immunosorbent assay (ELISA) is employed to detect antibodies targeting desmoglein 1 and desmoglein 3, aiding in the diagnosis of pemphigus vulgaris. Specifically, the presence of antibodies targeting only desmoglein 1 supports a diagnosis of pemphigus foliaceus. ELISA offers high specificity, while immunofluorescence is more sensitive in detecting antibodies. Antibody testing also serves to monitor treatment efficacy; remission often correlates with a reduction or absence of antibodies (Alshami et al., 2022).

Case Report

The patient is a 70-year-old man. He is a lecturer in veterinary medicine. He was referred to emergency department of Rumah Sakit Universitas Airlangga on 27th April 2021 from gastroenterology inpatient clinic for multiple diarrheas, nausea, vomiting and abdominal pain. He was suffering from diarrhea for a month, the diarrhea was as frequent as seven to eight times per day. There was a lot of mucus and water in his stool, with a little fecal material, bloody stool was come out in occasion. Nausea and vomiting are also frequent for the last 1 week, reaching five to six times per day. Patient’s appetite decreased vastly. Abdominal pain was presented also 1 week before admission, felt in all area of abdomen. The pain was excruciating mainly before patient defecate. There was no other complain such as fever, headache, shortness of breath, anosmia, decrease of conciouseness, muscle pain, and limb weakness.

The patient had an interesting history of past illness. First of all, patient was a survivor of pemphigus vulgaris, which happened 11 years ago. He was admitted to Rumah Sakit Dokter Soetomo Surabaya, under the care of dermatolo-venereology department in Kemuning ward. Hospitalized for twenty-five days, patient went throught a lot of complication including severe skin infection. But with proper treatment, patient survived the infection and gradually feel better and got discharged in a good condition. Patients also had food allergic history including egg and high protein milk. Hypertension was diagnosed in this patients since 20 years ago.

Usually he took amlodipine regularly, but he stopped recently along with worsening of his symptoms. Another medication he took before were activated attapulgite, loperamide, cotimoxazole, metronidazole, but none of them worked to alleviate his complaints.
Physical examination of this patient was as follows: blood pressure 139/80 mmHg, pulse rate 102 times per minute, respiration rate 20 times per minute, with 99% oxygen saturation and 36.5 degree celcius in axilla temperature. Head and neck examination is within normal limit. Chest examination is within normal limit. On abdominal examination, the abdominal surface was slightly distended, bowel sounds increased, there were no hepatomegaly nor splenomegaly. Edema of lower limb were observed in cruris bilateral. Capillary refill test was under two seconds.

Figure 1. Patient's Documentation of His Pemphigus Vulgaris History

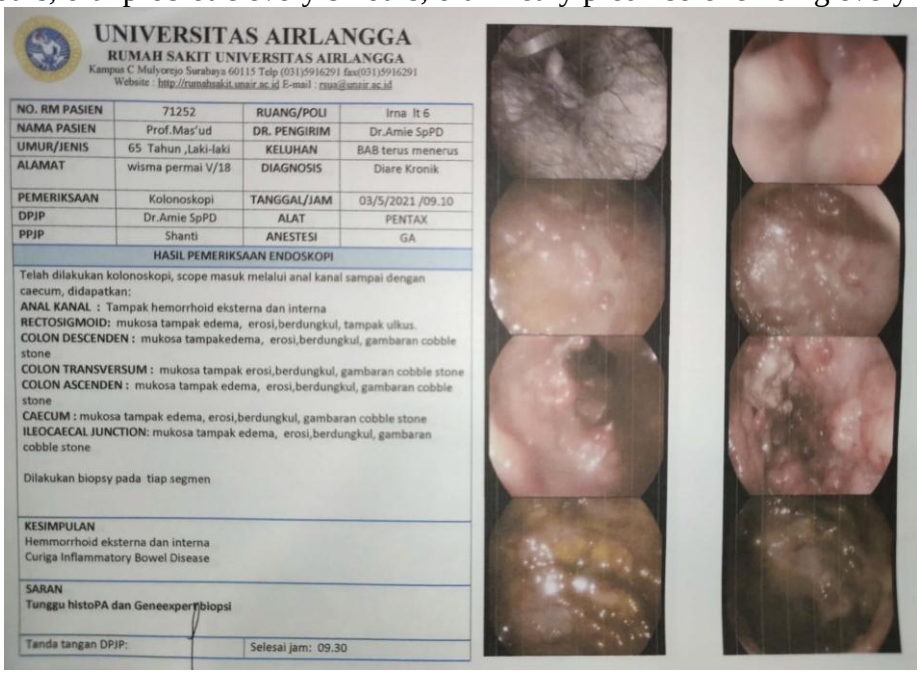
Laboratory examination results were haemoglobin (Hb) 11.3g/dL, white blood cells (WBC) 15,560, platelets (PLT) 369,000, blood urea nitrogen (BUN) 12.5, creatinine serum 1.25. Electrolyte serum results were natrium (Na) 132, Kalium (K) 3.6, Chloride (Cl) 102. Rapid covid was non-reactive. Chest X-Ray was within normal limit. Patient was diagnosed as follows: chronic diarrhea pro evaluation + acute kidney injury ec dehydration + limb edema + mild hyponatremia. Some diagnostic procedures were planned such as colonoscopy, albumin serum, evaluation of electrolyte serum, covid PCR swab, and anti-HIV. Initial therapy for this patient were IVFD Ringer lactate 1500cc every 24 hours, IV Omeprazole 20mg every 24 hours, IV Ondansetron 4mg every 12 hours, Oral Probiotic Lactobacillus every 8 hours.
Patient complaint wasn't relieved with initial therapy, watery diarrhea was still on going on the next day. Vital sign was stable. Additional therapy was given as follows: IVFD Ringer lactate 1500cc every 24 hours, IV Omeprazole 20mg every 24 hours, IV Ondansetron 8mg every 12 hours, Oral Probiotic Lactobacillus every 8 hours. Fecal smear examination was planned.
On the 3rd day of admission, patient still complained about watery diarrhea and abdominal pain. Vital sign was stable. Additional therapy of codein 20mg every 8 hours was given to alleviate pain, oral mesalazine 250mg every 8 hours was also given to reduce inflammation process. Oral activated Attapulgitte was stopped. We tried to monitor patient symptom wether it can be reduced with new therapy selection.
On the 4th day of admission, watery diarrhea and abdominal pain was there, but the patient said its somewhat decreasing than before. Vital sign was stable. Laboratory examination showed result of hypoalbuminemia (2.26 g/dL) and hypokalemia (3.1 mmol/L). The other result were within normal limit (Natrium 134 mmol/L, Chloride 106 mmol/L, Rapid Test HIV single method non-reactive). Additional therapy was given as follows: Albumin 20% 100cc

transfusion in 4 hours, Kalium Chloride 25 meq in normal saline 500cc every 12 hours, both administered twice. Colonoscopy was planned for the next day. Patient was asked to consume laxative and will be given enema for bowel cleaning. Unfortunately, the laxative was not consumed properly by the patient. As a result, colonoscopy have to be postponed until bowel cleaning completed. Bowel cleaning method was replaced with fleet enema every 12 hours for 2 days and patient was instructed to drink 1000cc of water minimum for 24 hours.

On the 6th day of admission, patient still complained about watery diarrhea and abdominal pain but a lot better if compared to the first condition he came in. Vital sign was stable. Laboratory examination showed result of hypoalbuminemia (2.36 g/dL), hypokalemia was already resolved (3.5 mmol/L). The other result were within normal limit (Natrium 135 mmol/L, Chloride 108 mmol/L). The second albumin 20% 100cc transfusion in 4 hours was given to patient to make sure hypoalbuminemia resolved as fast as possible.

On the 7th day of admission hypoalbyminemia showed a preferable result (2.51 g/dL). The complaint were only slight watery diarrhea. Abdominal pain was not presented. Vital sign was stable. Patient undergo colonoscopy procedure from anal canal to caecum. The result was: Anal canal: internal and external hemmoroid was observed. Rectosigmoid: mucosa edema, mucosal erosion was observed, with stooped surface and ulcus. Colon descenden: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Colon transverse: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Colon ascenden: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Caecum: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Ileocal junction: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance.

From the result above, patient was diagnosed with inflammatory bowel disease, but also suspected with colitis tuberculosa. So further examination such as histologic pathology anatomy and Geneexpert of biopsy tissue was planned. Some intravenous therapy was planned to be given to the patient, but unfortunately patient asked to be discharged. Patient went home later that day, given therapy as follows: oral metronidazole 500mg every 8 hours, oral mesalazine 500 mg every 8 hours, oral ondansetron 4mg every 12 hours, oral omeprazole 20mg every 12 hours, oral probiotic every 8 hours, oral methylprednisolone 16mg every 8 hours.



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PPJP	Shanti	ANESTESI	GA

HASIL PEMERIKSAAN ENDOSKOPI

Telah dilakukan kolonoskopi, scope masuk melalui anal kanal sampai dengan caecum, didapatkan:
ANAL KANAL : Tampak hemorrhoid eksterna dan interna
RECTOSIGMOID: mukosa tampak edema, erosi,berdungkul, tampak ulkus.
COLON DESCENDEN : mukosa tampakedema, erosi,berdungkul, gambaran cobble stone
COLON TRANSVERSUM : mukosa tampak erosi,berdungkul, gambaran cobble stone
COLON ASCENDEN : mukosa tampak edema, erosi,berdungkul, gambaran cobble stone
CAECUM : mukosa tampak edema, erosi,berdungkul, gambaran cobble stone
ILEOCAECAL JUNCTION: mukosa tampak edema, erosi,berdungkul, gambaran cobble stone

Dilakukan biopsy pada tiap segmen

KESIMPULAN
Hemmorrhoid eksterna dan interna
Curiga Inflammatory Bowel Disease

SARAN
Tunggu histoPA dan Geneexpert biopsi

Tanda tangan DPJP: Selesai jam: 09.30

Figure 2. Colonoscopy Result

Geneexpert result came out 3 days later, the result was negative. Biopsy result also came out 1 week later, the result was: a colon tissue with ulcers and erosion in some part of it. Crypt was distorted, some of them with neutrophilic inflammatory cell accumulation (crypts abcess). Area between lamina propria and muscle mucosa was stretched, filled with lymphocytic inflammatory cell and plasma cell (basal lymphoplasmacytocite). In lamina propria itself filled with numbers of inflammatory cell, such as lymphocyte, histiocyte, plasma cell, and neutrophil, that pushing crypt away (cryptitis). Fisurre, granuloma, dispasia were not observed. In conclusion, patient was diagnosed with inflammatory disease.
Patient was planned to control 1 week later in outpatient department. But only came once, never return again. Patient still take his medication regularly, some of the symptomatic drugs were stopped by himself. He also added some of herbal medicine. 3 months after discharged, patient symptoms were relieved, never had a lot diarrhea like before. Abdominal pain was gone. The quality of life of the patient were increased significantly in compare his first condition when admitted to hospital.

3. Method

This research was conducted using the case report method. In this case report, we detail the clinical journey of a 70-year-old male patient from Surabaya, East Java, whose inflammatory bowel disease (IBD) diagnosis was followed by the onset of Pemphigus vulgaris (PV) 11 years later. The patient's medical history, including the sequence and nature of symptoms, diagnostic procedures, treatment strategies, and outcomes, was meticulously documented. Data was collected through thorough medical record reviews and patient interviews to ensure accuracy and completeness. This case highlights the intersection of IBD and PV, offering valuable insights into the potential coexistence of multiple autoimmune diseases. The detailed observation and analysis of this unique case contribute to the understanding of the complex interplay between different autoimmune disorders, underscoring the importance of continuous monitoring and comprehensive care in patients with a history of autoimmune diseases.

4. Result and Discussion

Etiology of IBD

Inflammatory bowel disease (IBD) encompasses a group of chronic inflammatory conditions affecting the gastrointestinal tract, with Crohn's disease (CD) and ulcerative colitis (UC) as primary categories. These diseases share some clinical and pathological features while also exhibiting distinct characteristics. The precise pathophysiology of IBD remains incompletely understood. However, it is believed to involve dysregulation of intestinal immune responses, leading to gastrointestinal damage. Genetic predisposition and environmental factors such as alterations in gut microbiota and heightened intestinal permeability contribute significantly to the development of IBD (Bernstein CN et al., 2015).

Table 1. World Health Organization diagnostic criteria for Crohn’s disease

Criteria	Clinical	Radiological	Endoscopy	Biopsy	Resected Specimen
Discontinous or segmental lesions		+	+		+
Cobblestone appearance or longitudinal ulcer		+	+		+
Transmural inflamation	+	+		+	+

Noncaseating granulomas				+	+
Fissures and fistulas	+	+			+
Perianal disorders	+				

In underdeveloped areas, tuberculosis is a common differential diagnosis. IBD susceptibility genes have been discovered in a number of genetic regions. Identifying genetic loci associated with predisposition to Crohn's disease (CD) or ulcerative colitis (UC) is essential for advancing diagnostic markers and potential treatment targets, despite the generally low-risk nature of these loci. These genetic variations show varying distributions across different populations, particularly in regions with diverse ethnic backgrounds (SC Ng et al., 2012; Inadomi JM et al, 2020).

IBD is a chronic, intermittent condition characterized by varying symptoms that can range from mild to severe during relapses and may subside or diminish during periods of remission.

Symptoms depend on the specific part of the digestive tract affected:

a. Chronic diarrhea, often with mucus or blood in the stool
b. Nocturnal diarrhea
c. Urgency and frequency of bowel movements
d. Constipation, especially in cases of rectal involvement (proctitis)
e. Intestinal obstruction, characterized by the absence of gas passage
f. Pain or rectal bleeding during bowel movements
g. Tenesmus (feeling of incomplete bowel movement)
h. Abdominal cramps and pain, typically in the right lower quadrant (common in Crohn's disease) or around the umbilicus or lower left quadrant (common in moderate to severe ulcerative colitis)
i. Nausea and vomiting, more prevalent in Crohn's disease than in ulcerative colitis (Anindita B et al, 2023; Inadomi JM et al, 2020).

Fever, loss of appetite, weight loss, fatigue, night sweats, growth retardation, and primary amenorrhea are common symptoms associated with both ulcerative colitis (UC) and Crohn's disease (CD). Additionally, these inflammatory bowel diseases can manifest with extraintestinal symptoms including musculoskeletal issues such as peripheral or axial arthropathy, cutaneous conditions like erythema nodosum and pyoderma gangrenosum, ocular conditions such as scleritis, episcleritis, and uveitis, as well as hepatobiliary conditions. These symptoms highlight the systemic nature of UC and CD, affecting various organ systems beyond the digestive tract (Bernstein CN et al., 2015).

Patient complained of multiple diarrheas, nausea, vomiting and abdominal pain. He was suffering from diarrhea for a month, the diarrhea was as frequent as seven to eight times per day. There was a lot of mucus and water in his stool, with a little fecal material, bloody stool was come out in occasion.

IBD Diagnostics

Adults with IBD undergo a comprehensive evaluation involving a detailed physical examination and medical history review. Diagnostic tests include blood work, stool examinations, endoscopy with biopsies, and imaging studies to confirm the diagnosis and rule out other conditions. Routine fecal investigations and cultures are conducted to exclude bacterial, viral, or parasitic causes of diarrhea. Testing for Clostridium difficile, even without prior antibiotic use, should be considered promptly. If there is no history of visible blood in the stool, tests for occult blood or fecal leukocytes can support the case for lower endoscopy. These tests are typically unnecessary when lower endoscopy is readily available. Lactoferrin and

alpha-1 antitrypsin tests are utilized primarily to rule out intestinal inflammation rather than as definitive diagnostic tools (Bernstein CN et al, 2015; Inadomi JM et al, 2020).

Intestinal tuberculosis (TB) is typically ruled out in areas where TB prevalence is high using diagnostic methods like the tuberculin purified protein derivative (PPD) skin test and blood tests for PPD antibodies. Interferon gamma release assays (IGRAs) such as QuantiFERON-TB and T-SPOT TB test are also employed due to their high specificity in diagnosing TB, particularly useful in distinguishing gastrointestinal TB (GITB) from Crohn's disease (CD), especially in Asian populations. Concurrent immunosuppression can affect the accuracy of these tests. Clinical symptoms like fever, rectal bleeding, diarrhea, and duration of symptoms are crucial for differentiating CD from GITB. Combining endoscopic examination with basic radiological and laboratory measures (e.g., ASCA, IGRA) is valuable in resource-limited settings for distinguishing between CD and intestinal TB (Bernstein CN et al, 2015; Inadomi JM et al, 2020).

Table 2. Feature for differentiating between UC and CD (CN Bernstein et al., 2015)

	Typical UC features	**Typical CD features**
Clinical	-Frequent small-volume diarrhea with urgency -Predominantly Bloody diarrhea	-Diarrhea accompanied by abdominal pain and malnutrition -Abdominal mass -Perianal lesions
Endoscopic and radiological	-Diffuse superficial colonic inflamation -Involvement of rectum -Shallow erosions and ulcers -Spontaneous bleeding	-Dyscontinous transmural asymmetric lesions -Mainly involving ileum and right-sided colon -Cobblestone appearance -Longitudinal ulcers -Deep fissures
Histopathological	-Diffuse inflammation in mucosa or submucosa -Crypt architecture distortion	-Ganulomatous inflamation -Fissure or aphtous ulcers can be seen, often transmural inflamation
Serological markers	-Antineutrophil cytoplasmic antibody	-Anti-Saccharomyces cerevisiae and other antibodies to microbial antigens

Endoscopy is routinely performed to obtain biopsies for several purposes in diagnosing and managing colitis. Biopsies are taken to assess crypt architectural distortion, crypt atrophy (crypt runting), increased subcryptal space, and basal plasmacytosis, which are characteristic features of chronic colitis rather than acute infectious colitis. The presence of noncaseating granulomas on biopsy may suggest Crohn's disease, while large or necrotic/caseating granulomas should raise suspicion of tuberculosis, especially in TB-endemic regions. Histologic evaluation of biopsies from visually normal appearing mucosa aids in staging the disease comprehensively. In cases where biopsies are taken for dysplasia surveillance or from mass lesions, examination for dysplasia is also conducted. Recognizing lymphocytic or collagenous colitis in a colon that seems normal endoscopically. These diagnoses should be sought in individuals with diarrhea, as they may coexist with smallbowel Crohn's disease (Bernstein CN et al., 2015; Inadomi JM et al, 2020).

Table 3. Distinguishing between tuberculosis (TB) and Crohn’s disease (CD)

Features	**TB**	**CD**

Clinical	-History of TB or recurrent TB -Positive TB contact -Less frequent fistulas, abdominal abcesses or perianal involvement -Abnormal CXR (not universal) -Rarely involves the rectum	-Fistulas -Bowel wall abcesses -Anal perirectal disorders -Bloody stools -Bowel perforation -Recurrence after intestinal resection
Endoscopic	-Superficial, irregular tranverse ulcers without predominant segmental distribution -Pseudopolyps -Caecum > ileum -ICV involved (gaping)	May appear similar to changes in TB TB features less common in intestinal TB (favoring CD): - Longitudinal ulceration - Cobblestoning - Apthous ulceration - Ileum > Caecum - ICV maybe stenosed or ulcerated
Histopathological	-Large, dense, confluent granulomas -Submucosal granulomas -Caseous necrosis and submucosal stenosis -Caseating changes in intestinal wall and mesenteric lymph nodes -Positive for acid-fast bacilli -Disproportionate submucosal inflammation -Bands of epitheloid histocytes lining ulcers	Noncaseous granulomas/necrosis may be found in up to 50%
Cross-sectional imaging	-Caecum > ileum -Asymmetric thickening -Ascites -Small pericaecal nodes -Mesenteric nodes > 1 cm with calcification and central attenuation -Fat wrapping is unusual	- Ileum > caecum - Symmetric thickening - Enlarged mesenteric vascular bundles (comb sign) - Mesenteric nodes 3 – 8 mm - Fat wrapping is common

Colonoscopy and sigmoidoscopy are pivotal procedures used to examine the colon and rectum in patients with inflammatory bowel disease (IBD). These examinations help detect ulcers, inflammation, bleeding, and strictures within the gastrointestinal tract. They also allow for the collection of multiple biopsies from various segments including the colon and terminal ileum, aiding in accurate diagnosis and disease monitoring. In severe or fulminant cases of IBD, the scope of colonoscopy may be limited due to the increased risk of perforation. Nevertheless, these procedures remain essential when standard treatments fail to alleviate symptoms. They are particularly valuable for investigating potential infections such as cytomegalovirus (CMV), especially in patients receiving chronic immunosuppressive therapy, or for confirming Clostridium difficile infection when stool tests yield inconclusive results. Furthermore, screening colonoscopy for dysplasia surveillance is recommended after 8 years of ulcerative colitis (UC) or Crohn's colitis to monitor for any signs of precancerous changes in the colon

(Bernstein CN et al., 2015; Inadomi JM et al., 2020). These diagnostic and surveillance measures play a critical role in managing and improving outcomes for patients with IBD.

Before confirming a diagnosis of inflammatory bowel disease (IBD), it is essential to exclude intestinal tuberculosis (TB). While a definitive link between Mycobacterium paratuberculosis and IBD remains unestablished, TB must be ruled out, especially in high-risk groups or regions. In such cases, a trial of anti-TB therapy may be warranted, and corticosteroids should be avoided. TB symptoms typically include fever, abdominal pain, and diarrhea, whereas Crohn's disease (CD) symptoms commonly involve abdominal pain, diarrhea, and occasionally fever. CD often presents with periods of remission and relapse, contrasting with TB's typically continuous course. Ascites and hepatosplenomegaly are more characteristic of TB but uncommon in CD (Bernstein CN et al., 2015; Inadomi JM et al., 2020).
Colonoscopic result: Anal canal: internal and external hemmoroid was observed. Rectosigmoid: mucosa edema, mucosal erosion was observed, with stooped surface and ulcus. Colon descenden: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Colon transverse: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Colon ascenden: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Caecum: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Ileocal junction: mucosal edema, mucosal erosion was observed, with stooped surface and cobblestone appearance. Geneexpert result was negative. Biopsy result was: a colon tissue with ulcers and erosion in some part of it. Crypt was distorted, some of them with neutrophilic inflammatory cell accumulation (crypts abcess). Area between lamina propria and muscle mucosa was stretched, filled with lymphocytic inflammatory cell and plasma cell (basal lymphoplasmacytocite). In lamina propria itself filled with numbers of inflammatory cell, such as lymphocyte, histiocyte, plasma cell, and neutrophil, that pushing crypt away (cryptitis).

IBD Therapy and Management
Aminosalicylates are primary anti-inflammatory compounds used in the treatment of inflammatory bowel disease (IBD). Common members of this class include 5-aminosalicylic acid (5-ASA) and its derivatives such as mesalazine (mesalamine). Oral formulations available in North America and Western Europe include sulfasalazine, mesalamine (various forms like pills, granules, or multi-matrix preparations), olsalazine, mesalazine, and balsalazide. Rectal therapies consist of mesalamine enemas (liquid or foam) and suppositories. Typically, dosages range from 2.0 to 4.8 grams per day for active disease and 2 grams per day for maintenance, with limited evidence suggesting additional benefit above 2 grams per day.
Corticosteroids provide potent anti-inflammatory effects and rapid symptom relief. They induce remission in patients with Crohn's disease (CD) during initial presentations or single inflammatory exacerbations within a 12-month period but are not used for maintaining remission. Administration routes vary based on disease location and severity: intravenous options include methylprednisolone and hydrocortisone, while oral options include prednisone, prednisolone, budesonide, and dexamethasone. Rectal corticosteroid formulations like enemas, foam preparations, and suppositories are also available (Bernstein CN et al., 2015; Inadomi JM et al., 2020).
In cases where there are two or more inflammatory exacerbations within a year, or if corticosteroid therapy cannot be tapered off successfully, additional medications such as azathioprine or mercaptopurine may be considered in conjunction with standard corticosteroids or budesonide to induce remission in Crohn's disease (CD). For patients with predictors of poor outcomes identified at the time of diagnosis—such as age over 40, initial treatment with corticosteroids, presence of perianal disease, smoking history, or perforating disease

characteristics—more aggressive treatment approaches may be warranted to manage the disease effectively and prevent complications. Moreover, patients with comorbidities are particularly susceptible to gastrointestinal inflammation, necessitating a comprehensive management approach tailored to their individual health needs (Bernstein CN et al., 2015; Inadomi JM et al., 2020; Syafei AR et al., 2022). These strategies aim to achieve remission, prevent disease progression, and enhance quality of life for individuals living with CD.

Metronidazole and ciprofloxacin are commonly used antibiotics in the management of Crohn's disease (CD), particularly for treating complications like perianal disease, fistulas, inflammatory masses, and bacterial overgrowth in the presence of strictures. Despite being frequently prescribed as first-line therapy for perianal fistulas, there is a lack of large randomized controlled trials demonstrating their efficacy in this specific context. It's important to note the increased risk of Clostridium difficile-associated illness (CDAD) associated with antibiotic use. Patients experiencing diarrhea should undergo testing for C. difficile and other fecal bacteria to guide appropriate management (Bernstein CN et al., 2015; Inadomi JM et al., 2020).

Changes in gut flora can contribute to the onset or exacerbation of inflammatory bowel disease (IBD). Bacterial biofilms may develop, potentially leading to antimicrobial resistance. Despite the widespread use of probiotics by many patients, there is insufficient evidence supporting their effectiveness in treating either ulcerative colitis (UC) or Crohn's disease (CD). One specific probiotic combination, VSL#3, consisting of eight probiotic strains, has shown promise in initiating and maintaining remission in UC, with effectiveness comparable to 5-aminosalicylic acid (5-ASA). However, its benefit in CD has not been well-established. VSL#3 has been studied in multiple trials, including studies from Italy and the UK, demonstrating its ability to reduce flare-ups of pouchitis, a condition associated with UC (Bernstein CN et al., 2015; Inadomi JM et al., 2020; Kalisah J et al., 2022).

Management strategies for inflammatory bowel disease (IBD) encompass various supportive treatments alongside medical therapies. Antidiarrheals like loperamide (Imodium) are recommended for non-fulminant colitis, while cholestyramine is considered if ileal resection has been performed. Analgesics such as acetaminophen are preferred; however, narcotic usage should be avoided due to associated risks in IBD patients, including increased mortality. Nutritional supplementation is crucial for malnourished individuals or during periods of reduced oral intake. Vitamin B12 supplementation is indicated for deficiency, and vitamin D supplements are recommended, particularly in regions with limited sun exposure or for patients using thiopurines and sunscreen. Corticosteroid users should also routinely take vitamin D and calcium supplements. For chronic iron deficiency anemia intolerant to oral iron, parenteral iron therapy is advised (Bernstein CN et al., 2015; Inadomi JM et al., 2020).

Patient was given therapy as follows: oral metronidazole 500mg every 8 hours, oral mesalazine 500mg every 8 hours, oral ondansetron 4mg every 12 hours, oral omeprazole 20mg every 2 hours, oral probiotic every 8 hours, oral methylprednisolone 16mg every 8 hours.

Patients with inflammatory bowel disease (IBD) are at an elevated risk of developing additional autoimmune disorders, as evidenced by several studies. A large US cross-sectional study conducted by Weng et al. reported increased likelihoods of asthma (OR 1.5, 95% CI 1.4–1.6), psoriasis (OR 1.7, 95% CI 1.5–2.0), rheumatoid arthritis (OR 1.9, 95% CI 1.5–2.3), and multiple sclerosis (OR 2.3, 95% CI 1.6–3.3) in IBD patients compared to those without IBD. Similar findings were corroborated by Cohen, who analyzed US claims datasets and found significantly higher risks of rheumatoid arthritis, multiple sclerosis, and ankylosing spondylitis among IBD patients. Previous UK-based population studies also observed an increased incidence of multiple sclerosis among individuals with IBD. Furthermore, a UK Clinical Practice Research Datalink (CPRD) study indicated a slightly elevated risk of new autoimmune diseases in IBD patients compared to those without IBD. The severity of IBD appeared to

correlate with higher autoimmune disease risks, and there was also a noted association between current antibiotic use and a modestly increased relative risk (Wilson JC et al., 2015).

Pemphigus vulgaris (PV) is a chronic autoimmune disease affecting mucocutaneous tissues, characterized by antibodies targeting desmoglein 1 and desmoglein 3, which disrupt the keratinocyte cell membrane. It is the most prevalent and severe form of pemphigus, initially presenting with blisters and erosions on the oral mucosa, followed by lesions and vesicles on other mucosal and skin surfaces, and potentially spreading throughout the body. PV is frequently associated with multiple autoimmune conditions, necessitating investigation for concurrent autoimmune comorbidities in affected patients. Previous studies have shown that 27.8% of PV cases exhibit concurrent autoimmune diseases, with type 1 diabetes mellitus being the most commonly observed comorbidity, underscoring the immune dysregulation underlying skin lesions in PV (Komoni F, et al. 2021).

Komoni et al. (2021) reported a rare case of Crohn's disease (CD) co-occurring with pemphigus vulgaris (PV), which is not commonly documented in the literature. The case involved a patient with a longstanding history of PV, who was later diagnosed with CD ten years after the initial PV diagnosis. While associations between CD and PV are not well-established in medical literature, cutaneous manifestations such as erythema nodosum are more frequently observed in inflammatory bowel disease (IBD), with an incidence ranging from 4% to 6%. Pyoderma gangrenosum, another skin manifestation in IBD, has a lower incidence of 0.6% to 2.2%. Pyostomatitis vegetans, characterized by pustules and ulcerations in the oral buccal mucosa and lips, is also a rare manifestation. Cutaneous polyarteritis nodosa is exceedingly rare in IBD, with fewer than 20 cases reported in the literature (Komoni F, et al. 2021).

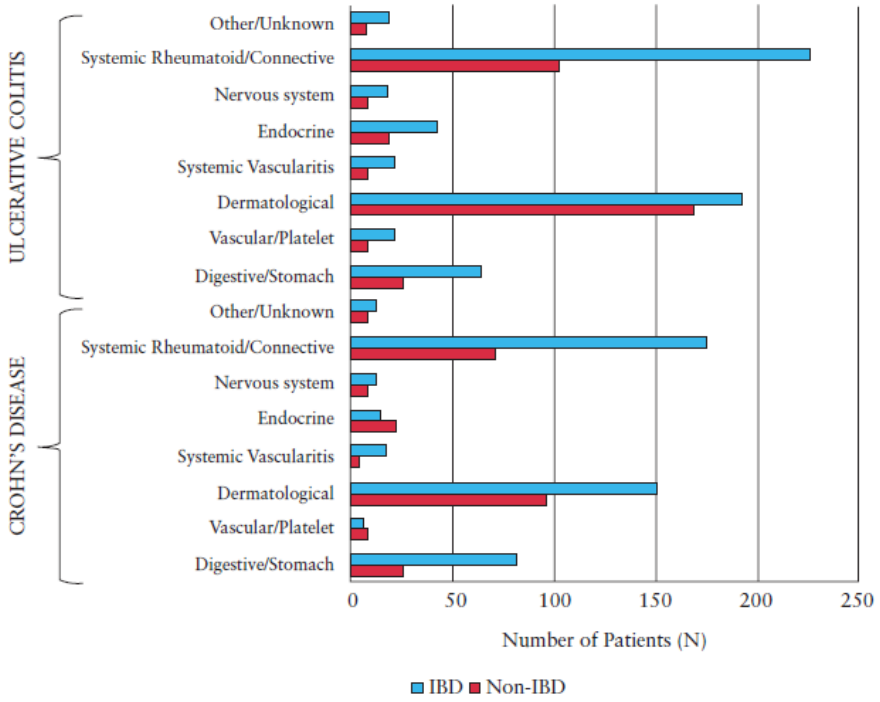

Figure 3. Number of autoimmune disease events identified in the inflammatory bowel disease (IBD) and non-IBD comparison group categorised into involved body system and stratified by IBD type (Wilson JC et al, 2015)

In 2016, Alatas et al. documented a case involving a 39-year-old Turkish man who presented to a polyclinic with erythema on his trunk and shoulders, accompanied by pruritus. The patient had a history of Crohn's disease spanning 10 years. Histopathological examination of a blister revealed pemphigus vulgaris. This case highlights the importance for physicians to be aware

that Crohn's disease may be associated with autoimmune skin diseases such as pemphigus vulgaris (Alatas ET et al., 2016).

In 2017, Kridin et al. conducted a large-scale population-based study involving 1985 pemphigus patients and 9874 controls. The study found a higher prevalence of ulcerative colitis (UC) in pemphigus patients compared to controls (0.9% vs. 0.4%, respectively; p=0.004). In multivariate analysis, pemphigus was independently associated with UC (odds ratio 1.9, 95% confidence interval 1.1–3.3, p=0.034). In 2018, another study by Kridin et al. investigated the association between Crohn's disease (CD) and pemphigus using the same cohort. The prevalence of CD was similar between pemphigus patients and controls (0.4% vs. 0.3%, respectively; odds ratio 1.2; 95% CI: 0.5–2.5; p=0.688). However, in an age-stratified analysis, a significant association between pemphigus and CD was observed in patients younger than 40 years (2.1% vs. 0.4%, respectively; OR: 5.1; 95% CI: 1.0–25.7; p=0.027). After adjusting for potential confounding factors in multivariate analysis, no independent association between pemphigus and CD was found (OR: 0.9; 95% CI: 0.4–2.0; p=0.828). Therefore, unlike ulcerative colitis, Crohn's disease was not found to be associated with pemphigus (Kridin K et al., 2017; Kridin K et al., 2018).

In a study by Chen et al. in 2020, the coexistence of inflammatory bowel disease (IBD) and bullous pemphigoid (BP) was investigated. The study included 20 cases of IBD among BP patients, with ulcerative colitis (17 cases) being the most prevalent subtype. This represented a significantly higher prevalence compared to the control group, which had 33 IBD cases. On multivariate analysis, ulcerative colitis was found to be independently associated with bullous pemphigoid (adjusted odds ratio 3.60, 95% confidence interval 1.91–6.77, $p < 0.001$). The study did not find any association between treatment for IBD and the development of BP. However, information regarding diet, lifestyle, alcohol consumption, and smoking habits was not available for analysis. Therefore, the conclusion drawn was that ulcerative colitis is independently associated with bullous pemphigoid (Chen YJ et al., 2020).

The patient had an interesting history of past illness. Patient was a survivor of pemphigus vulgaris, which happened 11 years ago. He was admitted to Rumah Sakit Dokter Soetomo Surabaya, under the care of dermatolo-venereology department.

5. Conclusion

A case was reported of a 70-year-old man from Surabaya, East Java, who survived Pemphigus Vulgaris and later developed Inflammatory Bowel Disease (IBD). The patient had a history of Pemphigus Vulgaris, diagnosed 11 years prior, which had since been managed successfully. Recently, he presented with gastrointestinal symptoms that led to a colonoscopy, revealing a distinctive cobblestone appearance throughout the colon, caecum, and ileocaecal junction. Biopsy findings further confirmed the presence of ulcers, cryptitis, and crypt abscesses, consistent with a diagnosis of IBD. This complex case highlights the potential for autoimmune diseases like Pemphigus Vulgaris to predispose individuals to other inflammatory conditions, emphasizing the need for vigilant long-term monitoring and comprehensive care strategies for survivors of such chronic illnesses. The patient was promptly treated with a regimen of oral mesalazine, 500mg every eight hours, and methylprednisolone, 16mg every eight hours. This treatment effectively alleviated his symptoms, allowing for significant improvement. Given the positive response to the medication, the patient requested to be discharged. His case underscores the importance of timely and appropriate therapeutic interventions in managing IBD, particularly in patients with a history of severe autoimmune disorders. Continued follow-up and tailored treatment plans are crucial in ensuring long-term remission and quality of life for patients facing such multifaceted health challenges. This case serves as a reminder of the

intricate interplay between different autoimmune diseases and the importance of personalized medical care.

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