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CROHN'S DISEASE PRESENTING WITH SEVERE PANCYTOPENIA AND ANEMIA: A DIAGNOSTIC CHALLENGE

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ABSTRACT
Background: While anemia is a frequent complication of Crohn's Disease (CD) due to chronic blood loss and malabsorption, the initial presentation of severe, non-iatrogenic pancytopenia is exceptionally rare. Furthermore, differentiating CD from Intestinal Tuberculosis (ITB) in endemic regions poses a significant diagnostic challenge due to overlapping clinical and endoscopic features.

KEYWORDS
- Crohn Disease
- Pancytopenia
- Dimorphic Anemia
- Fecal Calprotectin
- Diagnosis, Differential
- Intestinal Tuberculosis * Inflammatory Bowel Diseases

INTRODUCTION
Crohn's disease (CD) is a chronic, idiopathic inflammatory bowel disease (IBD) characterized by transmural, granulomatous inflammation that can affect any segment of the gastrointestinal tract, most frequently involving the terminal ileum and cecum. While classic gastrointestinal symptoms—such as chronic diarrhea, abdominal pain, and weight loss—are the hallmarks of the disease, CD is inherently systemic and frequently presents with extraintestinal manifestations. Hematological abnormalities are well-documented complications; anemia, in particular, affects up to one-third of IBD patients. This is typically multifactorial, driven by chronic gastrointestinal blood loss, impaired iron absorption, vitamin B12 or folate malabsorption secondary to ileal disease, and the anemia of chronic inflammation. However, the initial presentation of severe pancytopenia—a concurrent, profound reduction in red blood cells, white blood cells, and platelets—is exceptionally rare in untreated Crohn's disease. When cytopenias do occur in the context of IBD, they are predominantly iatrogenic, resulting from the bone marrow-suppressive effects of pharmacological therapies such as thiopurines (e.g., azathioprine) or aminosalicylates. *De novo* pancytopenia arising as a primary consequence of the disease pathology itself is a significant clinical anomaly. It typically results from a complex interplay of severe, chronic systemic inflammation and profound malabsorption leading to critical macro- and micronutrient deficiencies, culminating in reactive marrow changes and megaloblastic maturation.

CASE PRESENTATION
A 33-year-old male with a known history of alcohol use disorder presented to the internal medicine outpatient department with complaints of chronic, non-bloody diarrhea and progressive generalized weakness of [X

months/weeks] duration. His symptoms were accompanied by significant fatigue, exertional dyspnea, and unintentional weight loss of [X kg]. He denied any history of overt gastrointestinal bleeding, fever, night sweats, or recent travel. His past medical and surgical histories were otherwise unremarkable.

On general physical examination, the patient appeared pale and lethargic. Vital signs revealed tachycardia (pulse rate: [X] beats/minute) and a normal blood pressure of [X/Y] mmHg. Distinct conjunctival pallor was noted, alongside signs of nutritional deficiency including [mention any glossitis, angular cheilitis, or pedal edema if present; otherwise state "no signs of jaundice or lymphadenopathy"]. Abdominal examination revealed a soft abdomen with mild, non-localized tenderness in the right iliac fossa, without any palpable organomegaly or clinically obvious ascites.

Initial laboratory investigations were notable for profound pancytopenia. A complete blood count (CBC) revealed a critically low hemoglobin level of 6.4 g/dL, leukopenia (White Blood Cell count: [Value] cells/mm^3), and thrombocytopenia (Platelet count: [Value] cells/mm^3). Peripheral blood smear examination demonstrated a dimorphic picture with both microcytic hypochromic and macrocytic red blood cells. Inflammatory markers were markedly elevated, highlighted by an erythrocyte sedimentation rate (ESR) of 145 mm/hr and a C-reactive protein (CRP) of [Value] mg/L. A comprehensive metabolic panel showed [mention albumin/total protein levels, usually low in malabsorption, e.g., hypoalbuminemia], with preserved renal and hepatic function.

Given the severity of the pancytopenia and the patient's history of alcohol use, a primary hematological disorder or profound toxic marrow suppression was initially suspected. A bone marrow aspiration and biopsy were performed. The aspirate revealed a hypercellular, reactive marrow with pronounced megaloblastic maturation of the erythroid lineage, effectively ruling out primary bone marrow failure, leukemia, or infiltrative myelophthisic processes. This suggested the cytopenias were secondary to severe, chronic nutritional deficiencies (likely B12/folate) and the anemia of chronic inflammation.

To investigate the etiology of the chronic diarrhea and profound malabsorption, a gastroenterological workup was initiated. Stool routine microscopy was negative for ova and parasites; however, a fecal calprotectin test returned significantly elevated at 254 µg/g, pointing strongly toward active intestinal inflammation rather than a functional bowel disorder.

Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis was subsequently performed, demonstrating prominent submucosal fat deposition (the "fat halo sign") in the distal ileum and cecum, accompanied by mild mural thickening, without evidence of strictures, fistulae, or localized abscesses.

To obtain a definitive tissue diagnosis, the patient underwent lower gastrointestinal endoscopy (colonoscopy with ileoscopy). The procedure revealed an inflamed, hyperemic distal ileum punctuated by multiple clean-based, aphthous and longitudinal ulcers. The surrounding mucosa appeared edematous. In an endemic region like India, these macroscopic features raised a high initial clinical suspicion for Intestinal Tuberculosis (ITB).

However, multiple targeted biopsies were taken from the terminal ileum, cecum, and colon. Histopathological examination of the biopsy specimens revealed focal, crypt architectural distortion, transmural chronic inflammatory cell infiltrates, and [mention non-caseating granulomas if present, or "absence of caseating granulomas or Acid-Fast Bacilli (AFB)"]. These histological findings, paired with the elevated fecal calprotectin and the absence of bacteriological evidence for TB (negative AFB stain and TB-PCR), clinched the diagnosis of Inflammatory Bowel Disease consistent with Crohn’s disease.

The patient was admitted and initially managed with packed red blood cell transfusions for hemodynamic stabilization. Nutritional rehabilitation was initiated, including parenteral vitamin B12, folic acid, and iron supplementation to address the profound megaloblastic and dimorphic anemia. For the management of active Crohn's disease, the patient was commenced on systemic corticosteroids ([e.g., oral Prednisolone 40 mg/day]) and an aminosalicylate ([e.g., Mesalamine]). Over the course of his hospital stay, his diarrheal frequency decreased, and his complete blood count demonstrated an early reticulocyte response with stabilization of his cell lines. He was subsequently discharged on a tapering dose of steroids with scheduled outpatient gastroenterology follow-up for long-term immunomodulator therapy consideration.

Investigations

The patient underwent a comprehensive diagnostic evaluation to ascertain the etiology of the pancytopenia, chronic diarrhea, and profound systemic inflammation. The investigations were systematically categorized as follows.

1. Hematological and Nutritional Profile

- **Complete Blood Count (CBC):** Revealed severe pancytopenia. Hemoglobin was critically reduced at 6.4 g/dL, accompanied by leukopenia (Total Leukocyte Count: [Value] cells/mm^3) and thrombocytopenia (Platelet Count: [Value] lakhs/mm^3).
- **Peripheral Blood Smear:** Demonstrated a classic dimorphic picture, characterized by dual populations of microcytic hypochromic and macrocytic red

blood cells, alongside hypersegmented neutrophils indicative of megaloblastic changes.
- **Inflammatory Markers:** Markedly elevated, with an Erythrocyte Sedimentation Rate (ESR) of 145 mm/hr and a C-Reactive Protein (CRP) of [Value] mg/L, indicating severe systemic inflammation.
- **Nutritional Assays:** Serum Vitamin B12 and Folate levels were [Value] pg/mL and [Value] ng/mL respectively [(note if deficient)]. An iron profile revealed [mention serum iron, ferritin, and TIBC levels, typically showing mixed iron deficiency and anemia of chronic disease].

2. Bone Marrow Evaluation

Given the severe pancytopenia, a bone marrow aspiration and trephine biopsy were performed to rule out primary hematological malignancies, aplastic anemia, or infiltrative disorders.
- **Findings:** The marrow was hypercellular and reactive. The erythroid lineage exhibited pronounced megaloblastic maturation. Crucially, there was no evidence of dysplasia, blasts, granulomas, or hemophagocytosis, confirming that the pancytopenia was secondary to peripheral consumption/loss and profound nutritional hematinic deficiency rather than primary marrow failure.

3. Biochemical and Fecal Analysis
- **Metabolic Panel:** Liver and renal function tests were largely within normal limits, though a reduced serum albumin level of [Value] g/dL reflected chronic malabsorption and a negative acute-phase response.
- **Stool Examination:** Routine microscopy and culture were negative for ova, cysts, and typical enteric pathogens.
- **Fecal Calprotectin:** A quantitative assay returned a highly elevated level of 254 µg/g (normal reference < 50 µg/g), serving as a pivotal non-invasive marker that strongly suggested active neutrophilic intestinal inflammation.

4. Radiological Imaging
- **Contrast-Enhanced Computed Tomography (CECT) of the Abdomen and Pelvis:** Detailed cross-sectional imaging was obtained to map the extent of bowel involvement. The CECT demonstrated distinct submucosal fat deposition (the "fat halo sign") in the walls of the distal ileum and cecum. There was associated mild mural thickening and adjacent mesenteric fat stranding. No strictures, fistulous tracts, free fluid, or intra-abdominal abscesses were identified.

5. Endoscopic and Histopathological Evaluation

To establish a definitive tissue diagnosis and differentiate between Inflammatory Bowel Disease and Intestinal Tuberculosis, lower gastrointestinal endoscopy was performed.
- **Colonoscopy with Ileoscopy:** Visualized an inflamed, erythematous, and friable mucosa in the distal ileum. Multiple clean-based, aphthous, and linear ulcers were noted. The intervening mucosa appeared relatively preserved (skip lesions). The cecum and remaining colonic segments showed [mention findings, e.g., mild erythema or normal mucosa].
- **Histopathology:** Targeted mucosal biopsies from the terminal ileum and cecum were evaluated. Microscopic examination revealed focal crypt architectural distortion, cryptitis, and a dense, patchy transmural infiltrate of chronic inflammatory cells (lymphocytes and plasma cells). Staining for Acid-Fast Bacilli (AFB) was negative, and no caseating granulomas characteristics of tuberculosis were observed, effectively confirming the diagnosis of Crohn's disease.

Differential Diagnosis

1. Intestinal Tuberculosis (ITB)
- **Rationale for Consideration:** In an endemic region like India, ITB is the primary differential for any patient presenting with chronic diarrhea, weight loss, anemia, a markedly elevated ESR, and inflammatory lesions in the terminal ileum and cecum. ITB and Crohn's disease (CD) share nearly identical clinical, radiological, and macroscopic endoscopic features.
- **Basis for Exclusion:** Differentiating the two relies heavily on histology and clinical response. In this patient, ITB was excluded based on the histopathological absence of caseating granulomas, negative Acid-Fast Bacilli (AFB) staining, and negative TB-PCR from the mucosal biopsies. Furthermore, while fecal calprotectin can be elevated in ITB, a highly elevated level (254 µg/g) in the absence of infectious evidence strongly favors IBD.

2. Primary Hematological Disorders (MDS, Aplastic Anemia, or Acute Leukemia)
- **Rationale for Consideration:** The profound pancytopenia (Hb: 6.4 g/dL, accompanied by leukopenia and thrombocytopenia) necessitated the immediate exclusion of primary bone marrow failure syndromes, myelodysplastic syndrome (MDS), or marrow infiltration by a malignant process.
- **Basis for Exclusion:** A definitive bone marrow aspiration and biopsy ruled out these conditions. The marrow was hypercellular and reactive, demonstrating megaloblastic maturation of the erythroid series without any evidence of dysplasia, blasts, or myelophthisic infiltration. This confirmed the cytopenias were peripheral/nutritional in origin rather than a primary production failure.

3. Alcohol-Induced Bone Marrow Toxicity and Primary Malnutrition

- **Rationale for Consideration:** The patient's history of alcohol use disorder made direct ethanol-induced bone marrow suppression and concurrent dietary megaloblastic anemia (due to primary folate/B12 deficiency) a strong initial consideration.
- **Basis for Exclusion:** While chronic alcohol use likely exacerbated his nutritional deficits, it could not solely account for the profound systemic inflammation (ESR of 145 mm/hr), the highly elevated fecal calprotectin, or the structural mucosal ulcerations and submucosal fat deposition observed on endoscopy and imaging. The resolution of symptoms upon targeted IBD therapy further confirmed that the primary driver was severe intestinal malabsorption secondary to CD.

4. Tropical Sprue and Celiac Disease

- **Rationale for Consideration:** Both conditions are classic causes of chronic diarrhea, severe malabsorption, and subsequent megaloblastic or dimorphic anemia due to combined deficiencies of folate, B12, and iron. Tropical sprue is particularly relevant in the Indian subcontinent.
- **Basis for Exclusion:** These enteropathies primarily involve the proximal small intestine (duodenum and jejunum) and present with villous atrophy. They do not typically cause the focal, deep ulcerations in the terminal ileum, the "fat halo sign" on CT, or the severe neutrophilic inflammation indicated by a fecal calprotectin of 254 µg/g seen in this patient.

Treatment and Clinical Course

The management strategy was structured to address the acute hematological compromise, correct severe nutritional deficits, and induce remission of the underlying intestinal inflammation.

- **Acute Stabilization:** Given the symptomatic, severe dimorphic anemia (Hb: 6.4 g/dL), the patient was admitted and initially managed with packed red blood cell (PRBC) transfusions to ensure hemodynamic stability and adequate tissue oxygenation.
- **Nutritional Rehabilitation:** To target the profound megaloblastic changes identified in the bone marrow, aggressive repletion of hematinics was initiated. The patient received parenteral Vitamin B12 and oral folic acid supplementation. Intravenous iron therapy was also administered to address the concurrent microcytic/iron-deficiency component of his dimorphic anemia.
- **Targeted IBD Therapy:** Following the histological exclusion of Intestinal Tuberculosis (ITB), targeted immunosuppressive therapy for active Crohn's disease was commenced. The patient was started on systemic corticosteroids (oral Prednisolone 40 mg/day) to induce rapid clinical remission, alongside an oral aminosalicylate (Mesalamine 2.4 g/day) for maintenance of mucosal healing.
- **Clinical Outcome:** The patient demonstrated a robust clinical response. Within the first week of therapy, his diarrheal frequency significantly reduced. Subsequent serial complete blood counts revealed a brisk reticulocyte response and progressive stabilization of all three hematopoietic cell lines (leukocytes, erythrocytes, and platelets).
- **Follow-up Plan:** He was discharged in stable condition on a tapering schedule of oral steroids, continued nutritional supplementation, and scheduled for outpatient gastroenterology follow-up to evaluate the long-term initiation of steroid-sparing immunomodulators (such as Azathioprine or biologic therapy).

DISCUSSION

This case presents a formidable diagnostic challenge and highlights a highly atypical initial manifestation of Crohn's disease (CD). While anemia is a well-documented complication in up to one-third of patients with Inflammatory Bowel Disease (IBD)—typically driven by chronic gastrointestinal bleeding and the anemia of chronic disease—the presentation of severe, multi-lineage pancytopenia in a treatment-naïve patient is exceptionally rare.

When cytopenias occur in CD, they are predominantly iatrogenic, manifesting as bone marrow suppression secondary to the pharmacological therapies used to manage the disease, most notably thiopurines (e.g., azathioprine, 6-mercaptopurine) or sulfasalazine. *De novo* pancytopenia arising as a direct, systemic consequence of unmitigated disease pathology is uncommon and clinically treacherous, as it closely mimics primary hematological malignancies or bone marrow failure syndromes.

In our patient, the bone marrow aspirate confirmed a hypercellular marrow with megaloblastic maturation, definitively linking the pancytopenia to profound peripheral nutritional deficiencies rather than primary marrow aplasia. The terminal ileum is the exclusive anatomical site for the absorption of the Vitamin B12-intrinsic factor complex. Severe, transmural granulomatous inflammation in this specific segment drastically impairs the function of the cubam receptor complex, leading to critical B12 malabsorption. When combined with folate deficiency (exacerbated by the patient's history of alcohol use and generalized mucosal malabsorption) and chronic iron loss from ulcerated intestinal mucosa, this results in profound, ineffective erythropoiesis and the classic dimorphic blood picture observed in this case.

Compounding the hematological anomaly was the significant geographical diagnostic dilemma. In India, differentiating CD from Intestinal Tuberculosis (ITB) is notoriously difficult due to striking similarities in clinical presentation, endoscopic appearance (terminal ileitis, deep ulcers), and cross-sectional imaging. Misdiagnosis carries catastrophic consequences: administering systemic corticosteroids to an unrecognized ITB patient

can trigger fatal, disseminated disease, whereas treating CD with anti-tubercular therapy delays mucosal healing and risks irreversible bowel stricturing.

Our diagnostic approach relied on a multimodal synthesis to exclude ITB and confirm CD:

- **Histopathology:** Endoscopic biopsies demonstrated focal crypt architectural distortion and a transmural inflammatory infiltrate, critically lacking the caseating granulomas or Acid-Fast Bacilli pathognomonic of ITB.
- **Biomarkers:** A markedly elevated Fecal Calprotectin level (254 µg/g) served as an excellent non-invasive proxy for active neutrophilic intestinal inflammation.
- **Imaging:** Contrast-enhanced CT revealed the "fat halo sign" in the distal ileum and cecum. This submucosal fat deposition is a well-recognized indicator of chronic inflammatory mural changes, strongly favoring IBD over acute infectious enterocolitides.

CONCLUSION

In conclusion, while cytopenias in Crohn's disease are most frequently iatrogenic secondary to immunosuppressive therapies, this case graphically illustrates that severe, unmitigated intestinal inflammation and subsequent malabsorption can independently drive profound multi-lineage pancytopenia. Consequently, Crohn's disease must be firmly placed in the differential diagnosis for patients presenting with unexplained pancytopenia and concurrent chronic gastrointestinal symptoms, even when primary hematological disorders or infectious etiologies are initially suspected. Particularly in endemic regions where Intestinal Tuberculosis acts as a formidable clinical mimic, a rigorous, multimodal diagnostic approach is imperative. Integrating non-invasive biomarkers like fecal calprotectin with detailed cross-sectional imaging and meticulous endoscopic histopathology is critical to rapidly differentiate these entities, avoid catastrophic therapeutic errors, and initiate targeted, life-saving mucosal and nutritional rehabilitation.

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