Extraintestinal Granuloma in Crohn's Disease

Gino Rony Philip[1], Sandesh K[1], Ramu M[1], Deni Joseph[1], Sheela Varghese[2], Lalkrishna U[1], Saji Sebastian[1], Aswin Kumar[1], Harikrishnan S[1], Milan George[1], Gaurav Khatana[1]

[1]Department of Medical Gastroenterology, Government Medical College, Kottayam, India
[2]Department of Pathology, Government Medical College, Kottayam, India

Cite this article as: Philip et al. Extraintestinal Granuloma in Crohn's Disease. *J Enterocolitis.* 2025;4(2):40-43.

Corresponding author: Gino Rony Philip, e-mail: ginorony@gmail.com

Received: May 02, 2025 **Accepted:** May 06, 2025

DOI:10.14744/Jenterocolitis.2025.96953

Abstract

Objective: Crohn's disease is a subtype of inflammatory bowel disease characterized by transmural inflammation of the bowel wall and granuloma formation. There is neutrophilic infiltration of the crypts and lymphoid infiltration into all three layers of the intestines in varying proportions, leading to ulcers, fissures, and fistulae. These granulomas consist of a vague collection of lymphocytes, macrophages, and histiocytes. However, granulomas are not specific to Crohn's disease but contribute to diagnosis when paired with clinical presentation, endoscopic findings, additional histological evidence, and cross-sectional imaging. Here, we present three cases of patients with Crohn's disease exhibiting extraintestinal granulomas in the liver, lymph nodes, and skin.
Keywords: Crohn's disease, diarrhea, granuloma.

INTRODUCTION

Crohn's disease is a subtype of inflammatory bowel disease that may involve any part of the gastrointestinal tract, from the mouth to the anal canal. The affliction may be transmural and granulomatous, distinguishing it from ulcerative colitis, which is usually limited to the mucosa.[1] Crohn's disease typically presents with chronic diarrhea, weight loss, perianal disease, anemia, protein-losing enteropathy, or abdominal pain.[2] Because the disease is transmural, Crohn's disease often results in complications such as fistulae, strictures, and deep ulcers.[3]

Crohn's disease may also affect extraintestinal locations. Nearly half of all Crohn's disease patients experience an extraintestinal manifestation of the disease at some point.[4] These extraintestinal manifestations (EIMs) may be either specific—meaning they are histologically supportive of Crohn's disease—inflammatory, which are due to the inflammatory cascade associated with Crohn's disease, or associated, representing other manifestations linked to HLA association.[5]

Specific EIMs may be metastatic (affecting anatomically distinct sites such as the liver, lymph nodes, and lungs) or represent direct extensions of the disease, which are usually dermatologic.

Hepatic manifestations of inflammatory bowel disease are multifaceted and may include steatosis, granulomatous hepatitis, primary sclerosing cholangitis (PSC), autoimmune hepatitis overlap, cholelithiasis, hepatic amyloidosis, and treatment-related complications such as drug-associated liver injury and secondary infections, including tuberculosis and liver abscess.[6]

Granulomas in Crohn's disease are typically detected in 10–40% of cases and are more easily appreciated in surgical resection specimens.[7,8] Discussed below are three different cases of Crohn's disease in which extraintestinal granulomas were identified on biopsy.

Case One

A 50-year-old female was diagnosed three years ago with Crohn's colitis during an evaluation for chronic diarrhea. She was started on azathioprine, which she took for six months. Subsequently, she developed jaundice with elevated alkaline phosphatase levels. Ultrasound revealed a liver with grade 1 fatty changes and no biliary system dilatation. A liver biopsy was not performed at that time. The cholestatic jaundice was attributed to azathioprine. Azathioprine was discontinued, and she defaulted on treatment for one year.

She later presented again with chronic diarrhea and weight loss. At present, her liver function tests were normal (Bilirubin 1.1 mg/dL, Albumin 3.5 g/dL, Alkaline phosphatase 122 IU/dL). An abdominal ultrasound showed increased liver echotexture and a liver stiffness measurement of 9.2 kPa.

Her viral markers, autoimmune hepatitis (AIH) profile, ceruloplasmin, and iron studies were within normal limits. IgG levels were elevated at 1834 mg/dL. A liver biopsy was performed.

The liver biopsy showed severe macrovesicular steatosis (approximately 90%) and moderate portal inflammation with occasional non-necrotizing granulomas, consistent with hepatic changes associated with Crohn's disease (Figure 1,2).

She was treated with infliximab at a dose of 5 mg/kg. However, she has attained only a partial response at 14 weeks, with occasional persistence of small bowel diarrhea, but improvement in C-reactive protein (CRP) levels and anemia.

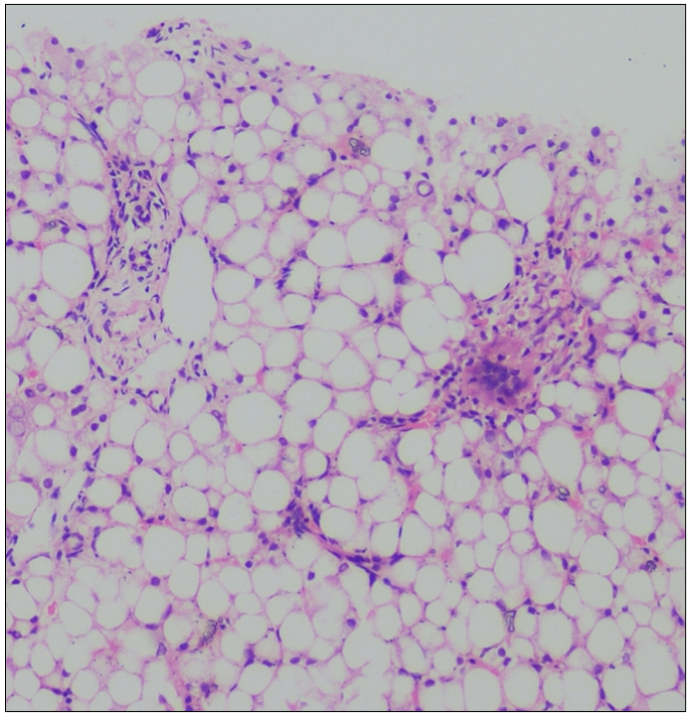

Figure 1. Liver biopsy showing severe macrovesicular steatosis and moderate portal inflammation with occasional non-necrotizing granulomas.

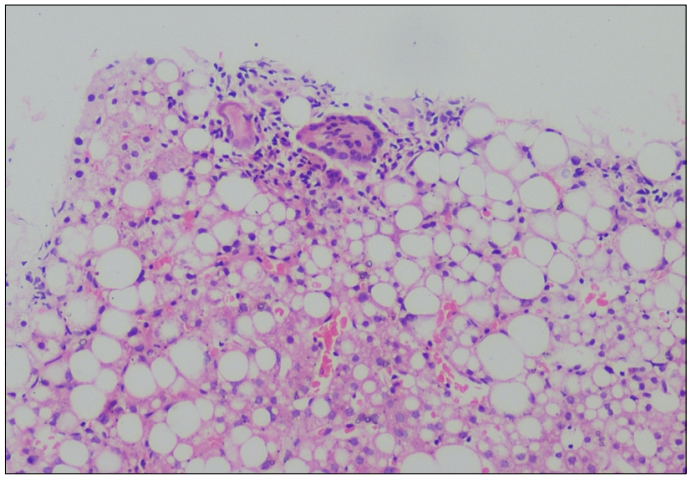

Figure 2. Magnified image of granuloma.

Case Two

A 27-year-old female was evaluated for periumbilical abdominal pain, loose stools, and weight loss over the past six months. She reported a history of an occasional ball-rolling sensation near the right lower abdomen, associated with borborygmi. A CT enterogram of the abdomen revealed bowel wall thickening at the distal ileum, cecum, and ascending colon, with a suspicious entero-enteric fistula. Mural stratification was also noted.

Colonoscopy showed ulcers with narrowing at the ascending colon, and the scope could not be advanced further due to luminal narrowing. Histopathological examination demonstrated cryptitis, crypt abscesses, and occasional granulomas with multinucleated giant cells—findings suspicious for intestinal tuberculosis (ICTB) versus Crohn's disease. Auxiliary tests for tuberculosis, including the tuberculin skin test, IGRA, and screening chest CT, were all normal. TB PCR of the colonic tissue was negative.

She was started on infliximab at a dose of 5 mg/kg. However, even after 14 weeks, she continued to exhibit features of partial intestinal obstruction. A right hemicolectomy with ileocolonic anastomosis was performed. The surgical specimen was sent for histopathological examination.

Sections from the large bowel showed colonic mucosa with dense chronic inflammation composed of plasma cells, lymphocytes, and eosinophils. Marked congestion and foci of crypt distortion were observed. Sections from the ileal mucosa showed congestion and submucosal edema. Both resected ends showed submucosal edema, with the lamina propria exhibiting moderate inflammation composed of lymphoplasmacytic infiltrates.

Sixteen out of nineteen lymph nodes from pericolic and mesenteric fat demonstrated granulomatous lymphadenitis (microgranulomas), suggestive of extraintestinal granulomatous inflammation of Crohn's disease (Figure 3 and Figure 4).

Postoperatively, she was restarted on infliximab and is currently without features of intestinal obstruction.

Case Three

A 44-year-old woman, diagnosed with IBD–Crohn's disease at the age

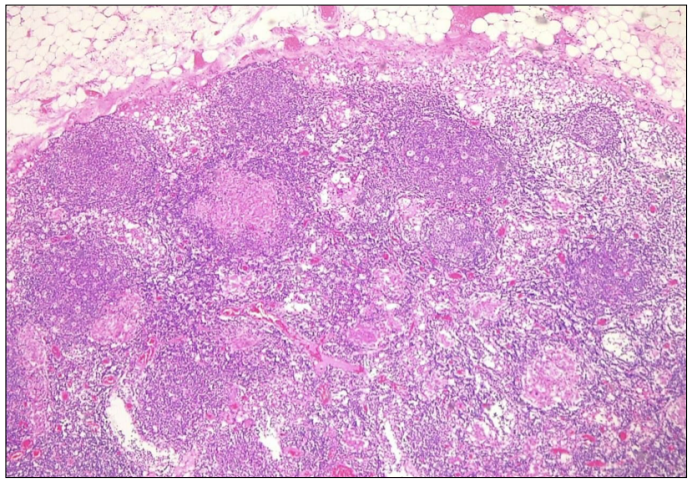

Figure 3. Lymph node showing granulomatous lymphadenitis.

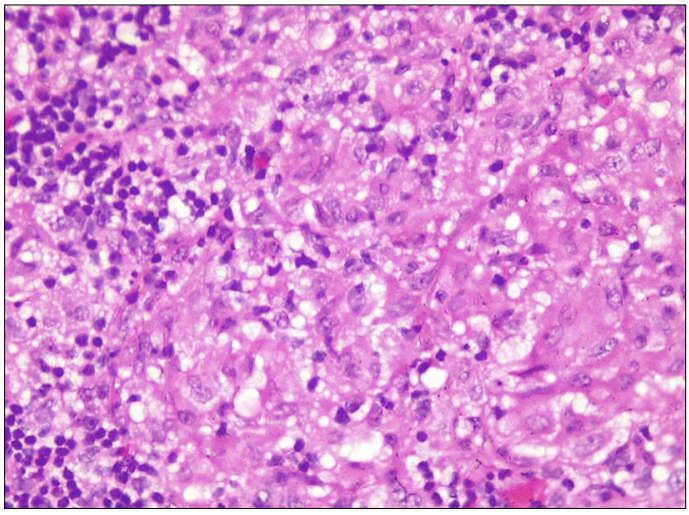

Figure 4. Magnified image of microgranuloma.

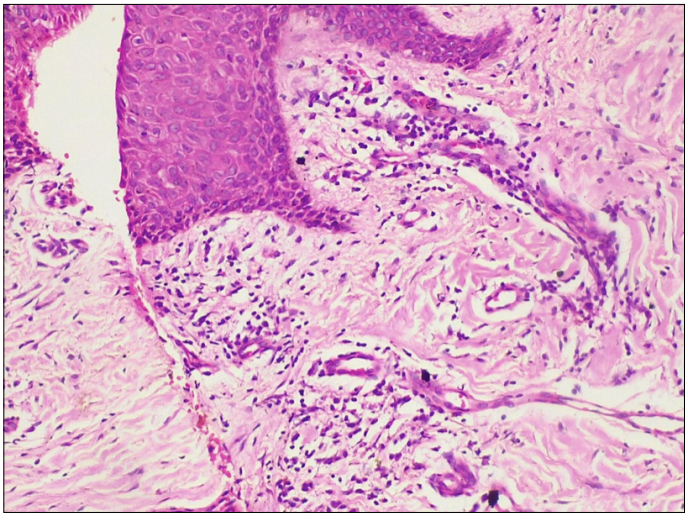

Figure 5. Section of skin: epidermis shows hyperkeratosis, acanthosis, parakeratosis, spongiosis, and denudation of the epithelium. The dermis contains numerous dilated lymphatic channels filled with eosinophilic material, dense lymphoplasmacytic infiltration, and fibroblasts. Dilated lymphatics are lined by flattened epithelium. Dense perivascular lymphoplasmacytic infiltration is present. Focal perivascular inflammatory infiltrates composed of lymphocytes and histiocytes form a granuloma.

of 32 and started on azathioprine and mesalamine, presented with discharge from the vulva. The patient had a Crohn's Disease Activity Index (CDAI) of 166, suggestive of mild activity.[9] On examination, the right labia majora showed an indurated nodular lesion with serosanguinous discharge, along with a plaque-like lesion over the left labia majora.

MRI of the pelvis revealed disruption of the wall of the mid and lower anal canal, with diffuse T2 hyperintense signals and post-contrast enhancement in the anterior wall of the anal canal extending into the vulvar region. A sinus tract measuring 2.8 cm in length was seen in the left perineal region, with the posterior tract abutting the anal verge. Linear fluid collections were observed in the intersphincteric space of the lower canal at the level of the anal verge.

A skin biopsy was taken from the nodular lesion on the right labia majora. The section showed skin with epidermal hyperkeratosis, acanthosis, parakeratosis, spongiosis, and epithelial denudation. The dermis demonstrated numerous dilated lymphatic channels filled with eosinophilic material, dense lymphoplasmacytic infiltration, and fibroblasts. The dilated lymphatics were lined by flattened epithelium and showed dense perivascular lymphoplasmacytic infiltration. Focal perivascular inflammatory infiltrates composed of lymphocytes and histiocytes formed a granuloma (Figure 5 and Figure 6).

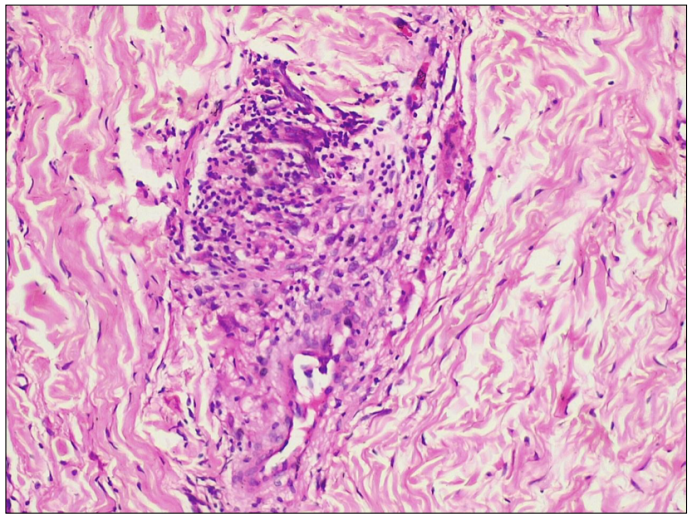

Figure 6. Magnified image of granuloma.

She was treated with infliximab at a dose of 5 mg/kg, along with steroids that were tapered and stopped. Her CDAI has decreased, with noted improvement in quality of life.

DISCUSSION

Crohn's disease may present with a wide range of intestinal and extraintestinal manifestations. The presence of extraintestinal granulomas in Crohn's disease reflects the true systemic impact of the condition. These granulomas may result from a direct extension of the disease or may be secondary to other causes, such as medications or infections like tuberculosis.

The presence of extraintestinal disease should be carefully investigated and confirmed through appropriate diagnostic measures. At the same time, other potential causes must be ruled out. Identifying Crohn's-specific granulomas at extraintestinal sites highlights the extent of disease burden and may complicate treatment strategies.

Extraintestinal granulomas are often associated with patients exhibiting an aggressive phenotype of the disease and may therefore necessitate escalation in therapy.

Informed Consent: Consent was obtained from all three patients included in the report for featuring in the publication

Peer-review: Externally peer-reviewed.

Author Contribution: Concept – G.R.P.; Design – G.R.P., R.M.; Supervision – S.K., S.V.; Resource – D.J.; Materials – L.U., G.K.; Data Collection and/or Processing – A.K.G., M.G.; Analysis and/or Interpretation – H.S.; Literature Review – S.S.; Writing – G.R.P., R.M.; Critical Review – S.K.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: Authors declare that this study have not received any financial support.

REFERENCES

1. Pulimood AB, Amarapurkar DN, Ghoshal U, et al. Differentiation of Crohn's disease from intestinal tuberculosis in India in 2010. World J Gastroenterol. 2011;17(4):433-443. [CrossRef]
2. Gordon H, Minozzi S, Kopylov U, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2024;18(10):1531–1555.
3. Kellermann L, Riis LB. A close view on histopathological changes in inflammatory bowel disease, a narrative review. Dig Med Res. 2021;4. [CrossRef]
4. Gordon H, Burisch J, Ellul P, et al. ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2024;18(1):1-37. [CrossRef]
5. Bernett CN, Krishnamurthy K. Cutaneous Crohn Disease. Treasure Island (FL): StatPearls Publishing; 2023.
6. Restellini S, Chazouillères O, Frossard JL. Hepatic manifestations of inflammatory bowel diseases. Liver Int. 2017;37(4):475-489. [CrossRef]
7. Saade MC, Wehbe H, Mourad FH, et al. Significance of granulomas in the outcomes of Crohn's disease patients. Ann Gastroenterol. 2022;35(5):503-508. [CrossRef]
8. Molnár T, Tiszlavicz L, Gyulai C, Nagy F, Lonovics J. Clinical significance of granuloma in Crohn's disease. World J Gastroenterol. 2005;11(20):3118-3121. [CrossRef]
9. Freeman HJ. Use of the Crohn's disease activity index in clinical trials of biological agents. World J Gastroenterol. 2008;14(26):4127-4130. [CrossRef]