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Review Article

Rituximab-Associated Gastrointestinal Mucosal Injury: A Comprehensive Review

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Abstract: Rituximab a chimeric anti-CD20 monoclonal antibody, has transformed the treatment of B-cell malignancies and autoimmune disorders [1, 2]. While its therapeutic efficacy is well-established, developing evidence has revealed a complex and increasingly recognized spectrum of gastrointestinal mucosal injuries associated with its use. This review synthesizes recent literature including landmark 2025 studies, to present a comprehensive overview of rituximab-associated gastrointestinal mucosal injury. We describe clinical presentations, endoscopic findings and histopathologic features across the entire gastrointestinal tract from the esophagus to the colon. A particular focus is placed on the newly characterized rituximab-associated common variable immunodeficiency (CVID)-like enteropathy, a severe and late-onset syndrome characterized by hypogammaglobulinemia, malabsorption and distinctive histologic features [3, 4]. We also discuss the proposed pathogenic mechanisms, clinical approach to diagnosis, management strategies and areas for future research.

Keywords: Rituximab, Gastrointestinal Mucosal Injury, CVID-Like Enteropathy, Esophagitis, Colitis, Plasma Cell Depletion, Hypogammaglobulinemia.

INTRODUCTION

Rituximab (RTX) is a chimeric human/murine immunoglobulin G1 (IgG1)-kappa monoclonal antibody that targets the CD20 phosphoprotein expressed on the surface of developing B-lymphocytes [1, 2]. Since its introduction in 1997, Rituximab has become central to the management of an array of B-cell lymphoproliferative disorders, including non-Hodgkin's lymphoma and chronic lymphocytic leukemia as well as autoimmune conditions such as rheumatoid arthritis, granulomatosis with polyangiitis and systemic lupus erythematosus [1-5]. The mechanism of action involves B-cell depletion through antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and direct apoptotic signaling [1-6].

While rituximab has a generally favorable safety profile, its use has been associated with a range of adverse effects; including infusion reactions, neutropenia, hypogammaglobulinemia and infections [7, 8]. Among the organ-specific toxicities, gastrointestinal (GI) side effects have appeared as a significant clinical concern. The spectrum of gastrointestinal (GI) injuries linked with rituximab has greatly grown since it was initially characterized as moderate diarrhea or abdominal pain that would go away on its own. Large retrospective investigations conducted in the past have indicated that roughly four percent of those who were exposed to rituximab developed colitis [9]. A research that was conducted more recently on gastrointestinal biopsies taken from patients who had been exposed to rituximab found indications of persisting inflammatory processes in 39 percent of the instances [10]. During the past two years, we have witnessed significant advancements in our understanding of rituximab-associated mucosal damage in the gastrointestinal

tract. The clinical landscape has been radically transformed as a result of the formal characterization of a CVID-like enteropathy in the year 2025. This characterization revealed a severe immunodeficiency-mimicking condition that had different histologic characteristics [3, 4]. The recognized damage spectrum has been broadened to include the upper gastrointestinal system, including esophageal signs that are uncommon but important [11]. This expansion occurred simultaneously with case reports. As a result of the important implications that these advancements have for clinical practice, gastroenterologists, pathologists, and oncologists need to be more aware of the situation. The purpose of this review is to provide a comprehensive summary of the present state of knowledge concerning rituximab-associated gastrointestinal mucosal damage, with a specific focus on recent medical advancements. A full description of the clinical and histopathologic spectrum is provided, as well as a discussion of the putative pathogenic pathways and an overview of practical approaches to diagnosis and care.

Pathophysiology: Unifying Mechanisms of Mucosal Injury

Emerging evidence suggests that immunological dysregulation as a result of B-cell depletion is the primary mechanism behind rituximab-associated gastrointestinal mucosal injury [3-12]. However, the etiology of this injury is still not fully understood.

B-Cell Depletion and Immune Dysregulation

It is possible for the depletion of peripheral B-cells that is caused by rituximab to last for a period of time ranging from months to years [1-6]. Mucosal immunity is significantly impacted as a result of this loss in the gastrointestinal tract. It is through the synthesis of secretory immunoglobulins, particularly IgA, and the regulation of T-cell responses that B lymphocytes and plasma cells play a significant role in the maintenance of gut homeostasis [12], [13]. There is a possibility that the loss of regulatory B-cell activity could halt the generation of anti-inflammatory cytokines like IL-10, which would then lead to unregulated activation of T-cells, infiltration of T-cells, and inflammation of the mucosal lining [14]. It has been demonstrated through research that severe colitis is brought about by the reduction of regulatory B cells and IL-10 in mice models [15]. In the gut mucosa, the uneven distribution of pro-inflammatory and anti-inflammatory signals that results from this imbalance provides an environment that is conducive to the development of inflammatory injury [12].

Plasma Cell Depletion and Impaired Humoral Immunity

Rituximab-associated enteropathy is characterised by the depletion or malfunction of plasma cells in the gastrointestinal mucosa [3, 4]. This condition is an intriguing discovery. Not only do mature plasma cells in the lamina propria of the small bowel exhibit CD19 and CD138, but they do not express CD20. Because of this, rituximab does not immediately kill plasma cells during treatment. As an alternative, it may have an effect on the process by which B lymphocytes in the gastrointestinal tract differentiate into mature plasma cells that are able to function [3]. Microbial dysbiosis is a microbial imbalance within the body that occurs when beneficial bacteria are outnumbered or when harmful bacteria, yeast, or other microorganisms overgrow. The resultant reduction in local immunoglobulin production, particularly IgA, compromises the function of the mucosal barrier and may contribute to microbial dysbiosis as well as increased susceptibility to inflammatory triggers [3-16]. A significant similarity exists between this process and the etiology of primary CVID enteropathy, which is characterized by defective B-cell development that results in a deficit of plasma cells and inflammation of the gastrointestinal tract [17, 18].

T-Cell Dysregulation

The loss of B cells and the concomitant decrease in IL-10 may result in the uncontrolled activation of CD4+ T cells and an increase in the production of cytokines that promote inflammation [14-19]. According to research [12], it is believed that this dysregulation of T-cells plays a significant part in the development of colitis and enteropathy. When it comes to primary cardiovascular disease, patients who have a lower number of lamina propria plasma cells frequently have elevated levels of T-cell and monocyte activation [18].

The Role of Hypogammaglobulinemia

Post-rituximab hypogammaglobulinemia is a well-known systemic consequence that has been described in 19.3% to 23.7% of patients who had normal IgG levels at the beginning of the treatment. Furthermore, up to 15.8% of patients develop prolonged pan-hypogammaglobulinemia that requires intravenous immunoglobulin (IVIG) therapy [20, 21]. It would appear that the time course is highly variable, with intervals ranging from seven months to seven years between the last dosage of rituximab and the beginning of intravenous immunoglobulin (IVIG) [22]. This hypogammaglobulinemia has a high association with the development of CVID-like enteropathy, which suggests that there is a shared underlying impairment in the function of B-cells and plasma cells [3, 4].

Upper Gastrointestinal Tract: Esophageal Injury

Despite the fact that esophageal involvement in rituximab-associated gastrointestinal damage is extremely uncommon, it is becoming more recognized as an important clinical entity [11-21].

CLINICAL PRESENTATION

A typical presentation of esophageal damage caused by rituximab is increasing dysphagia, which is characterized by difficulty swallowing, and odynophagia, which is characterized by painful swallowing [11-23]. There is also the possibility that patients will have pain in the retrosternal chest, regurgitation, and food impaction [24]. As was the case in the most recent case that was described, the beginning of symptoms can take place either during the induction therapy or during the maintenance therapy [11].

In the seminal case report that was published in 2025 by Abdulrazzak *et al*., a patient who was 53 years old and had stage IV follicular lymphoma had mild dysphagia following two cycles of induction with bendamustine and rituximab. The symptoms became more severe while she was receiving maintenance rituximab therapy that was administered. One of the most important diagnostic clues is the sequential link between the administration of rituximab and the progression of symptoms.

Endoscopic Findings

Extensive esophageal injury is diagnosed with endoscopic examination, which reveals distinctive signs. According to the case that was reported, esophagogastroduodenoscopy (EGD) revealed several cratered and linear esophageal ulcers with active bleeding, in addition to benign-appearing esophageal stenoses at 16 and 30 centimetres from the incisors, as depicted in figure 1 [11].

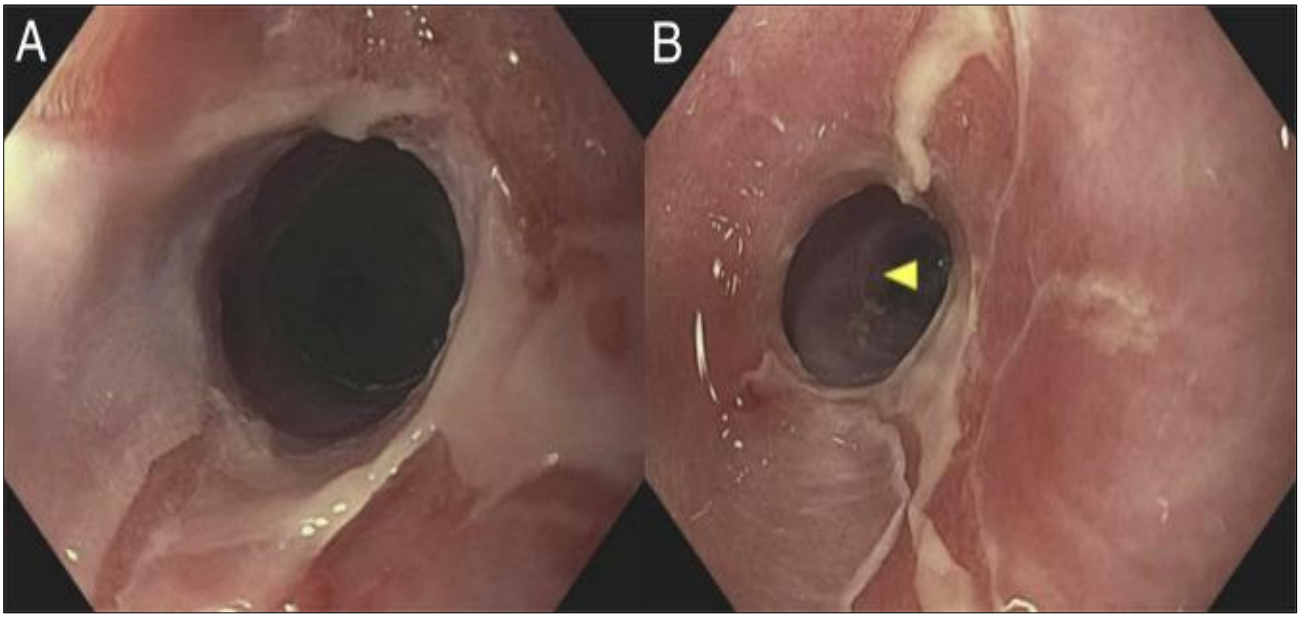

Figure 1: Endoscopical Images of Rituximab Induced Esophageal Injury [11]

The esophageal stenosis that is located 16 centimetres away from the incisors is benign, and the EGD reveals several esophageal ulcers in the upper portion of the oesophagus. EGD reveals the presence of several esophageal ulcers in the bottom portion of the oesophagus, as well as a benign-appearing esophageal stenosis at a distance of thirty centimetres from the incisors. Esophagogastroduodenoscopy, also known as EGD.

Histopathology

The oesophagus was subjected to a biopsy, which revealed both acute and chronic oesophagitis. By using a periodic acid-Schiff stain, it was shown to be negative for fungus, as well as for cytomegalovirus and HSV I/II, as illustrated in Figure 2 [11]. These results are distinct from oesophagitis dissecans superficialis (EDS), which is an uncommon illness that is characterised by the sloughing of large chunks of esophageal mucosa and is related with medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates [11].

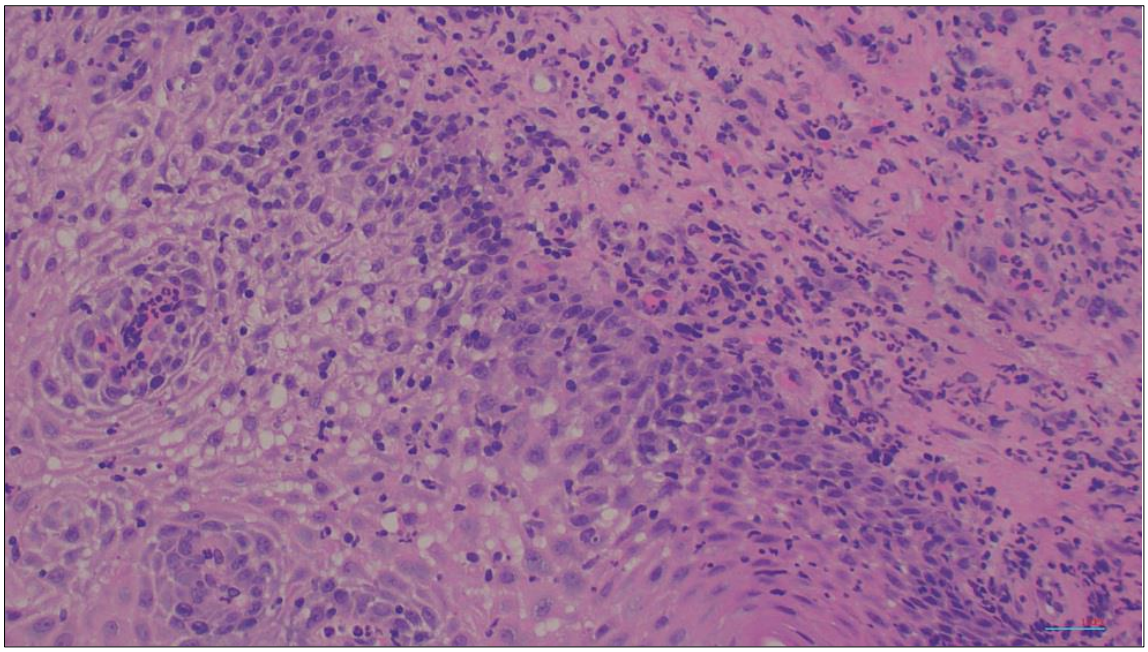

Figure 2: H&E histology stain, 100x magnification

Neutrophils and infiltrating squamous epithelium and underlying stroma are visible in the squamous mucosa of the oesophagus, which is characterised by acute and chronic oesophagitis patients. Haematoxylin and eosin or H&E for short.

Diagnosis and Diagnostic Challenges

The diagnosis of esophageal damage caused by rituximab results in the exclusion of other possible causes. Key diagnostic criteria include the following:

1. A sequential relationship between the administration of rituximab and the beginning or progression of oesophagitis [11].
2. The absence of any abnormalities on biopsies that were infectious, malignant, or autoimmune in nature [11].
3. A limited response to treatment with a proton pump inhibitor [11].
4. After discontinuing rituximab treatment, there was a significant improvement in both the symptoms and the endoscopic results [11].

The differential diagnosis is broad and includes infectious esophagitis (Candida, HSV, CMV), eosinophilic esophagitis, pill-induced esophagitis (from other medications), reflux esophagitis and esophagitis dissecans superficialis [24, 25].

Clinical Course and Management

Involves discontinuation of rituximab when clinically possible. In the reported case, after rituximab was stopped the patient experienced significant symptomatic improvement within 4 months, with progressive resolution of esophagitis and successful dilation of strictures on follow-up EGD [11]. Acid suppression with vonoprazan (a potassium-competitive acid blocker) or high-dose proton pump inhibitors may provide symptomatic relief though they are often insufficient as monotherapy [11]. This case highlights the importance of considering rituximab-induced esophageal injury in patients presenting with dysphagia while on rituximab therapy and the potential for significant improvement upon drug discontinuation [11].

Table 1: Comparison of Rituximab-Induced Esophagitis vs. Esophagitis Dissecans Superficialis (EDS)

Feature	Rituximab-Induced Esophagitis	Esophagitis Dissecans Superficialis (EDS)
Endoscopic Findings	Deep ulcers, strictures, friability [11]	Sloughing of large mucosal fragments [25]
Histology	Active esophagitis with ulceration [11]	Parakeratosis, intraepithelial splitting [25]
Associated Medications	Rituximab [11]	NSAIDs, bisphosphonates, psychoactive agents [25]
Treatment	Response Improves with rituximab discontinuation [11]	Variable; may resolve with drug cessation
Prognosis	Good with drug discontinuation [11]	Generally benign [25]

Lower Gastrointestinal Tract: Colitis and Ileocolitis

The most frequently reported GI adverse event associated with rituximab is colitis, with an increasing number of case reports and series elucidating its clinical and histologic manifestations [9-27].

Clinical Presentation

Patients with rituximab-induced colitis typically present with chronic diarrhea, abdominal pain and weight loss [5-9]. The onset of symptoms can vary widely from immediately after infusion to up to two years after the last rituximab dose [10]. In some cases, symptoms may be severe with reports of fulminant colitis requiring colectomy [9]. A 2021 case report by Tsuzuki *et al*., described a 65-year-old man with gastric mucosa-associated lymphoid tissue lymphoma (MALToma) who developed bloody diarrhea after Rituximab therapy, with mucosal inflammation on colonoscopy indicating rituximab-induced ileocolitis and the patient responded to corticosteroid treatment [27].

Endoscopic Findings

Colonoscopy typically reveals diffuse colonic inflammation, mucosal friability and ulceration [5-12]. In patients with granulomatosis with polyangiitis (GPA) who develop colitis, endoscopy may show pancolitis with diffuse mild inflammation throughout the entire colon [5]. The pattern of inflammation can mimic inflammatory bowel disease (IBD) with features overlapping with both ulcerative colitis and Crohn's disease [5-26].

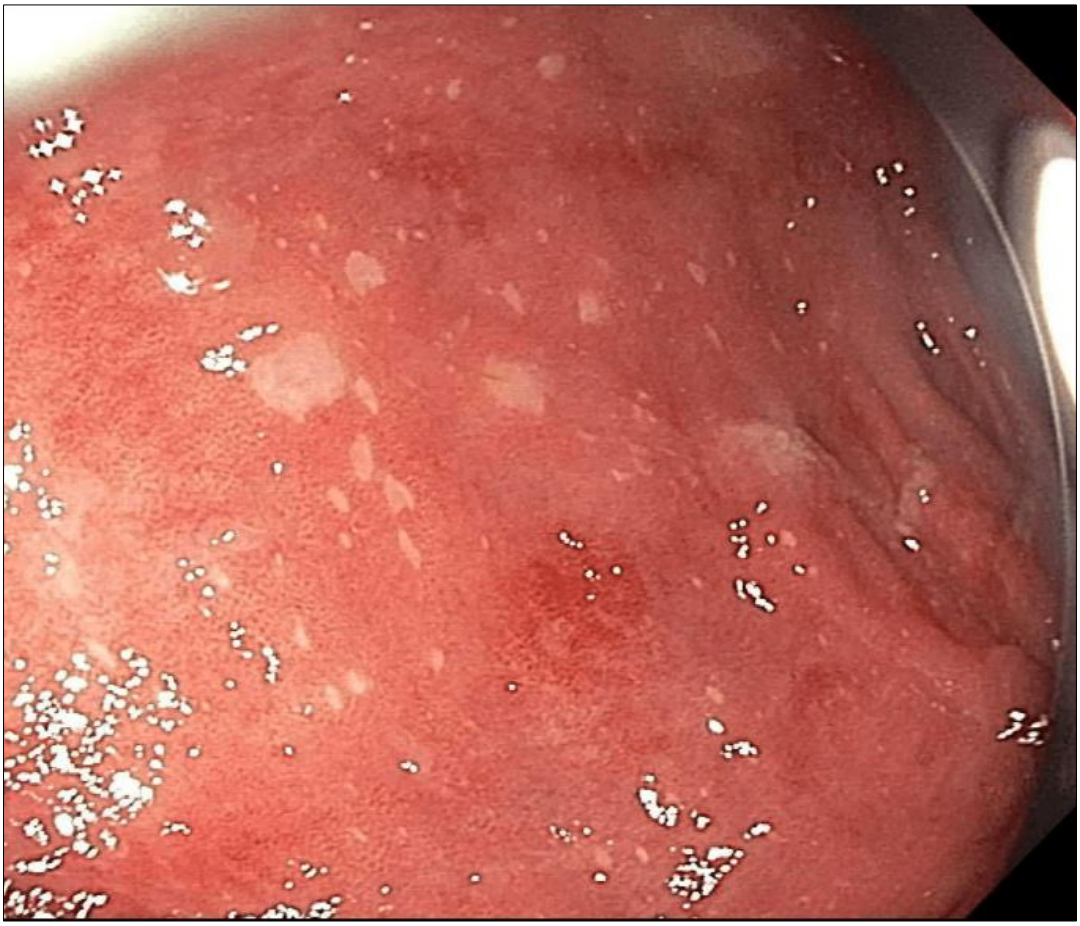

Figure 3: Endoscopic Images of Rituximab-Induced Colitis: Colonoscopy finding of diffuse mild inflammation in the sigmoid colon [5]

Histopathology

Biopsies from affected colonic mucosa show active colitis with features including; Cryptitis and crypt abscesses, non-caseating granulomas (in some cases) and absence of vasculitis or necrosis as shown in figure 4 [5]. A critical diagnostic feature is the absence of vasculitis on colonic mucosal biopsy, which helps distinguish drug-induced colitis from a flare of the underlying autoimmune disease (such as Granulomatosis with Polyangiitis) [5]. The presence of granulomas in some cases has led to classification as Crohn's disease-like colitis [5-26].

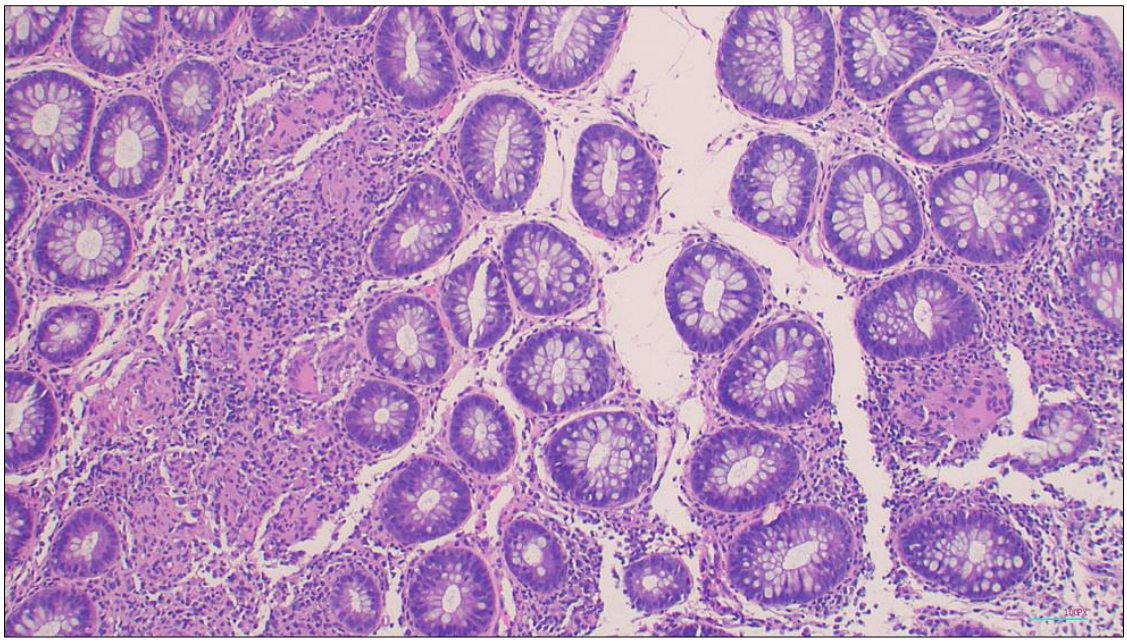

Figure 4: H&E histology stain, 100x magnification:

There is a single granuloma in the right mid-field located in the transverse mucosa, in addition to a large number of non-caseating granulomas that are producing coalescent lesions in the lamina propria. Haematoxylin and eosin or H&E for short.

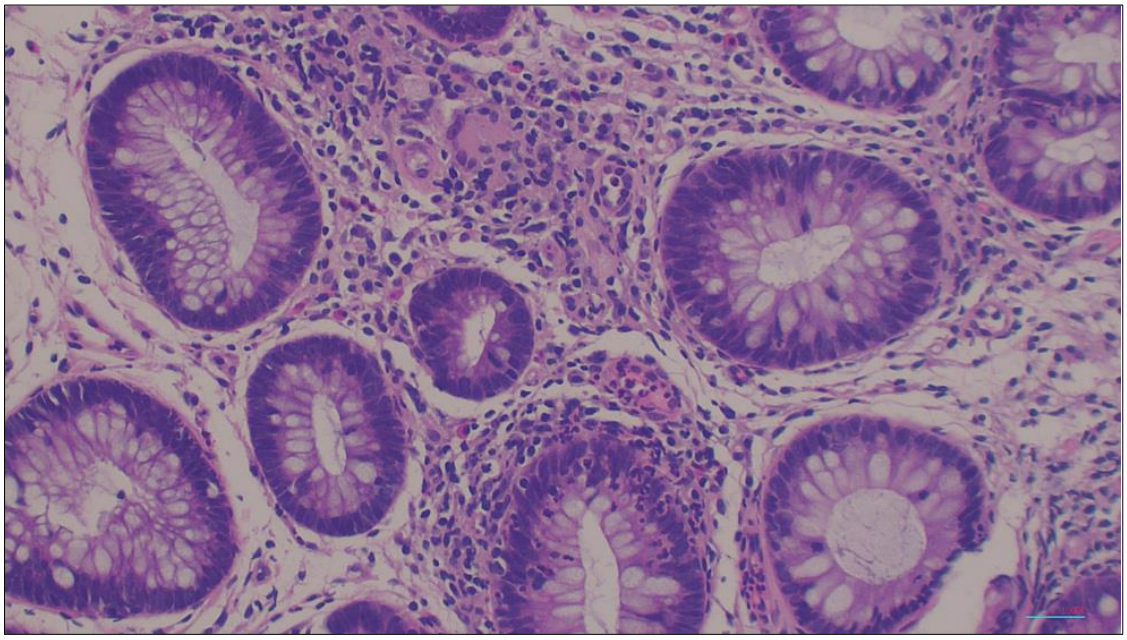

Figure 5: H&E histology stain, 100x magnification:

Active colitis is present in the rectal mucosa, which is characterised by cryptitis and neighbouring non-caseating granulomas. Haematoxylin and eosin or H&E for short.

Classification of Rituximab-Associated Colitis

Based on literature review, rituximab-associated colitis has been classified into several patterns:

1. Ulcerative colitis-like: Diffuse colonic inflammation with cryptitis, crypt abscesses and mucosal ulceration [26, 27].
2. Crohn's disease-like: Presence of granulomas and transmural inflammation [5-26].
3. Microscopic colitis: Lymphocytic or collagenous colitis pattern [9].
4. Ileocolitis: Involvement of both small bowel and colon [27].

Diagnostic Approach

Diagnosis of rituximab-induced colitis requires:

1. Exclusion of infectious etiology (stool cultures, C. difficile, ova and parasites, viral PCR) [5]
2. Exclusion of autoimmune disease flare (negative ANCA serology, absence of vasculitis on biopsy) [5]
3. Temporal relationship with rituximab exposure [10]
4. Endoscopic and histologic confirmation of colitis
5. A notable diagnostic challenge is distinguishing rituximab-induced colitis from an IBD flare in patients with pre-existing autoimmune conditions. The absence of vasculitis on biopsy and the temporal relationship with rituximab administration favor drug-induced injury [5].

Management

Treatment approaches for rituximab-induced colitis have varied in reported cases:

1. Symptomatic treatment: Anti-diarrheal drugs and nutritional support [5]
2. Corticosteroids: Oral or intravenous, with variable success [5-27]
3. Budesonide: Limited efficacy [3]
4. Biologic therapies: Infliximab and vedolizumab have been tried but are often ineffective [3-5].
5. IVIG: May be helpful in patients with concomitant hypogammaglobulinemia [3]

Table 2: Classification and Features of Rituximab-Associated Colitis

Subtype	Endoscopic Features	Histologic Features	Key References
Ulcerative Colitis-Like	Diffuse inflammation, mucosal ulceration	Cryptitis, crypt abscesses, mucosal ulceration	[26] [27]
Crohn's Disease-Like	Segmental inflammation, strictures	Non-caseating granulomas, transmural inflammation	[5] [26]
Microscopic Colitis	Normal or near-normal mucosa	Lymphocytic or collagenous infiltration	[9]
Ileocolitis	Inflammation of ileum and colon	Active inflammation in both ileum and colon	[27]

The CVID-Like Enteropathy: A Newly Recognized Entity

The most significant recent advance in our understanding of rituximab-associated GI mucosal injury is the formal characterization of a CVID-like enteropathy [3, 4]. This severe, late-onset syndrome mimics primary common variable immunodeficiency and has profound clinical implications.

Historical Context

[3]. In the year 2025, Hakimian and colleagues were the first to describe a group of patients who had a history of being exposed to rituximab and who came with hypogammaglobulinemia, severe chronic diarrhoea, and malabsorption. These symptoms brought together the seemingly unrelated toxicities of B-cell depletion and gastrointestinal injury. Primary CVID is a primary immunodeficiency that is characterised by hypogammaglobulinemia, impaired mucosal immunity, and dysregulated immunological tolerance [17, 18]. This unusual clinical presentation was strikingly suggestive of basic CVID.

Clinical Presentation

The clinical features of rituximab-associated CVID-like enteropathy are striking and severe:

1. Diarrhea: Chronic, persistent and often profound [3]
2. Weight loss: Significant with median weight loss of 15 kg in one series [3]
3. Malabsorption: Evidenced by decreased serum total protein, albumin, and pre-albumin [3]
4. Hypogammaglobulinemia: Low serum levels of IgG, IgA and IgM [3]
5. Malnutrition: Severe with 70% of patients meeting criteria for severe malnutrition [3]

Endoscopic Findings

Endoscopic evaluation of the GI tract reveals the following abnormalities;

- Atrophic or scalloped/fissured duodenal mucosa [3]
- Duodenitis [3]
- Erythema and/or erosions of duodenal, ileal and colonic mucosa [3]

Histologic Spectrum:

The key histologic features include:

Small Bowel Findings:

- Sparse/absent lamina propria plasma cells.

- Intraepithelial lymphocytosis.
- Villous atrophy.
- Increased crypt apoptotic bodies.
- Active inflammation [3]

Colonic Findings:

- Sparse/absent plasma cells.
- Increased crypt apoptotic bodies.
- Active inflammation.
- Intraepithelial lymphocytosis [3].

The histologic hallmark of this enteropathy-sparse or absent lamina propria plasma cells- is shared with primary CVID enteropathy [4-17]. The combination of plasma cell depletion, villous atrophy and intraepithelial lymphocytosis creates a histologic pattern that is highly suggestive of rituximab-associated injury in the appropriate clinical context [4].

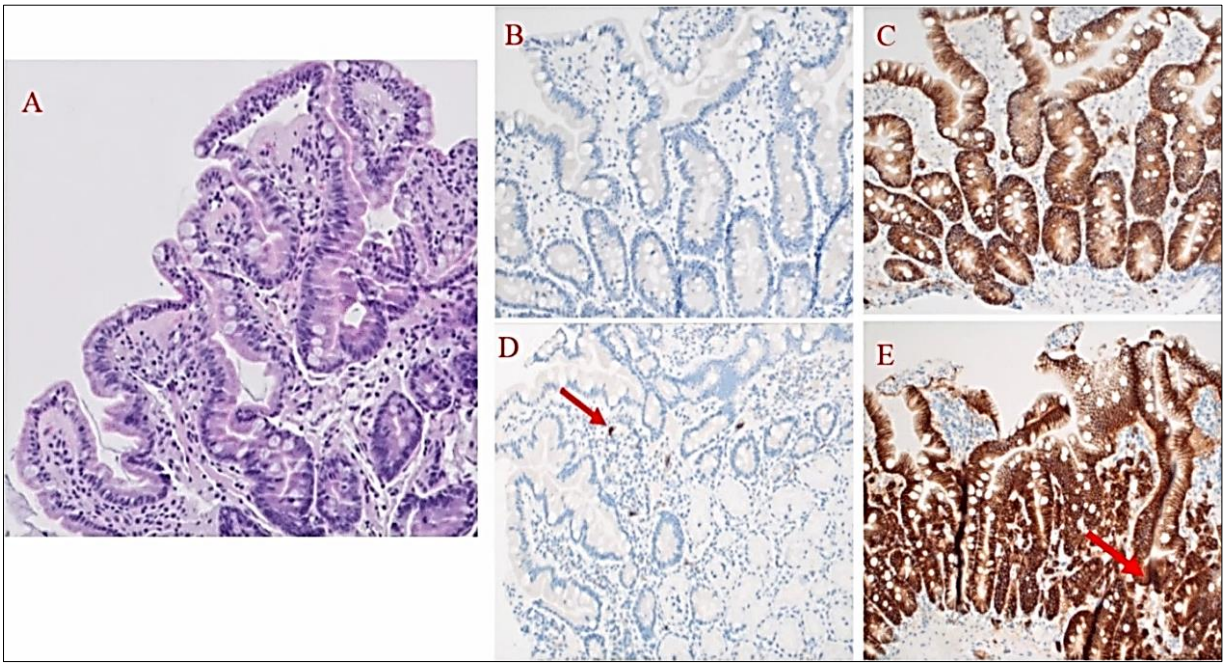

Figure 6: The pathologic findings of a CVID-like enteropathy accompanied with Rituximab chemotherapy. A to C Individual who has developed post-Rituximab enteropathy. According to the results of the haematoxylin and eosin staining, the villous atrophy and reduced plasma cells in the lamina propria were observed in the duodenal sample (A). It appears that there is a depletion of B lymphocytes (B) because the CD20 immunostain does not indicate any cells staining in the lamina propria. In the duodenal lamina propria (C), the CD138 immunostain serves to identify the presence of uncommon plasma. A patient who is healthy. In the duodenal lamina propria, there are a few CD20-positive B lymphocytes that are dispersed throughout the area (red arrow, D). Clusters of plasma cells in the duodenal lamina propria are highlighted by the CD138 immunostain (red arrow, E) [3].

Pathogenesis

The pathogenesis of rituximab-associated CVID-like enteropathy appears to involve:

1. B-cell depletion and impaired plasma cell differentiation: Rituximab may affect the differentiation of B cells to mature functioning plasma cells in the GI tract leading to local immunoglobulin deficiency [3, 4]
2. Local mucosal immune dysregulation: The loss of plasma cells and immunoglobulins may compromise mucosal barrier function, increase susceptibility to microbial triggers and promote aberrant T-cell responses [3-12]
3. Systemic hypogammaglobulinemia: Enteropathy is consistently associated with systemic immunoglobulin deficiency suggesting a shared underlying defect [3]

Uncertainty exists regarding the precise mechanism by which the depletion of plasma cells results in a reduction in the absorptive capacity of the small bowel [3]. As is the case with primary CVID enteropathy, low mucosal IgA levels, resident bacteria, and B-cell depletion can all contribute to T-cell abnormalities, which can then culminate in small intestinal enteropathy [3-18].

Clinical Course and Management

The clinical course of rituximab-associated CVID-like enteropathy is often severe and challenging to manage [3]:

1. IVIG therapy: All patients received IVIG; only two reported partial improvement in diarrhea [3]
2. Immunosuppressants: Treatment with prednisone (n=6, budesonide (n=2), infliximab (n=2), or vedolizumab (n=1) was ineffective [3]
3. Nutritional support: Five patients required parenteral nutrition [3]
4. Mortality: Two patients (20%) died; one from lymphoma and the other from sepsis [3]

The lack of response to standard immunosuppressive and biologic therapies underscores the distinct pathogenesis of this enteropathy and the need for novel treatment strategies [3].

Clinical Implications and Awareness:

The recognition of rituximab-associated CVID-like enteropathy has several important clinical implications [3, 4]:

1. Early recognition: Clinicians should suspect this diagnosis in patients presenting with diarrhea and weight loss in the setting of prior rituximab use [3]
2. Pathologist awareness: Pathologists should be aware of this entity and seek a history of rituximab use in patients whose biopsies exhibit CVID enteropathy-like features [4]
3. Multidisciplinary approach: Management requires coordination between gastroenterologists, pathologists, oncologists, and nutrition support teams [3]
4. Prognosis: The propensity to develop severe malabsorption and malnutrition often requires parenteral nutrition support and carries significant morbidity and mortality [3]

Table 3: Comparison of Rituximab-Associated CVID-Like Enteropathy vs. Primary CVID Enteropathy

Feature	Rituximab-Associated CVID-Like Enteropathy [3] [4]	Primary CVID Enteropathy [17] [18]
Underlying Cause	Rituximab-induced B-cell depletion	Genetic immunodeficiency
Hypogammaglobulinemia	Present	Present
Small Bowel Pathology	Plasma cell depletion (50%), villous atrophy (55%), IELs (60%)	Plasma cell depletion, villous atrophy, IELs
Colonic Pathology	Plasma cell depletion (41%), crypt apoptosis (41%)	Variable
Treatment Response	Poor response to IVIG, steroids, biologics	Poor response to IVIG, steroids, biologics
Prognosis	20% mortality in one series	Variable; depends on complications

Clinical Approach and Diagnostic Algorithm

Based on the available evidence, we suggest a diagnostic algorithm for patients with suspected rituximab-associated GI mucosal injury [3-11].

Clinical Suspicion

Rituximab-associated GI mucosal injury should be suspected in patients with:

1. History of rituximab exposure (any time frame) [3-11]
2. New-onset GI symptoms:
   - Dysphagia, odynophagia (esophageal involvement) [11]
   - Chronic diarrhea, abdominal pain, weight loss (colitis/enteropathy) [3-5]
3. Laboratory findings:
   - Hypogammaglobulinemia [3]
   - Evidence of malabsorption (low albumin, pre-albumin, protein) [3]

Diagnostic Workup

Step 1: Rule out Infection

- Stool cultures, C. difficile testing, ova and parasites [5]
- Viral PCR (norovirus, CMV, HSV) [3] [5]
- Stool multiplex PCR panels [3]

Step 2: Endoscopic Evaluation

- EGD with biopsies for suspected upper GI involvement [11]
- Colonoscopy with ileal intubation for suspected colitis/enteropathy [5]
- Multiple biopsies from affected areas [4]

Step 3: Histologic Evaluation

- Assess for:
- Plasma cell density (CD138 immunostain helpful) [4]
- Villous atrophy [4]
- Intraepithelial lymphocytosis [4]
- Crypt apoptotic bodies [4]
- Active inflammation [4]
- Absence of vasculitis [5]

Step 4: Exclusion of Other Etiologies

- Autoimmune disease flare (ANCA testing if indicated) [5]
- Malignancy [11]
- Medication-induced injury from other agents [11]

Diagnostic Criteria

Based on published case series, the following features support a diagnosis of rituximab-associated GI mucosal injury [3-11]

1. Temporal relationship between rituximab exposure and symptom onset [11]
2. Absence of alternative etiology (infection, autoimmune disease, malignancy) [5-11]
3. Characteristic histologic findings:
    - Sparse/absent plasma cells [4]
    - Active inflammation without vasculitis [5]
    - Villous atrophy and IELs [4]
4. Improvement upon rituximab discontinuation (when observed) [11]

Management Strategies

Management of rituximab-associated GI mucosal injury should be individualized based on the severity and location of involvement [3-11].

General Principles

1. Discontinuation of Rituximab

- When clinically feasible, rituximab should be discontinued [11]
- The timing of discontinuation must be balanced against the need for ongoing treatment of the underlying malignancy or autoimmune condition [11]

2. Nutritional Support

- Malnutrition is common and can be severe [3]
- Early involvement of nutrition support team [3]
- Consider parenteral nutrition in cases of severe malabsorption [3]

3. Symptom Management

- Antidiarrheal agents for colitis/enteropathy [5]
- Acid suppression for esophagitis (PPIs or vonoprazan) [11]

Esophageal Injury

Treatment Approaches:

- High-dose proton pump inhibitors or vonoprazan [11]
- Endoscopic dilation for strictures (maybe required) [11]
- Corticosteroids (reported in one case) [5]
- Discontinuation of rituximab [11]

Outcomes

- Significant improvement upon rituximab discontinuation [11]
- Resolution of ulcers and improvement in strictures over months [11]

Colitis and Ileocolitis

Treatment Approaches:

- Corticosteroids (oral or intravenous) [5] [27]
- Budesonide (limited efficacy) [3]

- Biologic therapies (infliximab, vedolizumab) - largely ineffective [3]
- IVIG (may be helpful in patients with hypogammaglobulinemia) [3]

Outcomes

Variable response to corticosteroids [5]

- Limited response to biologics [3]
- Some patients require surgery (fulminant colitis) [9]

CVID-Like Enteropathy

Treatment Approaches:

- IVIG (standard therapy, but often insufficient) [3]
- Immunosuppressants: prednisone, budesonide (largely ineffective) [3]
- Biologics: infliximab, vedolizumab (largely ineffective) [3]
- Nutritional support: parenteral nutrition frequently required [3]

Outcomes

A lack of optimal response to conventional treatments [3]. Malnutrition and malabsorption are the primary causes of high morbidity [3].

- With a mortality rate of twenty percent in a single series, [3]
- The necessity for innovative treatment approaches [3]

Future Directions and Research Needs

The identification of rituximab-associated CVID-like enteropathy has opened up a number of potential avenues for further investigation [3, 4].

Understanding Pathogenesis

In the gastrointestinal mucosa, please provide an explanation of the mechanism that explains how rituximab causes plasma cell dysfunction or depletion [3, 4].

- It is important to investigate the role that microbial dysbiosis plays in the etiology of disease.
- Research should be conducted to investigate the relationship between systemic hypogammaglobulinemia and local mucosal damage [3].
- Determine the biomarkers that are capable of predicting severe enteropathy [4]

Risk Stratification

Determine the parameters that are associated with the development of gastrointestinal mucosal injury, including cumulative rituximab dose, baseline immunoglobulins, and the underlying diagnosis [3]. Create screening procedures that can be utilized for early detection [3]. Establish strategies for long-term follow-up for patients who are considered to be at risk [3].

Therapeutic Inventions

1. Develop targeted therapeutics for an enteropathy that is similar to CVID that is related with rituximab [3].
2. Conduct research into different innovative biologics, such as JAK inhibitors, anti-IL-12/23 agents, and other novel biologics [3].
3. Is to assess the effectiveness of various IVIG dosage strategies [3].
4. To investigate the possibility of fecal microbiota transplantation [3].

Clinical Guidelines

Develop a set of standardized histologic criteria for the purpose of diagnosis [4]. Develop clinical algorithms for the purpose of monitoring patients who are undergoing rituximab therapy [3].

CONCLUSION

Injury to the mucosal lining of the gastrointestinal tract that is associated with rituximab is a spectrum of adverse effects that is becoming increasingly recognized and associated with severe clinical concerns. Our understanding of this disorder has been profoundly modified as a result of the official characterization of rituximab-associated CVID-like enteropathy in the year 2025. This characterization revealed a severe immunodeficiency-mimicking syndrome that possesses distinctive clinical and histologic characteristics [3, 4]. The range of injuries encompasses the entire gastrointestinal tract, beginning with the esophagus and ending with the colon, and the clinical manifestations of these injuries can vary. Recent research has provided support for the expansion of the recognized damage spectrum to include esophageal signs that are uncommon but substantial [11]. Plasma cell depletion, villous shrinkage, intraepithelial

lymphocytosis, crypt apoptotic bodies, and active inflammation are all components of the histologic spectrum of gastrointestinal damage that includes rituximab-associated gastrointestinal injury [4]. The immunological dysregulation that occurs as a result of B-cell depletion appears to be the unifying pathogenic mechanism. This dysregulation results in decreased local humoral immunity, T-cell activation, and mucosal inflammation [3-12]. The depletion of plasma cells and the loss of regulatory B-cell function are two of the most important factors in the development of both enteropathy and colitis [3-12]. Due to the fact that therapeutic techniques for these adverse effects are different from those utilized for autoimmune disease flares or primary inflammatory bowel disease, clinical detection of these consequences is critical. In particular, the CVID-like enteropathy appears to be generally unresponsive to traditional immunosuppressive therapy and frequently necessitates the use of parenteral feeding support [3]. The importance of increased awareness among gastroenterologists, pathologists, and oncologists cannot be overstated when it comes to the treatment and diagnosis of cancer [3-11]. Explanation of the pathogenic mechanisms, identification of risk factors, and development of tailored treatment options should be the primary focuses of future research [3, 4]. This illness is becoming increasingly recognized and is clinically significant.

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Research Ethics: This is a review article and does not include any patient data.

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