

CASE REPORT

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Crohn's disease-like perianastomotic ulcerations after neonatal necrotizing enterocolitis surgery: a case of successful anti-TNF therapy

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Abstract

Background Digestive perianastomotic ulcerations (DPAU) are rare Crohn's disease (CD)-like lesions that develop following intestinal surgery. Although enteral nutrition and anti-inflammatory agents constitute first-line therapies, 59% of refractory cases require advanced interventions. Emerging evidence implicates tumor necrosis factor (TNF)- α -driven inflammation as a key pathogenic mechanism, yet optimal therapeutic strategies remain undefined.

Case summary A 12-year-old girl with a surgery history of neonatal necrotizing enterocolitis (NEC) presented with severe anemia (hemoglobin: 51 g/L) and chronic abdominal pain. Endoscopy revealed circumferential ulcers at the ileocolonic anastomosis, histologically confirmed as active inflammation without granulomas or evidence of infections. Initial therapy with 3 months enteral nutrition and mesalamine failed. Subcutaneous adalimumab induced endoscopic ulcer healing and hemoglobin normalization (111 g/L) within 3 months. At the 12-month follow-up, sustained clinical remission was observed (hemoglobin: 120 g/L, fecal calprotectin: 45 μ g/g), with complete mucosal healing and no adverse events.

Conclusions Early anti-TNF therapy induced rapid and sustained remission in a pediatric patient with DPAU, reinforcing the mechanism that TNF- α -driven inflammation underlies disease pathogenesis. While promising, these findings require validation in larger cohorts. Individualized therapeutic decisions should weigh the risks of recurrence, cost, and long-term biologic safety.

Keywords Crohn's disease-like lesions, Necrotizing enterocolitis, Anastomotic ulcer, Anti-TNF therapy, Adalimumab

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Introduction

Digestive perianastomotic ulcerations (DPAU) are rare, long-term complications occurring after intestinal resection and anastomosis in neonates or children [1, 2]. They may develop following surgical interventions for conditions including necrotizing enterocolitis (NEC), intestinal polyps, intestinal atresia, Hirschsprung disease (HD), or gastroschisis, with an incidence rate of approximately 8%. The most common sites of DPAU in pediatric patients include ileocolic anastomosis and colocolic anastomosis. The interval between surgical anastomosis and DPAU onset ranges from several months to years postoperatively [1, 3]. Clinical manifestations encompass unexplained iron deficiency anemia, abdominal pain, dysphagia, nausea, vomiting, feeding intolerance, melena or hematochezia depending on the site of the anastomotic ulcer. DPAU are rare Crohn's disease (CD)-like inflammatory lesions localized to intestinal anastomoses [4, 5]. In fact, in the absence of a documented surgical history, DPAU may be misdiagnosed as primary CD, posing significant diagnostic challenges.

The management of DPAU remains challenging, with no single therapeutic modality universally recommended. Current approaches including enteral nutrition, antibiotic therapy, mesalamine, immunosuppressive medications, corticosteroids, hydrocortisone enemas, and budesonide and anti-TNF agents, yet have been proposed with variable success rates and robust evidence supporting standardized protocols is lacking. Enteral nutrition and anti-inflammatory agents are first-line therapies, but up to 59% of patients require surgical revision due to refractory ulcers [4]. Emerging evidence highlights anti-TNF- α biologics as a promising option [5], but the efficacy of early anti-TNF intervention and its long-term outcomes remain underexplored. Herein, we report a case of a 12-year-old girl who developed DPAU after surgery for neonatal necrotizing enterocolitis (NEC) and refractory to conventional supportive therapy, achieving rapid and continuous endoscopic remission following adalimumab therapy. This case provides real-world evidence for the role of anti-TNF- α therapy in DPAU and underscores the need for further research to optimize treatment strategies for this underrecognized complication.

Case presentation

The patient was a 12-year-old female patient with a history of intermittent abdominal pain, accompanied by dizziness, weakness and severe anemia persisting for over three months. Born prematurely at 35 weeks' gestation, she had undergone a medical history of NEC diagnosed at 1 week of age, which required emergent surgical intervention at the neonatal surgery department of our institution. Intraoperatively, 45 cm of terminal ileum (proximal to the ileocecal valve), the entire ascending

colon, and a 3-cm transverse colon near the hepatic flexure were resected; intestinal continuity was restored via an end-to-end ileotransverse anastomosis. Postoperatively, the patient required a 7-day stay in the neonatal intensive care unit for respiratory support (non-invasive ventilation) and parenteral nutrition (PN). PN was successfully weaned at 4 weeks of age, and the patient was discharged home uneventfully without severe complications such as anastomotic leak, sepsis, or short bowel syndrome. Over the 12 years following the initial surgery, the patient remained asymptomatic until the current admission.

Upon admission, she presented with lower gastrointestinal bleeding (positive fecal occult blood tests) and severe anemia (hemoglobin: 51 g/L). Monitoring labs showed IL(Interleukin)-1 β was slightly higher (13.49 pg/mL) and other inflammatory indicators, including hyper-sensitive C-reactive protein, erythrocyte sedimentation rate and fecal calprotectin were normal. Vitamin D, zinc and iron deficiency were detected by blood biochemical examination. Complement, cellular immune and humoral immunity were normal. Autoantibody series including anti-Saccharomyces cerevisiae antibodies (ASCA)/perinuclear antineutrophil cytoplasmic antibodies (ANCA) were negative. The examination ruled out infections caused by bacteria, viruses, fungi and mycobacterium tuberculosis. Bone marrow cytology examination excluded hematologic disorders. Intestinal ultrasound and abdominal CT revealed no abnormalities and capsule endoscopy did not detect any lesions in the small intestine. Gastroscopy suggested chronic superficial gastritis, while colonoscopy and capsule endoscopy revealed anastomotic ulcer (Figure 1A). Histopathological examination reported active mucosal inflammation at the ulcer site and surrounding tissues without crypt abscesses or granulomas. Based on these findings, the patient was definitively diagnosed with DPAU and received symptomatic supportive therapy, including exclusive enteral nutrition (EEN), mesalamine (60 mg/kg/day) and micronutrient supplementation with iron, vitamin D, and zinc.

Three months after initial treatment, the patient's hemoglobin improved to 111 g/L, but repeat colonoscopy showed persistent ulcers (Figure 1B). Based on literature evidence implicating TNF- α -mediated inflammation in DPAU pathogenesis, subcutaneous adalimumab was initiated. The patient (41 kg) received a standard adalimumab induction regimen (160 mg, then 80 mg at week 2) for pediatric Crohn's disease, followed by maintenance therapy with 40 mg every other week. The patient achieved clinical remission within 14 weeks of biologic therapy, with both endoscopic improvement (Figure 1C) and hemoglobin normalization. Subsequent 12-month follow-up revealed complete resolution of symptoms. Laboratory evaluations revealed sustained hematologic

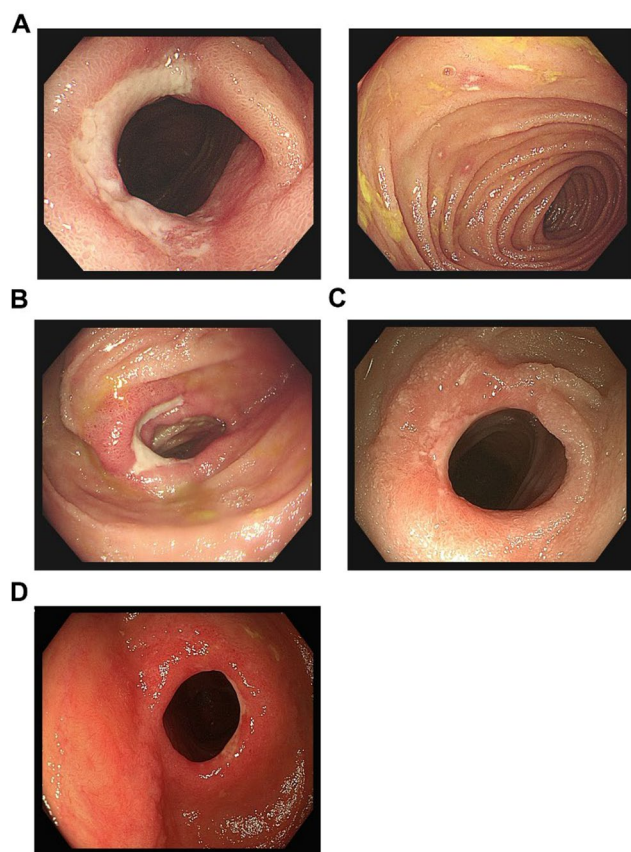


Fig. 1 Endoscopic images of the patient. **A.** Anastomotic ulceration at ileocolonic anastomotic site before treatment. Mucosa with an erythematous, friable base and a well-demarcated, semicircular ulcer (1.5 cm in diameter) covered by white fibrinoid exudate. Multiple patchy superficial ulcerations (0.3–0.5 cm) with surrounding mucosal erythema proximal to the anastomosis. **B.** Baseline (pre-treatment): Circumferential ulceration at the anastomotic site (diameter: 1.8 cm) with erythematous, friable mucosa and fibrinoid exudate. **C.** 3 months post-adalimumab: Partial mucosal healing with reduced ulcer size (diameter: 0.5 cm), minimal fibrin deposition, residual erythema and mild edema in the peri-anastomotic mucosa. **D.** 12 months post-adalimumab: Complete mucosal healing with smooth, pale scar tissue at the anastomosis, mild residual erythema without active ulceration or exudate.

recovery (120 g/L) levels. Repeat colonoscopy confirmed complete mucosal healing at the ileocolonic anastomosis, with only mild residual erythema and no active ulceration (Figure 1D). No adverse events, including infections or hypersensitivity reactions, were observed during the treatment period.

Discussion and conclusions

DPAU occurred in 39% of cases following NEC-specific surgery [1], representing a multifactorial lesions driven by the interplay of surgical, microbial, and genetic factors, with pathogenic mechanisms overlapping those of CD [4, 6]. Anastomotic ischemia caused by surgical devascularization during intestinal resection, disrupts blood supply to the anastomotic site, impairing tissue oxygenation and

reducing local repair capacity. This creates a pro-inflammatory microenvironment that predisposes to ulcer formation, serving as a critical early trigger for mucosal damage, particularly in infants who undergo extensive bowel resection in the neonatal period [7]. Additionally, loss of the ileocecal valve—a key barrier to colonic bacterial translocation—exacerbates microbial dysbiosis [2]. In its absence, small intestinal bacterial overgrowth (SIBO) develops, altering gut microbiota composition and triggering chronic inflammation via dysregulated microbiota–host crosstalk, thereby perpetuating mucosal injury at the anastomosis. Furthermore, genetic susceptibility represents a key contributing factor, underscored by the finding that 73% of DPAU patients harbor NOD2 mutations—a well-established CD susceptibility gene [8]. These mutations impair innate immune responses to bacterial peptidoglycans, compromising pathogen clearance and dysregulating inflammatory signaling, thereby establishing a mechanistic link between DPAU and CD through shared defects in innate immunity and intestinal barrier function. The elevated IL-1 β levels observed in our patient provide support for the hypothesis that innate immune activation plays a role in DPAU pathogenesis. Together, these interconnected factors drive the development of CD-like perianastomotic ulcerations, highlighting the complex pathogenesis underlying DPAU and its striking resemblance to CD.

DPAU poses a diagnostic dilemma due to its overlap with CD in clinical presentation, endoscopic morphology, and histopathology. However, a recent European multicenter survey highlights critical distinctions: DPAU lacks systemic inflammation and extraintestinal manifestations, emphasizing the critical role of surgical history in differential diagnosis [1, 2]. The latency period from surgical anastomosis to DPAU formation remains variable from a few months to years after surgery. Frémond et al. [1] reported a series of 14 DPAU cases with a median latency of 11.5 years after intestinal surgery, including NEC. Additionally, Sondheimer et al. [9] described 6 children with NEC who developed anastomotic ulcers 5.5–13 years post-surgery. Our patient's presentation > 12 years after neonatal NEC aligns with these findings. Our patient's negative ASCA/ANCA and normal ileal biopsy further supported DPAU over CD, as these markers are often positive in CD and help differentiate the two entities.

Recent studies suggest that TNF- α -mediated inflammation may drive DPAU pathogenesis, mirroring the immune dysregulation seen in CD [5]. In CD, TNF- α overexpression perpetuates inflammation by promoting macrophage activation and epithelial apoptosis. Similarly, in DPAU, TNF- α -driven pathways may exacerbate mucosal damage at anastomotic sites, as evidenced by rapid ulcer healing and hemoglobin normalization following

adalimumab (a TNF- α inhibitor) therapy in our case. Frémond et al. [8] reported analogous findings in post-surgical CD-like lesions, where anti-TNF agents restored mucosal integrity by suppressing TNF- α -mediated neutrophil recruitment. Notably, anti-TNF agents demonstrate therapeutic efficacy in DPAU, with reporting 67% remission rates in pediatric cohorts [5].

Therapeutic strategies for DPAU remain contentious due to limited high-quality evidence. Although enteral nutrition and mesalamine are first-line options, their failure in our case with deep, refractory circumferential ulcers highlights the limitations of conventional approaches in severe phenotypes [2]. This failure may be attributed to SIBO secondary to ileocecal valve loss, a mechanism proposed by Madre et al. [1] that promotes TNF- α -driven inflammation at anastomotic sites. The strategic use of anti-TNF agents in DPAU warrants emphasis. Despite only 14% of patients receiving biologics in European practice, our early intervention with adalimumab induced rapid mucosal healing and 12-month remission with no adverse events. This supports targeted TNF- α suppression as a viable second-line strategy for refractory ulcers, particularly when EEN fails.

Despite our favorable outcomes, long-term vigilance is critical. Studies report a 70% recurrence after surgical resection [3] and 59% persistent symptoms despite therapy [1]. We recommend proactive monitoring with quarterly fecal calprotectin and annual endoscopy to detect subclinical recurrence. Our favorable long-term outcomes with adalimumab align with emerging evidence advocating early anti-TNF intervention to prevent fibrosis and stricture formation [10].

This case has several limitations. First, the absence of NOD2 mutation testing limits insights into genetic predisposition, a key factor in CD and potentially DPAU. Additionally, single-center data constrain generalizability, the optimal timing of biologics, and relapse risk following biologic discontinuation require validation in larger prospective cohorts.

In conclusion, this case highlights DPAU as a clinically distinct postsurgical complication requires careful differentiation from IBD in pediatric patients with intestinal resection history. Early anti-TNF- α therapy can induce rapid mucosal healing and sustained clinical remission in pediatric DPAU who have failed to respond to traditional symptomatic supportive therapy, a rare long-term complication of neonatal NEC surgery. This response supports emerging evidence implicating TNF- α -driven inflammation in DPAU pathophysiology. While our findings support anti-TNF- α as a viable option for the cases refractory to conventional supportive therapy, larger prospective studies are needed to establish optimal dosing, duration, and long-term safety. Given the high recurrence risk of DPAU and potential for late complications,

long-term monitoring is essential to optimize patient outcomes.

Abbreviations

DPAU	Digestive perianastomotic ulcerations
CD	Crohn's disease
NEC	Neonatal necrotizing enterocolitis
IBD	Inflammatory bowel disease
TNF	Tumor necrosis factor
EEN	Exclusive enteral nutrition

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Authors' contributions

Sun Lina and Han Yanan contributed to the conceptualization and design of this study. Sun Lina wrote the initial draft of the manuscript. Han Yanan critically revised the important knowledge content of the article. Wang Xinyi and Ren Xiaoxia participated in clinical practice and revised the paper. All authors contributed to and reviewed the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study involving human participant was approved by the Ethics Committee of Xi'an Children's Hospital. Written informed consent was obtained from the patient's legal guardian for publication.

Consent for publication

Informed consent to publish this case report was provided by the patient's parents.

Competing interests

The authors declare no competing interests.

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