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Case Report

Post-Liver Transplant Lymphoproliferative Syndrome as a Cause of Intestinal Ischemia and Perforation: A Case Report

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Abstract

Introduction: Liver transplantation has evolved from its pioneering inception in 1967 to become the definitive treatment for end-stage liver disease, with contemporary five-year survival rates exceeding 80% in most transplant centers worldwide. In Uruguay, this lifesaving procedure was incorporated into the healthcare system through the National Resource Fund (FNR) in 1994, initially requiring patient transfer to Argentina's Hospital Italiano before establishing domestic transplantation capabilities in 2003. The program has since expanded to include indications such as Wilson's disease-related cirrhosis, significantly improving outcomes for patients with metabolic liver disorders. Despite remarkable advances in immunosuppressive regimens and perioperative care, posttransplant lymphoproliferative disorder (PTLD) remains a devastating complication, occurring in 1-5% of liver recipients and carrying mortality rates approaching 50%. This report details a fulminant case of intestinal PTLD in a young adult transplant recipient to highlight the diagnostic challenges and therapeutic dilemmas posed by this aggressive condition.

Case Report: A 20-year-old female developed progressive diarrhea and profound weight loss (14 kg, 20% body weight) 22 months after liver transplantation for Wilson's disease while maintained on standard immunosuppression with tacrolimus and mycophenolate mofetil. Initial evaluation revealed Clostridioides difficile colitis and severe pancytopenia (hemoglobin 7.2 g/dL, leukocytes 2,400 cells/mm^3). Despite appropriate antibiotic therapy and conversion to mycophenolate sodium, her condition deteriorated rapidly with development of septic shock, multiorgan dysfunction, and concerning radiographic findings of intestinal pneumatosis. Emergency laparotomy demonstrated extensive necrosis affecting the distal ileum, right colon, with ischemic perforation sites requiring extended right colectomy with ileostomy and jejunal ischemia requiring resection. Histopathological examination confirmed the diagnosis of diffuse B-cell lymphoproliferative disorder with transmural intestinal infiltration. Despite maximal surgical intervention and intensive care support including vasopressors and renal replacement therapy, the patient succumbed to refractory shock within 48 hours of presentation.

Conclusions: Intestinal PTLD represents an uncommon but frequently fatal complication in transplant recipients, often presenting with nonspecific gastrointestinal symptoms that delay diagnosis until irreversible damage occurs. This case highlights the critical importance of maintaining high clinical suspicion for PTLD when evaluating immunosuppressed patients with persistent digestive complaints, particularly in young adult and Hispanic populations where risk may be elevated. The rapid clinical progression observed underscores the need for early diagnostic consideration and multidisciplinary management. These findings emphasize the value of protocolized surveillance strategies and preventive approaches in high-risk transplant recipients to improve outcomes for this devastating complication.

Introduction

The first successful liver transplantation in 1967 marked the beginning of a significant evolution in hepatobiliary therapy, transforming what was once an experimental procedure into an effective treatment option for end-stage liver disease, now achieving five-year survival rates exceeding 80%. In Uruguay, this procedure was incorporated into the coverage system of the National Resource Fund (FNR) in 1994, initially involving patient referrals to the Hospital Italiano in Buenos Aires. Domestic transplantation programs began in 2003, expanding to include indications such as Wilson's disease-related cirrhosis1,2.

Liver transplantation represents a milestone in the medical-surgical management of hepatic failure, demonstrating substantial benefits for both patient survival and quality of life. However, this procedure carries a broad spectrum of potential complications. Among these, graft rejection, disease recurrence, and complications stemming from immunosuppressive therapy remain particularly significant. The required immunosuppression increases susceptibility to both opportunistic infections and neoplastic development3.

This report presents a clinical case of post-transplant lymphoproliferative disorder (PTLD) with intestinal involvement, an uncommon but potentially severe complication. We aim to emphasize the critical importance of including PTLD in the differential diagnosis when evaluating transplant recipients presenting with gastrointestinal symptoms, particularly given its potential for rapid clinical deterioration.

Clinical Case

Personal History: A 20-year-old female patient underwent liver transplantation in 2023 for Wilson's disease (22 months prior to current presentation). Her immunosuppressive regimen consisted of tacrolimus and mycophenolate mofetil (later switched to mycophenolate sodium) and prednisone. Additional history included untreated anxiety disorder and previous laparoscopic appendectomy.

Current Illness History: Two months prior to admission, the patient presented with chronic diarrhea and weight loss, prompting hospitalization for diagnostic evaluation. Initial assessment revealed mild pure red cell anemia and Clostridioides difficile intestinal infection. Targeted intravenous antibiotic therapy was initiated. Due to the potential association between mycophenolate mofetil and diarrhea, the regimen was switched to mycophenolate sodium before discharge with oral vancomycin therapy, which the patient discontinued after three days due to intolerance. She failed to attend scheduled follow-up.

Current Disease Status: One month after initial consultation, she presented to the hepatology clinic with persistent diarrhea now accompanied by diffuse cramping abdominal pain, anorexia, and 14 kg weight loss (20% of total body weight), with associated fatigue and weakness. Upper gastrointestinal symptoms included nausea and vomiting. She denied fever, gross gastrointestinal bleeding, or other respiratory, urinary, musculoskeletal, cutaneous, or neurological symptoms.

Physical Examination: Notable for mild pallor of skin and mucous membranes, and signs of protein-calorie malnutrition. No lymphadenopathy was appreciated. Cardiopulmonary examination was unremarkable. Abdominal examination exhibited grade II splenomegaly (documented pre-transplantation) without tenderness at time of evaluation. No other significant findings were noted.

The decision was made to admit the patient for complete evaluation including colonoscopy and ileoscopy with biopsies.

Admission Laboratory Findings: Significant findings included hemoglobin 7.2 g/dL (normocytic/normochromic); leukopenia 2,400 cells/mm³ (lymphopenia and neutropenia); blood urea nitrogen 0.78 mg/dL; creatinine 1.5 mg/dL; positive EBV IgM and CMV IgG/IgM antibodies. Remaining tests including TSH, HIV, syphilis, hepatitis B and C serology, folic acid, vitamin B12 levels, ANA, ANCA, repeat C. difficile toxin assay, and EBV IgM antibodies were within normal limits.

Computed Tomography: Chest CT demonstrated a 14 mm cavitated lesion in the left upper lobe surrounded by ground-glass opacity. Initial neck, abdominal, and pelvic CT demonstrated no pathological findings.

Given concern for tuberculosis, fiberoptic bronchoscopy with alveolar lavage was requested for acid-fast bacilli staining, bacterial culture, and fungal detection. Digestive endoscopies were deferred pending these results, and stool testing for acid-fast bacilli was ordered.

Clinical Course: The patient developed dizziness, syncopal episodes, autonomic dysfunction, palpitations, and increased diarrhea frequency (up to 10 episodes in 12 hours). Physical examination demonstrated worsening pallor, dry tongue, peripheral coldness, blood pressure 70/50 mmHg, and serum lactate 1.2 mg/dL. Abdominal examination revealed distension with tympany and diffuse tenderness without clear peritoneal signs. Clear bile was noted via nasogastric tube.

ECG demonstrated narrow-complex tachycardia up to 150 bpm. Laboratory tests showed progressive pancytopenia, liver failure, and worsening renal failure.

The patient was transferred to the Intensive Care Unit

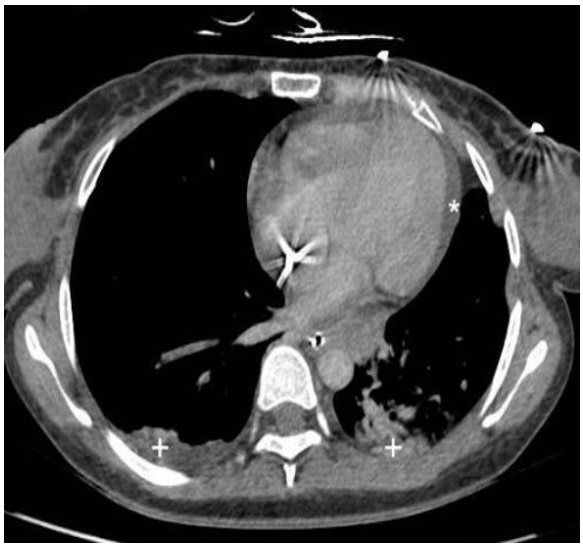

Figure 1: *Thoracic CT imaging and fluid (figure 1), pneumatosis in distal demonstrating persistent right lower ileum and cecum (without lobe consolidation with associated pneumoperitoneum), moderate free fluid pleural effusion (+) and pericardial predominantly in the lower and right effusion (*)*

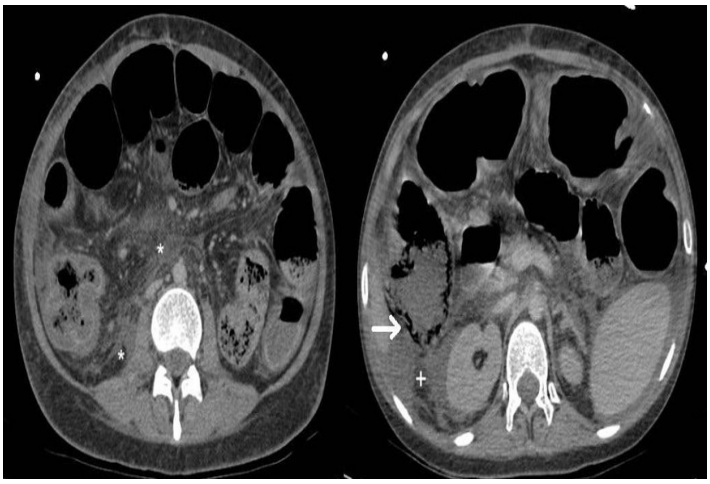

Figure 2: *Abdominal CT imaging demonstrating abdnormal mesenteric fat strading (*) free fluid predominantly in the right lower quadrant (+) and pneumatosis in the right colon (arrow)*

with presumed enteric septic shock. Management included packed red blood cell transfusion, fluid resuscitation, and broad-spectrum antibiotics (vancomycin, amikacin, metronidazole) with fluconazole.

Repeat abdominal CT showed new moderate bilateral pleural effusions, 9 mm pericardial effusion, persistent right lung consolidation abdomen, and abnormal mesenteric fat density (figure 2).

During exploratory laparotomy, turbid fluid and pseudomembranes were found. The distal ileum (last 20 cm) showed ischemic injury and aperistalsis, with associated ischemia of the right colon. An extended right colectomy was performed, resecting both segments with distal closure and proximal ileostomy. A fibrous band causing partial obstruction 100 cm from the ileocecal valve was lysed, and

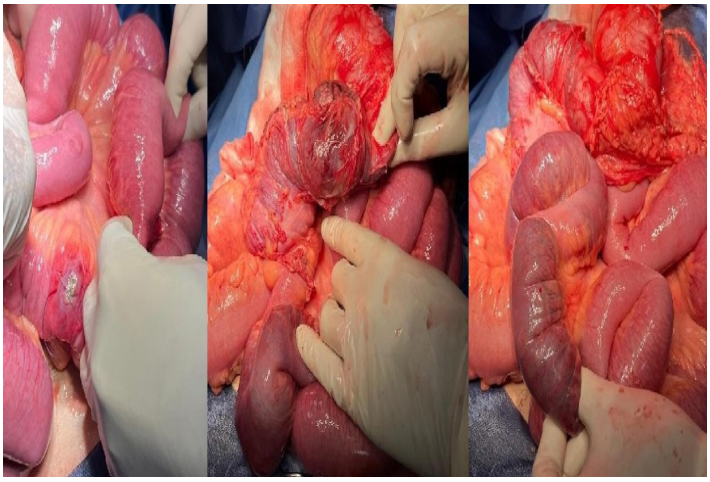

Figure 3: *On the left side, at 140 cm of ileocecal valve a segment of mid-jejunum with necrotic perforation, simple suture was performed. On central image, ischemic changes in the right colon. On the right side ischemic changes on the las 20cm of the ileum, right colectomy with ileostomy was performed.*

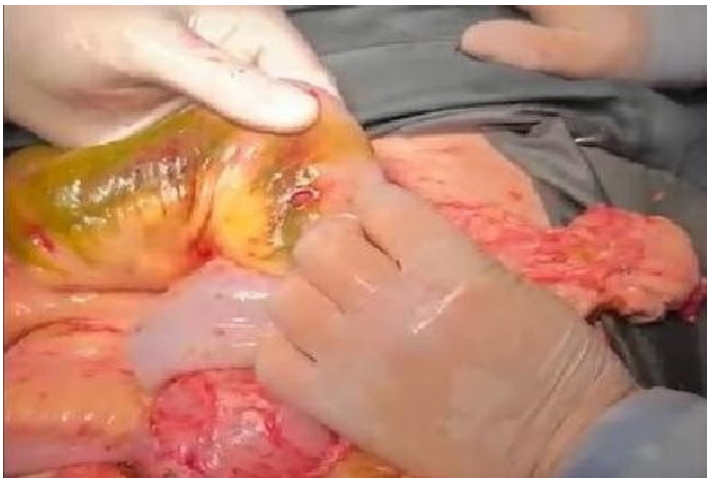

Figure 4: *Diffuse bile staining of peritoneal surfaces. A new ischemic perforation was identified along the mesenteric border of the proximal jejunum. Resection and primary anastomosis were performed*

the underlying serosal injury was repaired. At 140 cm from previous injury site, a segment of mid-jejunum showed necrosis with perforation, requiring resection and hand-sewn anastomosis. The abdomen was temporarily closed as a laparostomy (figure 3).

Postoperatively, the patient showed transient improvement with decreasing lactate and partial recovery of organ function. However, she developed anuria requiring hemodialysis, followed by clinical deterioration with increasing organ dysfunction and hypothermia. Antibiotic therapy was adjusted by the transplant infectious disease specialist.

Forty-eight hours past the first surgery, bilious drainage from the laparostomy system was noted and re-exploration was performed. It revealed bile-stained dressings with edematous but viable-appearing bowel. A new ischemic

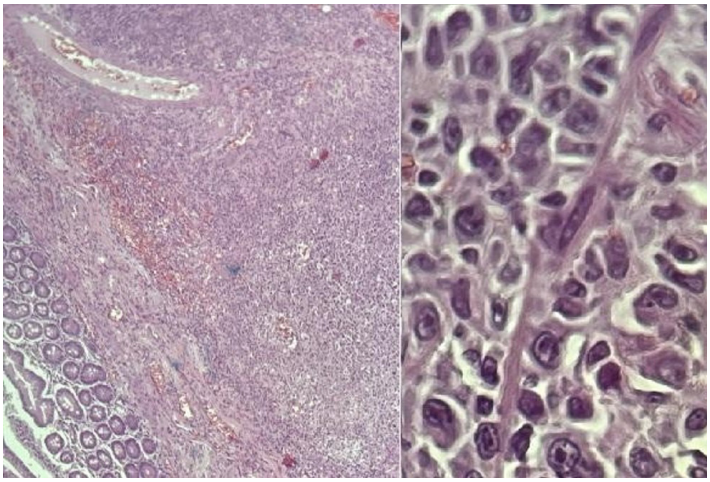

Figure 5: *On the left side HE 40x showing intestinal sections with extensive replacement by an atypical lymphoid cell proliferation showing a diffuse pattern. On the right side HE 400x showing atypical cellularity with lobulated nuclei, prominent nucleoli, and diffuse pattern.*

perforation was identified along the mesenteric border of the proximal jejunum (figure 4), which was managed with limited resection and primary anastomosis. Previous anastomotic sites appeared intact. The abdomen was again temporarily closed.

The patient progressed to refractory shock accompanied by escalating serum lactate levels, acidosis, and hemodynamic instability despite aggressive fluid resuscitation and high dose vasopressors. She died several hours later.

Pathological Findings: Histopathological examination of the specimens from both the first and second surgeries revealed necrotic and ulcerated areas with diffuse atypical lymphoid proliferation in the submucosa, composed of medium-sized cells exhibiting irregular nuclei, prominent nucleoli, and scant cytoplasm. A transmural mixed lymphomononuclear and polymorphonuclear inflammatory infiltrate was present, along with vascular thrombosis.

Immunohistochemical studies performed using available antibodies demonstrated that the atypical lymphoid cells were strongly and diffusely positive for CD45 (leukocyte common antigen), BCL2, and CD20, while negative for CD3, CD5, cytokeratin (CK), and CD10. The proliferation index, as assessed by Ki67 staining, was markedly elevated at 90%. Based on the morphological features and immunophenotypic profile including B-cell lineage differentiation, diffuse growth pattern, and high proliferative activity. The findings are consistent with a large B-cell lymphoproliferative disorder4 (figure 5).

Discussion

Solid organ transplant recipients demonstrate a significantly higher incidence of malignancies compared to the general population, with variation depending on the transplanted organ type and specific immunosuppressive regimen employed. Within this context, PTLD represents the second most frequent neoplasm in transplant patients4. This entity is characterized by abnormal lymphoid proliferation, predominantly of B-cell origin, facilitated by immunosuppressive therapy. The clinical spectrum ranges from polymorphic lymphoid hyperplasia to aggressive monomorphic lymphomas5.

PTLD occurs more frequently in children and adolescents, with reported incidence rates of 1-5% among adult liver transplant recipients6,7. Our patient, aged 20 years with symptom onset at 19 years, falls within the World Health Organization's classification of late adolescence. This demographic consideration may hold epidemiological significance, as this age group potentially carries higher PTLD risk compared to older adults, though conclusive studies remain lacking.

Furthermore, increased PTLD incidence has been documented among Hispanic populations compared to other ethnic groups3. This observation holds relevance in our clinical setting, where underreporting may be influenced by geographic, genetic, and socioeconomic factors, compounded by potential underestimation due to limited representation in international studies. These findings emphasize the importance of case recognition and reporting in our region to advance epidemiological and clinical understanding of PTLD in Hispanic America3.

While most authors report that 80% of PTLD cases occur within the first post-transplant year, others suggest incidence increases after this period. Regardless of timing, PTLD typically follows an aggressive clinical course with approximately 50% mortality4,5,6,7.

Established risk factors include EBV seropositivity, transplanted organ type, and immunosuppression protocol. These factors reflect compromised immune surveillance and activation of proto-oncogenic viruses. Notably, tacrolimus-based regimens demonstrate higher association with PTLD development compared to other immunosuppressants. Some reports suggest synergistic risk elevation with concurrent EBV and CMV infection5,6.

Clinically, patients may present asymptomatically or with nonspecific systemic manifestations including fever and asthenia, or with organ-specific symptoms. The gastrointestinal tract represents one of the most frequently involved extranodal sites, particularly the distal small intestine and proximal colon. Manifestations range from abdominal pain, diarrhea, and vomiting to acute abdominal signs secondary to intestinal ischemia, as in our case. Lesions may present as masses, ulcers, or diffuse intestinal wall infiltration 4,6.

Diagnostic evaluation requires peripheral blood EBV viral load quantification (albeit with 50% sensitivity) and tissue biopsy for CD20 lymphocyte expression analysis, both of which subsequently guide therapeutic decisions. Following diagnosis confirmation, staging should incorporate imaging modalities, with consideration of combined anatomical and functional imaging (e.g., SPECT-CT) in selected cases6.

Therapeutic approaches include immunosuppression reduction, which may suffice for early-stage or polymorphic cases. More advanced or monomorphic disease requires antiCD20 antibody therapy and chemotherapy. Radiotherapy and surgical intervention remain options for localized disease or complications, as exemplified by our case6,7.

Conclusions

Intestinal involvement by PTLD represents an uncommon yet potentially life-threatening complication in transplant recipients, typically characterized by nonspecific clinical presentation and rapid progression. The limited awareness of this condition in local clinical practice, even among specialized transplant teams, may contribute to diagnostic delays, particularly when manifestations involve unusual sites such as the gastrointestinal tract.

This case underscores the critical importance of including PTLD in the differential diagnosis of persistent gastrointestinal symptoms among immunosuppressed patients, while emphasizing the need for maintaining high clinical suspicion to facilitate early identification. We anticipate that this report will enhance local recognition of this entity, including its pathophysiology, diagnostic approach, and therapeutic alternatives in our clinical setting.

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Conflict of Interest: The authors declare no conflicts of interest.

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