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"Choledochoduodenal Fistula Arising From Pancreatic Lymphoma: An Exceedingly Rare Phenomenon"

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ABSTRACT

Choledochoduodenal fistula secondary to pancreatic lymphoma is a rare phenomenon, reflecting the complex relationship between lymphoproliferative disorders and gastrointestinal complications. Fistula formation should be suspected in patients with persistent liver function abnormalities and a history of treated hematological malignancies.

1 | Introduction

Choledochoduodenal fistulas (CDF) are an uncommon and complex clinical entity, characterized by an abnormal communication between the common bile duct and duodenum. These fistulas may arise from a number of underlying conditions, including chronic inflammatory pathologies, peptic ulcer disease, malignancies, and trauma [1]. While there are documented cases of CDF arising from diffuse large B-cell lymphoma (DLBCL) of the duodenum following initiation of systemic chemotherapy, their occurrence secondary to non-Hodgkin's lymphoma of the pancreas is an exceedingly rare phenomenon, with no previously documented cases in the literature [2].

CDF secondary to pancreatic non-Hodgkin's lymphoma is exceptionally rare. Non-Hodgkin's lymphomas encompass a diverse group of hematological malignancies characterized by the histological absence of Reed-Sternberg cells. Most originate from B-cell lines, with DLBCL being the most prevalent subtype [3]. Since the 1970s, the incidence of non-Hodgkin's lymphoma has doubled, affecting one in ten thousand individuals. While 75% of patients present with nodal disease, 25% may exhibit extranodal disease, involving the skin, oropharynx, gastrointestinal tract, bone, central nervous system, and lungs. The pancreas is an exceptionally rare site for primary lymphoma, accounting for just 1% of extranodal lymphomas and 0.5% of all pancreatic tumors [4].

High-grade lymphomas such as DLBCL are typically more aggressive than their low-grade counterparts but are often more amenable to curative treatment. They are characterized by rapidly enlarging lymphadenopathy and systemic symptoms such as fever, nocturnal diaphoresis, and weight loss. Conversely, pancreatic lymphomas tend to display a more insidious onset with non-specific symptoms, hence complicating the diagnostic process [3]. CDF in this context represents a rare, late-stage complication of lymphomatous infiltration and tissue destruction. These fistulas demonstrate the potential for serious complications, including biliary obstruction, cholangitis, and sepsis.

This case report elucidates the clinical course of a patient with CDF arising secondary to treated pancreatic DLBCL, as well as the diagnostic and management challenges encountered. The rarity of this complication of pancreatic DLBCL is underscored by the apparent absence of documented cases in the existing literature. Moreover, this report seeks to contribute to the growing body of knowledge surrounding the complex interplay between lymphoproliferative disorders and gastrointestinal

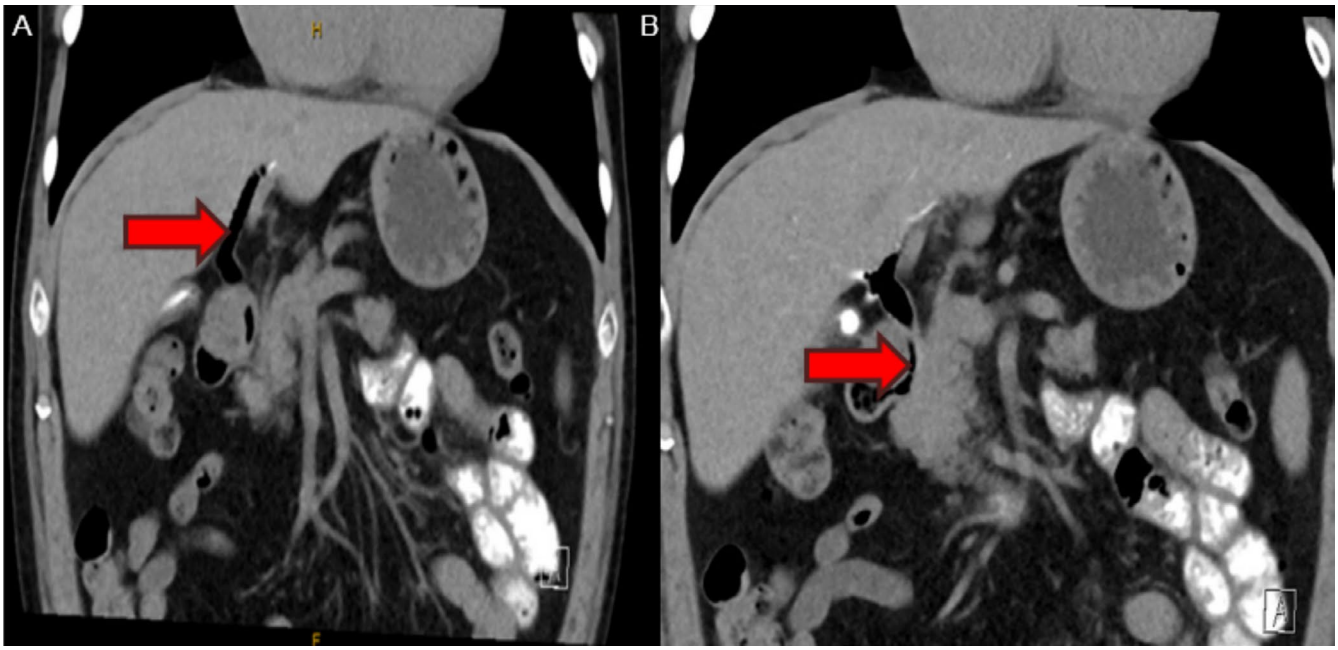

FIGURE 1 | (A) CT abdomen and pelvis coronal section demonstrating a conspicuous gas-filled CBD indicative of pneumobilia, as highlighted by the red arrow; (B) CT abdomen and pelvis coronal section demonstrating the absence of a clear tissue plane between the CBD and duodenum, and a subtle yet possible tissue bridge between the two (highlighted by a red arrow), suspicious for a CDF.

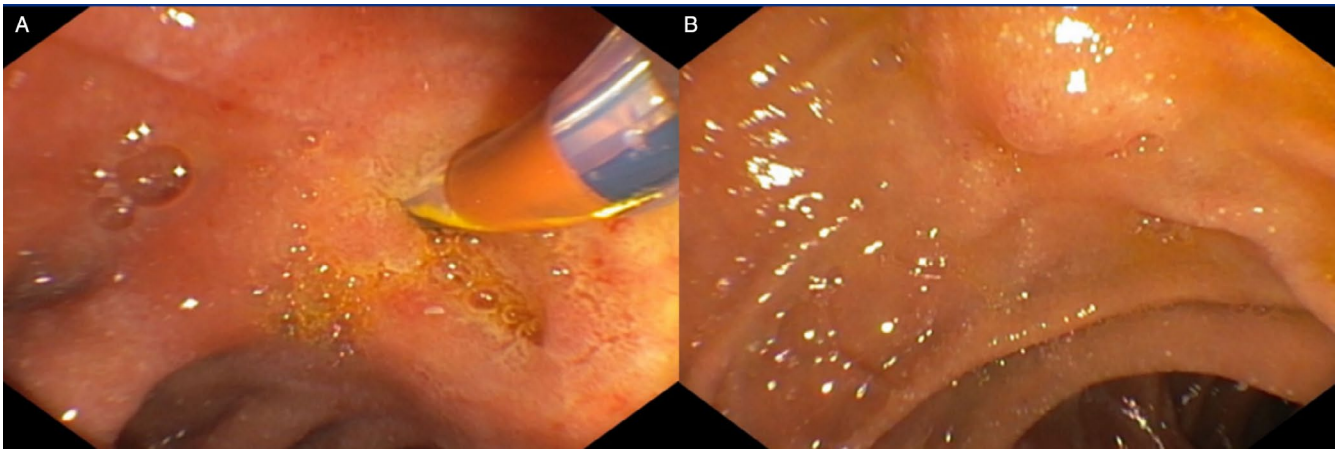

FIGURE 2 | (A) ERCP clinical image/view demonstrating cannulation of the distal fistula tract opening from the duodenum; (B) Endoscopic view of the ampulla, which was unable to be cannulated and without bilious drainage appreciable.

complications, emphasizing the importance of clinical vigilance in patients presenting with atypical symptoms.

2 | Case History/Examination

A 63-year-old male with a history of treated DLBCL of the pancreatic head presented to the surgical outpatient clinic at an Australian metropolitan hospital, reporting chronic lethargy, weight loss, and abnormal liver function tests (LFTs).

In 2014 he was diagnosed with pancreatic DLBCL, an extremely rare lymphoproliferative disorder. This was managed successfully with an R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy regimen. While undergoing chemotherapy, however, he experienced multiple episodes of sepsis requiring hospital admission for antibiotic therapy, although without a clear cause found at the time. In 2017, he presented with multiple clusters of lesions on the skin of his anterior abdominal wall, with punch biopsies demonstrating an atypical lymphoproliferative process. The differentials included lymphomatoid papulosis and anaplastic large-cell lymphoma (primary cutaneous). Histologically, this was not thought to represent a recurrence of the patient's previous DLBCL, and he underwent local radiotherapy to good effect.

When reviewed in clinic for chronic lethargy, the patient denied abdominal pain or systemic symptoms of infection and appeared otherwise well. On examination, the patient appeared well with vital signs within normal limits, and his abdomen was soft and non-tender. He was non-icteric and demonstrated no central or peripheral stigmata to suggest lymphoma recurrence.

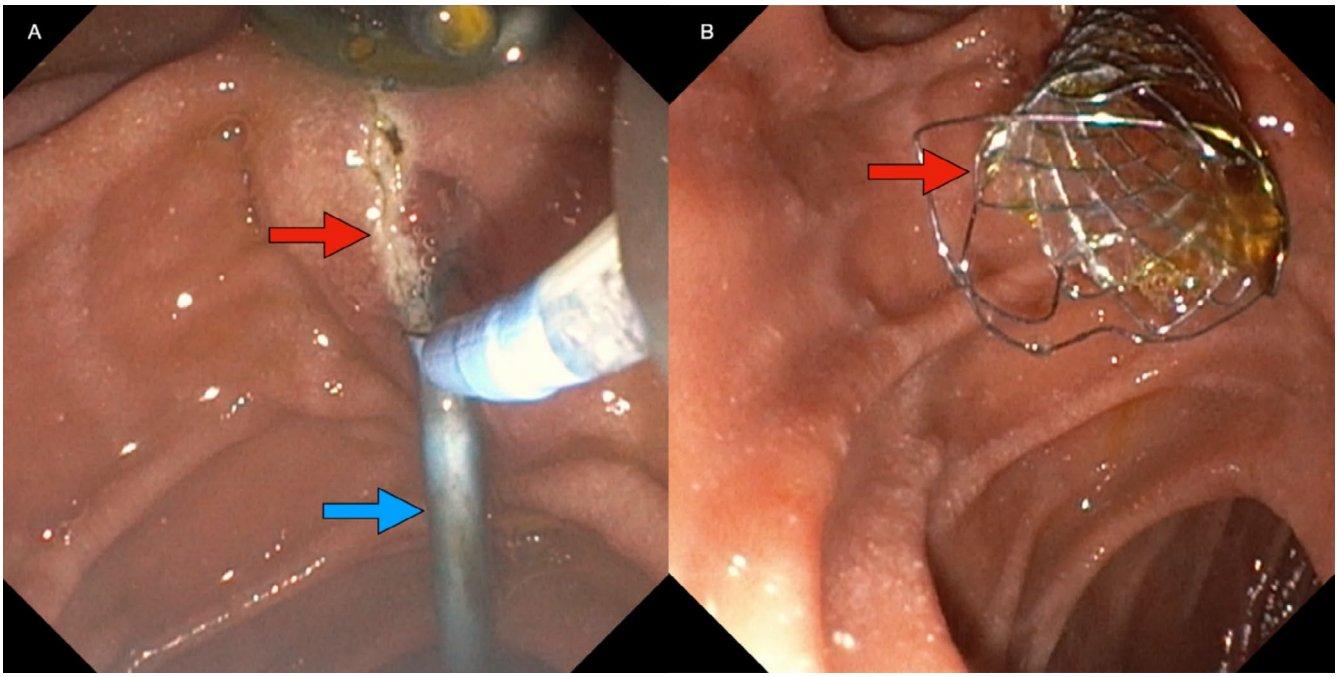

FIGURE 3 | (A) Repeat ERCP demonstrating the previously placed plastic stent emanating from the major duodenal papilla (indicated by the blue arrow), and a needle knife papillotomy cutting down on the stent at the papilla (denoted by the red arrow); (B) plastic stent replaced with a fully covered metal stent as indicated by the red arrow.

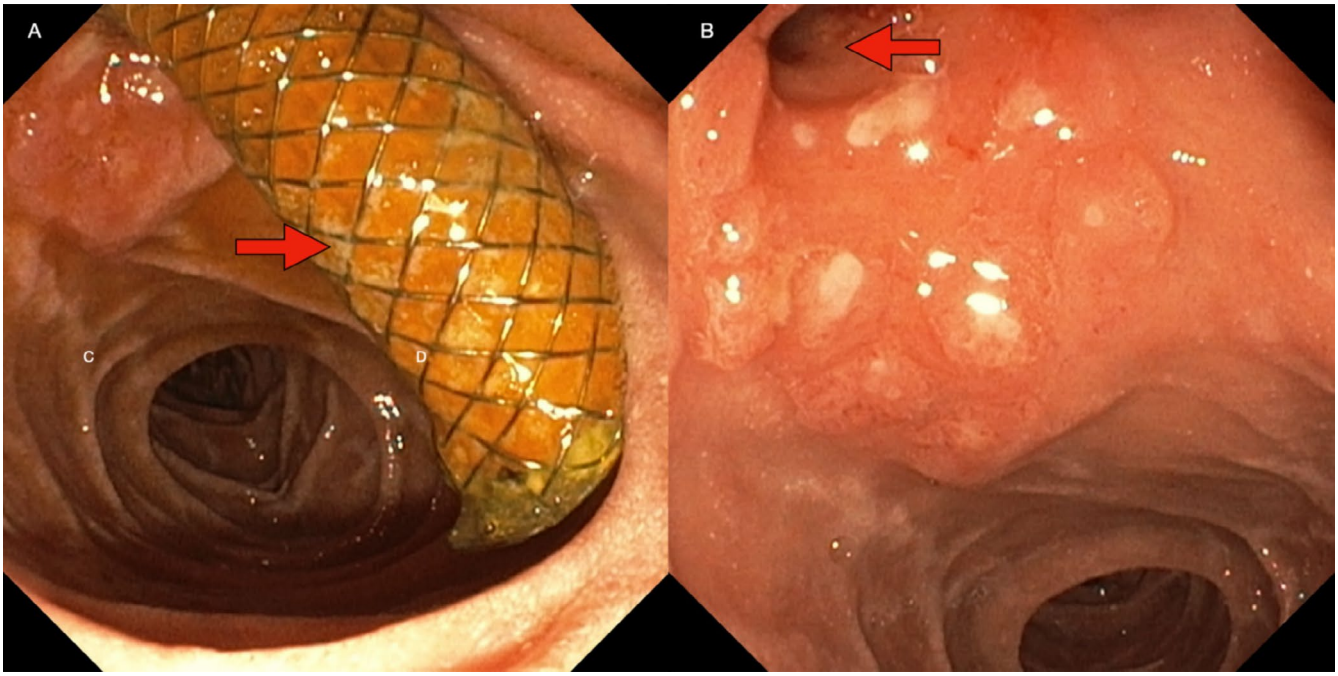

FIGURE 4 | (A) Final ERCP 6 months later demonstrating the fully covered metal stent emanating from the major duodenal papilla, as indicated by the red arrow; and (B) patent major duodenal papilla following the removal of the metal stent, denoted by the red arrow.

3 | Differential Diagnosis, Investigations, and Treatment

The patient's biochemistry revealed a chronic hyperbilirubinemia (32 μmol/L) and mildly elevated alkaline phosphatase (ALP) (119 IU/L), albeit with a normal alanine aminotransferase (ALT) (21 IU/L), gamma glutamyl transferase (GGT) (20 IU/L), aspartate transferase (AST) (26 IU/L), and white cell count (8.0×10^9/L). Computed tomography (CT) abdomen and pelvis demonstrated no recurrence of his previous lymphoma, but revealed extensive pneumobilia. A CT intravenous cholangiogram (CTIVC) further delineated the patient's biliary anatomy, revealing a fistula between the common bile duct and duodenum (Figure 1), likely causing his LFT derangement. The red arrow in Image A of Figure 1 highlights a conspicuously gas-filled common bile duct (CBD), while the red arrow in Image

B demonstrates the absence of a clear tissue plane between the CBD and duodenum, suggesting a tissue bridge suspicious for a CDF.

Endoscopic retrograde cholangiopancreatography (ERCP) was performed to further investigate and manage the fistula tract visualized on CTIVC. A fistula was identified between the D1/D2 junction and CBD, with a distal CBD stricture. Both the proximal and distal openings of the fistula tract were able to be cannulated (as demonstrated in Figure 2). A small volume of clear pancreatic fluid was noted to emerge from the major ampulla, but no bile was seen, suggesting a chronic distal CBD obstruction. Multiple attempts were made to cannulate the native ampulla to no avail, but the bile duct was able to be accessed both in anterograde and retrograde directions down to the ampullary opening. In light of this, a formal metallic stent was not inserted; instead, a temporary plastic stent was inserted to facilitate interim biliary drainage.

ERCP was repeated four months later, this time with the previously inserted plastic stent now emanating from the native ampulla. A needle-knife papillotomy was performed to cut down upon the stent at the native ampulla, and the stent was removed (see Figure 3A). The bile duct was cannulated from the native ampulla, with cholangiography demonstrating the previously identified fistula opening at the D1/D2 function, as well as the opening of the posterior sectoral duct (PSD). There were two centimeters between these two openings, and hence a six-centimeter fully covered self-expanding metallic biliary stent was deployed (see Figure 3B) to exclude the fistula opening, with its proximal end immediately below the PSD entrance. As a result, the CDF had now been formalized into the normal anatomical biliary drainage, with drainage occurring through the major papilla in D2, while the fistula opening was excluded by the metallic stent. During outpatient review post-procedure, he was asymptomatic and well, with stable LFT parameters (bilirubin 33 IU/L).

Following a six-month period to facilitate peri-stent connective tissue remodeling, a repeat ERCP was performed. The previously placed metallic stent was observed emanating into the duodenum through the native orifice of the bile duct, with good opening of the distal CBD (see Figure 4). The previous fistula appeared to have remodeled into a wide-open one centimetre defect without communication with the duodenum. Hence, the stent was removed and not replaced, and cholangiography revealed normal flow through the major ampulla. On post-procedure review in the outpatient clinic, the patient was now well and asymptomatic, with no further episodes of sepsis. No further ERCP is planned at this stage, with clinical and radiological monitoring (using magnetic resonance cholangiopancreatography (MRCP)) planned in a year's time to assess for maintenance of distal CBD patency.

4 | Discussion

CDF is a rare clinical entity, typically associated with chronic inflammatory pathologies, malignancies, and trauma [5, 6]. It is well established that chemotherapy for gastrointestinal neoplasms can be associated with complications such as hemorrhage and perforation and, in some instances, fistula formation [2, 5–7]. A comprehensive review of the literature utilizing the search terms "choledochoduodenal fistula" "pneumobilia" "lymphoma" "neoplasms" and "Non-Hodgkin's Lymphoma" across the databases Ovid Medline, PubMed, Scopus, and Google Scholar identified only two documented cases of CDF secondary to duodenal lymphoma and methotrexate-induced lymphoproliferative disease [2, 5]. This case, however, highlights the first-ever documented case of CDF in pancreatic lymphoma.

The pathogenesis of chemotherapy-induced fistula formation likely stems from rapid regression of tumor and lymph node size, along with tissue destruction [2, 5]. Chemotherapy regimens commonly used in the management of DLBCL, such as R-CHOP, as previously used in our case, possess a multifactorial pathogenesis in CDF development. Rituximab targets CD20-positive B-cells, promoting rapid tumor lysis in combination with cytotoxic agents. This rapid rate of lysis can destabilize tissues infiltrated by tumor at the interface of the CBD and duodenum, facilitating fistula formation [8]. Doxorubicin, an anthracycline, disrupts DNA repair mechanisms and generates reactive oxygen species causing DNA damage, while cyclophosphamide induces cellular apotosis through inter- and intra-strand DNA cross-linking, both of which cause tumor necrosis [9, 10]. Vincristine, however, can impair cellular division in rapidly dividing cells, such as those of the intestinal mucosa, through disruption of microtubule assembly. This can predispose to intestinal ulceration and subsequent erosion into local structures such as the CBD, promoting fistula formation [11].

In duodenal lymphoma, as presented by Scott et al. (2001), fistula development was postulated to arise from transmural invasion by the tumor, establishing a contiguous tissue bridge between the duodenum and CBD. As transmural invasion progresses, normal tissue is progressively replaced by the developing tumor. With chemotherapy, the tumor in the common wall established between the two organs undergoes necrosis and is destroyed, resulting in fistula formation [2]. Similarly, in a patient with methotrexate-associated lymphoproliferative disorder, as described by Eso et al. (2018), fistula development was thought to be a consequence of the chemotherapy regimen of rituximab, brentuximab, and nivolumab, causing rapid regression of lymph nodes adjacent to both the duodenal wall and CBD, leading to CDF formation [5].

The diagnosis of CDF can be challenging due to the non-specific nature of symptoms. In some instances, patients may present asymptomatically, further complicating early detection. The suspicion of CDF development in this patient was understandably low given the rarity of this condition and the non-specific clinical presentation, which included chronic lethargy and weight loss, along with chronic obstructive LFT derangement on biochemical investigation. Suspicion of CDF was raised when pneumobilia was identified on CTIVC, and a formal diagnosis of CDF was confirmed following ERCP. Even with the presence of MRCP as an emerging diagnostic tool for the assessment of biliary anatomy, the presence of pneumobilia and a possible tissue bridge between the CBD and duodenum was deemed sufficient to proceed with ERCP. It should be noted that at the time of writing, there are no large-scale studies comparing the sensitivity and specificity of CTIVC and MRCP in CDF diagnosis. In a review

article of CDF cases in China, most patients presented with epigastric pain (80.91%), cholangitis (54.26%) and fever (50.69%). In the same review, ERCP was determined to be the most reliable diagnostic modality, with 475 of 728 cases confirmed using this method, while ultrasound and CT were of limited utility for CDF diagnosis [6]. As such, the non-specific nature and scarcity of documented cases of CDF, combined with the necessity for invasive procedures such as ERCP to establish a formal diagnosis, make clinical recognition and diagnosis very challenging. Hence, a multi-disciplinary approach and advanced imaging modalities such as MRCP or CTIVC need to be considered.

5 | Conclusion

This case describes the first-known instance of choledochoduodenal fistula secondary to DLBCL of the pancreas, a novel and complex interplay between lymphoproliferative disorders and gastrointestinal manifestations. While DLBCL can present with nodal or extra-nodal involvement, its occurrence in the pancreas with subsequent fistula formation remains rare within the literature. This case underscores the importance of maintaining a high index of suspicion for fistula formation in patients presenting with persistently deranged liver function tests in the context of previously treated hematological malignancies. Clinical vigilance, early identification with CTIVC or MRCP, and a multidisciplinary approach are paramount for optimal management, although further research is needed to identify the mechanisms driving fistula formation.

Author Contributions

Shalvin Jassal: writing – original draft, writing – review and editing, writing – review and editing. **Nathan Ip:** writing – original draft. **Adrian Fox:** supervision. **Melanie Crispin:** supervision.

Disclosure

This manuscript has not been published or submitted elsewhere for consideration for publication. There are no further authors to list or acknowledge.

Consent

Appropriate verbal and written consent was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data available has been presented within this manuscript.

References

1. B. S. Bhaviya, A. Kar, M. Dutta, A. Mandal, and S. De Bakshi, "A Case of Choledochoduodenal Fistula—An Unusual Case Report," *Clinical Case Reports* 5, no. 9 (2017): 1462–1464.

2. J. Scott, J. A. Spencer, and K. A. MacLennan, "Choledochoduodenal Fistula Complicating Non-hodgkin's Lymphoma of the Duodenum During Chemotherapy," *Clinical Radiology* 56, no. 6 (2001): 508–510.

3. S. H. Swerdlow, E. Campo, N. L. Harris, et al., "The 2016 Revision of the World Health Organization Classification of Lymphoid Neoplasms," *Blood* 127, no. 20 (2016): 2375–2390.

4. L. Shi, J. Wang, L. Wei, Z. Ma, and X. Liu, "Pancreatic Diffuse Large B-Cell Lymphoma: A Case Report and Literature Review," *Frontiers in Oncology* 13 (2023): 1294385.

5. Y. Eso, N. Uza, K. Shirakawa, et al., "Choledochoduodenal Fistula During Chemotherapy With Brentuximab Vedotin for Methotrexate-Associated Lymphoproliferative Disorder," *Internal Medicine* 57, no. 15 (2018): 2203–2207.

6. M. B. Wu, W. F. Zhang, Y. L. Zhang, D. Mu, and J. P. Gong, "Choledochoduodenal Fistula in Mainland China: A Review of Epidemiology, Etiology, Diagnosis and Management," *Annals of Surgical Treatment and Research* 89, no. 5 (2015): 240–246.

7. J. Randall, M. L. Obeid, and G. R. Blackledge, "Haemorrhage and Perforation of Gastrointestinal Neoplasms During Chemotherapy," *Annals of the Royal College of Surgeons of England* 68, no. 5 (1986): 286–289.

8. T. Cerny, B. Borisch, M. Introna, P. Johnson, and A. L. Rose, "Mechanism of Action of Rituximab," *Anti-Cancer Drugs* 13, no. 2 (2002): S3–S10.

9. C. F. Thorn, C. Oshiro, S. Marsh, et al., "Doxorubicin Pathways: Pharmacodynamics and Adverse Effects," *Pharmacogenetics and Genomics* 21, no. 7 (2011): 440–446.

10. A. Emadi, R. Jones, and R. Brodsky, "Cyclophosphamide and Cancer: Golden Anniversary," *Nature Reviews. Clinical Oncology* 6 (2009): 638–647.

11. C. Wang, Z. Li, and W. Tian, "Tracheoesophageal Fistula Caused by Chemotherapy in Primary Thyroid Lymphoma: A Case Report," *Translational Cancer Research* 10, no. 7 (2021): 3582–3587.