Choledochoduodenal fistula arising from pancreatic lymphoma: An exceedingly rare phenomenon

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Key Clinical Message:

Choledochoduodenal fistula secondary to pancreatic lymphoma is an exceedingly rare phenomenon, highlighting the complex interplay between lymphoproliferative disorders and gastrointestinal manifestations. A high index of suspicion should be maintained for fistula formation in patients presenting with persistently deranged liver function tests in the context of previously treated haematological malignancies.

Introduction:

Choledochoduodenal fistulas (CDF) are an uncommon and complex clinical entity, characterised 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). Whilst 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).

Despite the myriad of causes of CDF, their occurrence secondary to non-Hodgkin's lymphoma of the pancreas is exceptionally rare. Non-Hodgkin's lymphomas encompass a diverse group of haematological malignancies characterised 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 extra-nodal disease, involving the skin, oropharynx, gastrointestinal tract, bone, central nervous system and lungs. The pancreas, however, remains an exceptionally uncommon site of primary lymphoma formation, accounting for only 1% of extranodal lymphomas and 0.5% of all pancreatic tumours (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 characterised 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). The formation of CDF in this context represents an extremely rare and late-stage manifestation, underscoring the intricate interplay between lymphomatous infiltration, local tissue destruction and subsequent fistula formation. 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 pancreatic DLBCL, as well as the diagnostic and managemental 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 complications, emphasising the importance of clinical vigilance in patients presenting with atypical symptoms.

Case History/Examination:

A 63-year-old male with a background of treated DLBCL of the pancreatic head presented to the surgical outpatient clinic of an Australian metropolitan hospital with chronic lethargy, weight loss and deranged liver function tests (LFT) for investigation. He was otherwise well, with no local or systemic symptoms of infection, and denied abdominal pain. On examination, the patient appeared well with vital signs within normal limits, and his abdomen was soft and non-tender.

By way of past medical history, in 2014 he was diagnosed with a primary pancreatic lymphoma, an extremely rare lymphoproliferative disorder. This was managed successfully with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). While undergoing chemotherapy, however, he experienced multiple episodes of sepsis requiring hospital admission for antibiotic therapy. 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.

Differential diagnosis, investigations and treatment:

His biochemistry revealed a chronic mixed LFT derangement, with a chronic hyperbilirubinaemia (60 micromol/L), and mildly elevated alanine aminotransferase (42 IU/L), gamma glutamyl transferase (132 IU/L), alkaline phosphatase (119 IU/L), albeit a normal white cell count (8.0x10ˆ9/L). Computed tomography (CT) abdomen and pelvis demonstrated extensive pneumobilia, with a bridge of tissue between the gallbladder and duodenum, suspicious for a fistula. The distal common bile duct could not be visualised. CT cholangiogram to further delineate the patient's biliary anatomy revealed a fistula between the common bile duct and duodenum (Figure 1), and hence was the suspected cause for his LFT derangement.

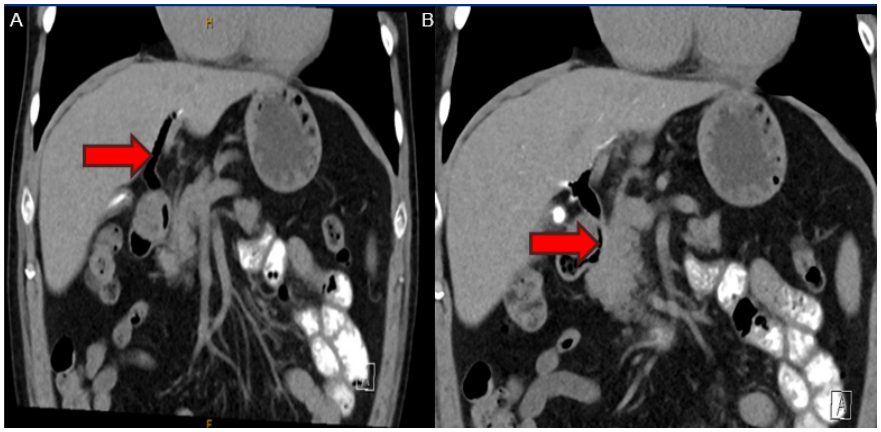

Figure 1: (A) CT abdomen and pelvis coronal section demonstrating the presence of pneumobilia, as indicated by the red arrow; (B) CT coronal section demonstrating the presence of a subtle yet possible tissue bridge between the common bile duct and duodenum, suspicious for a CDF, as indicated by the red arrow.

Endoscopic retrograde cholangiopancreatography (ERCP) was performed to further investigate and manage the fistula tract visualised on CT. A fistula was identified between the D1/D2 junction and common bile duct. Both the proximal and distal openings of the fistula tract were able to be cannulated (see Figure 2). Small volume clear pancreatic fluid was noted to emerge from the major ampulla, but no bile was seen, suggesting a chronic distal bile duct obstruction. Multiple attempts were made to cannulate the native ampulla, albeit to no avail. A fully-covered metal stent was inserted into the fistula tract for formalisation, facilitating biliary drainage. The patient tolerated the procedure well, with resolution of his symptoms and normalisation of his biochemistry.

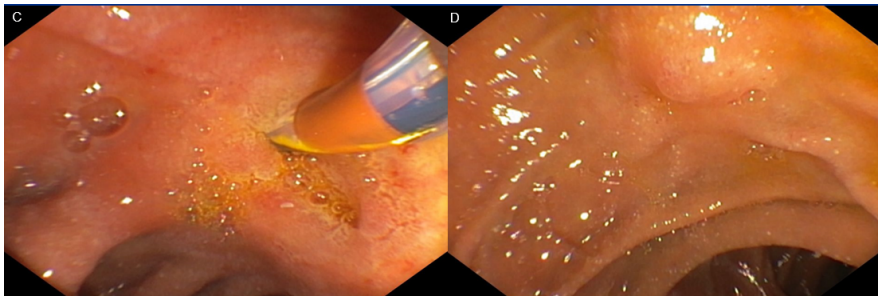

Figure 2: (C) ERCP clinical image/view demonstrating cannulation of the distal fistula tract opening; (D) Endoscopic view of the ampulla, unable to be cannulated and without bilious drainage appreciable.

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 haemorrhage and perforation, and, in some instances, fistula formation (2,5,6,7). A comprehensive review of the literature using the terms "choledochoduodenal fistula", "pneumobilia", "lymphoma", "neoplasms" and "Non-Hodgkin's Lymphoma" across the databases Ovid Medline, PubMed, Scopus and Google Scholar identified two documented cases in which chemotherapy treatment of duodenal lymphoma and methotrexate-induced lymphoproliferative disease led to CDF formation. However, no documented cases of CDF arising from chemotherapy for pancreatic lymphoma were identified (2,5).

The pathogenesis of fistula formation secondary to chemotherapy is thought to stem from the rapid regression

in tumour and lymph node size, as well tumour tissue destruction (2,5). In cases of duodenal lymphoma, fistula development is postulated to arise from transmural invasion by the tumour, establishing a contiguous tissue bridge between the duodenum and CBD. As transmural invasion progresses, normal tissue is progressively replaced by the developing tumour. With chemotherapy, the tumour in the common wall established between the two organs becomes necrotic and is destroyed, resulting in fistula formation. (2) Similarly, in a patient with methotrexate-associated lymphoproliferative disorder, the development of their fistula 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 common bile duct, leading to CDF formation (5). In our case, the CDF likely developed from inflammation, necrosis, and the formation of a distal biliary stricture, following chemotherapy for pancreatic lymphoma.

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. In our case, the only symptoms reported were chronic lethargy and weight loss, with chronic LFT derangement on biochemical investigation. The suspicion of CDF development in this patient from his initial presentation was understandably low given the rarity of this condition and the non-specific clinical presentation. Suspicion of CDF was raised when pneumobilia was identified on CT, and a formal diagnosis of CDF was confirmed following ERCP. 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 in 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.

Conclusion:

This case describes the first known instance of choledochoduodenal fistula secondary to DLBCL of the pancreas, an extremely rare 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 is exceedingly 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 haematological malignancies. Clinical vigilance, early identification and a multidisciplinary approach are paramount for optimal management, although further research is needed to identify the mechanisms driving fistula formation.

Consent: Appropriate verbal and written consent was obtained from the patient.

Author Contributions: Author 1: Writing - Original Draft Preparation, Writing - Review and Editing Author 2: Writing - Original Draft Preparation, Writing - Review and Editing Author 3: Supervision Author 4: Writing - Review and Editing, Supervision

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