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Fatal Journey: Acute Liver Failure as a Complication of Nasal NK/T-Cell Lymphoma in a 53-Year-Old Male

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Abstract
Acute liver failure is a rare but catastrophic complication in nasal-type NK/T-cell lymphoma, typically occurring in terminal stages and associated with mortality rates nearing 94%. This report describes a 53-year-old male with NKTCL who developed ALF after his third cycle of Gemox chemotherapy, presenting with severe right upper quadrant pain, rapid jaundice, and diffuse bruising. Laboratory findings showed marked hepatic injury with extreme transaminitis, hyperbilirubinemia, hypoalbuminemia, and thrombocytopenia, while ultrasound revealed hepatomegaly and multiple complex masses consistent with extensive malignant hepatic infiltration. The ALF was determined to result from a dual mechanism: direct lymphoma infiltration combined with chemotherapy-induced hepatotoxicity, creating a synergistic injury that overwhelmed hepatic function. Despite aggressive supportive care, the patient deteriorated rapidly and died shortly after the onset of liver failure. This case underscores the highly aggressive course of NKTCL complicated by hepatic involvement and highlights the need for strict liver function monitoring during systemic therapy, as transplantation is generally contraindicated and therapeutic options remain extremely limited.

INTRODUCTION

Nasal-type NK/T-cell lymphoma (NKTCL) is a rare, highly aggressive subtype of extranodal non-Hodgkin lymphoma, recognized as a distinct entity in the World Health Organization classification (MyLymphomaTeam, 2025). The disease exhibits a marked geographic variation, being more common in Asian and Latin American populations, and is universally characterized by its strong association with Epstein–Barr virus (EBV) infection (MyLymphomaTeam, 2025). NKTCL typically presents outside the lymph nodes, commonly involving the nasal cavity, nasopharynx, and palate, but possesses a strong propensity for systemic dissemination to sites including the skin, gastrointestinal tract, and liver (de Azevedo et al., 2024; Haverkos et al., 2016; Kidwai et al., 2015).

Hepatic involvement by hematological malignancies is not uncommon, reported in 15% to 22% of cases, often observed during advanced stages of the disease (Worapongpaiboon et al., 2019). However, the development of severe functional hepatic decompensation, specifically acute liver failure (ALF) defined by severe acute liver injury coupled with encephalopathy and coagulopathy, is exceedingly rare. Malignant infiltration, particularly by non-Hodgkin lymphoma, constitutes less than 1% of all ALF etiologies, yet when it occurs, it carries a reported mortality

rate soaring up to 94%, underscoring its exceptional lethality (Worapongpaiboon et al., 2019).

This report documents the clinical course of a 53-year-old man diagnosed with NKTCL who developed ALF rapidly following the initiation of the third cycle of Gemox chemotherapy (Gemcitabine and Oxaliplatin). This case is unique as it encapsulates the critical therapeutic challenge inherent in oncology: deciphering whether acute hepatic collapse stems from overwhelming tumor progression, chemotherapy-induced liver injury (DILI), or a critical combination of both. The profound difficulty in managing this complication, coupled with the rapid, devastating outcome, necessitates detailed case documentation to inform future clinical decision-making regarding aggressive monitoring and treatment modification in this high-risk patient population (McIntyre et al., 2022; Moparthi et al., 2024; Scali & Stone, 2023; Șerban et al., 2025).

Previous research has well-documented the clinical trajectory of NKTCL, its frequent extranodal spread, and the hepatotoxic potential of various chemotherapy regimens, including Gemox. Studies such as those by Worapongpaiboon et al. (2019) and the review on non-Hodgkin lymphoma presenting as ALF (Alexopoulou et al., 2006) have established the grim prognosis of ALF in this context. However, there remains a critical gap in the literature regarding the precise timing and synergistic mechanism of failure in patients undergoing active treatment. Most documented cases describe ALF either at initial presentation or during late-stage, refractory disease. The novelty of the present case lies in its specific documentation of catastrophic hepatic failure precipitated precisely during the third cycle of Gemox chemotherapy. This timing suggests a critical threshold phenomenon where cumulative subclinical injury from both the tumor and prior chemotherapy cycles culminates in a final, fatal insult—a scenario not widely highlighted in existing case reports.

This report's urgency is underscored by the broader clinical challenge in oncology: balancing aggressive antitumor therapy with the management of life-threatening organ toxicity in patients with high-burden, infiltrative cancers. The case exemplifies the extreme end of chemotherapy-related morbidity, where standard monitoring may fail to predict a sudden, irreversible decline. Therefore, this detailed documentation is imperative to inform future clinical decision-making.

The objectives of this case report are to: (1) describe the unique clinical and laboratory profile of ALF occurring mid-chemotherapy in NKTCL; (2) analyze the probable synergistic pathogenesis of direct tumor infiltration and drug-induced liver injury (DILI); and (3) derive practical implications for risk stratification and management. The implications for clinical practice are significant. This case highlights the necessity for heightened vigilance and potentially more frequent liver function monitoring in patients with NKTCL, especially those with any radiological evidence of hepatic involvement. It argues for a low threshold to suspend chemotherapy upon detecting progressive liver enzyme elevations, even in the absence of overt symptoms, to potentially avert irreversible failure. Furthermore, it reinforces the critical role of advanced imaging to assess tumor burden and the difficult but essential consideration of early diagnostic biopsy when safe, to differentiate progression from toxicity and guide therapy. Ultimately, this report serves as a stark reminder of the lethal synergy between aggressive malignancy and

cytotoxic therapy, aiming to enhance clinical preparedness and improve the safety framework for managing these high-risk patients.

Method

Patient Information

Patient Identification and Initial Diagnosis

The patient was a 53-year-old male with a documented diagnosis of nasal-type NK/T-cell lymphoma. Due to the de-identified nature of this report, detailed socio-demographic, family, and comprehensive past medical history are limited. However, it is known that the patient had commenced systemic treatment following the staging of his aggressive lymphoma.

Prior Interventions and Clinical Course

The patient had received and completed two prior cycles of Gemox chemotherapy, a regimen combining Gemcitabine and Oxaliplatin, commonly used in the treatment of various aggressive lymphomas. Gemox is often selected as a non-anthracycline-based regimen in NKTCL, frequently incorporated into treatment protocols that involve L-asparaginase due to the recognized high susceptibility of NKTCL to L-asparaginase and the desire to minimize anthracycline-related toxicities. The fact that the patient tolerated the first two cycles suggests that any initial, subclinical liver injury was compensated, but the third cycle proved to be the critical precipitating event leading to hepatic decompensation.

Primary Concerns and Clinical Findings

Following the third cycle of chemotherapy, the patient presented with the chief complaint of sudden and severe right upper quadrant (RUQ) abdominal pain, signaling acute hepatic distress. Other prominent signs of synthetic liver failure and impaired hepatobiliary function quickly emerged.

Physical examination was remarkable for the presence of visibly icteric sclera, confirming jaundice. Furthermore, the examination revealed the presence of generalized bluish bruises (ecchymoses), indicating an underlying severe coagulopathy. Palpation of the abdomen confirmed organomegaly, specifically hepatomegaly. The constellation of RUQ pain, jaundice, coagulopathy, and hepatomegaly constitutes the classic presentation of severe, rapidly progressive acute liver failure, often associated with a lethal process such as massive necrosis or widespread malignant infiltration (Worapongpaiboon et al., 2019). The presence of active bleeding tendencies (manifested as bruising) is particularly critical as it often precludes invasive diagnostic procedures necessary for definitive diagnosis, such as liver biopsy (Nguyen & Wan, 2019; Mayo Clinic, 2025).

Timeline

The progression from tolerance of chemotherapy to acute liver failure and death was exceptionally rapid, emphasizing the aggressive nature of both the underlying malignancy and the resulting hepatic complication. The chronology below details the sequence of events leading to the

patient's critical state.

Table 1. Clinical and Therapeutic Timeline of Acute Liver Failure Progression

Time Point	Event Description	Clinical Status/Intervention	Key Implication
Initial Diagnosis	Diagnosis of Nasal NK/T-Cell Lymphoma	Initiation of Gemox Chemotherapy (Cycle 1)	High-risk hematologic malignancy established.
Prior Weeks	Completion of Cycle 1 and 2	Treatment tolerated (assumed)	Liver functional capacity maintained despite therapy.
Day 0	Initiation of Gemox Cycle 3	Administration of cytotoxic agents	Final hepatotoxic insult delivered.
Day 1 Post Cycle 3	Onset of Symptoms	Sudden RUQ abdominal pain, icterus, lethargy	Precipitating event: Rapid onset of hepatic failure.
Day 2 of ALF Crisis	Hospital Admission/Initial Labs	AST 691 U/L, ALT 213 U/L, Total Bilirubin 4.39 mg/dL, Platelets 51,000/μL	Diagnosis of Grade 4 Acute Liver Failure (ALF).
Day 3 of ALF Crisis	Diagnostic Imaging	Abdominal Ultrasound confirmed hepatomegaly with multiple complex hepatic masses	Objective evidence of structural disease/infiltration.
Subsequent Days	Management Period	Intensive Supportive Care, Transfusion/Coagulopathy Management	Deterioration despite maximum management efforts.
Outcome	Patient Death	Death due to Multi-Organ Failure (MOF)	Confirmation of extremely poor prognosis associated with this presentation.[2]

Source: Synthesized from Patient Medical Records, Laboratory Reports, Radiology Reports, and Clinical Documentation

Diagnostic Assessment

Diagnostic Testing: Laboratory and Imaging Findings

The initial laboratory results upon admission demonstrated profound hepatic dysfunction and compromised hematopoietic function.

Table 2. Key Laboratory Parameters at ALF Presentation (Peak Values)

Parameter	Patient Value (Units)	Reference Range (Typical Adult)	Clinical Significance
AST (U/L)	691	< 40	Severe Cytotoxicity (Grade 4: > 20 time ULN) [12]
ALT (U/L)	213	< 45	Moderate-Severe Cytotoxicity (Grade 3: > 5 time ULN) [12]
Total Bilirubin (mg/dL)	4.39	0.2–1.2	Severe Hyperbilirubinemia/Cholestasis [1]
Albumin (g/dL)	2.71	3.5–5.0	Impaired Hepatic Synthesis/Hypoalbuminemia [1]
Platelets (x10³/μL)	51	150–450	Severe Thrombocytopenia [1]
Hemoglobin (g/dL)	8.4	13.5–17.5	Anemia [1]

Source: Patient Laboratory Report (Day 2 of ALF Crisis)

The pattern of enzyme elevation is noteworthy. The AST value (691 U/L) was significantly higher than the ALT value (213 U/L). Although both markers indicate severe hepatocyte injury (Grade 3-4 according to NCI criteria), this disproportionate elevation, particularly an AST/ALT

ratio approaching 3:1, frequently suggests an element of non-hepatocellular injury, such as ischemia, mitochondrial damage, or rapid, widespread lytic tumor infiltration and necrosis, which is characteristic of aggressive hematologic malignancies. Furthermore, the low albumin level (2.71 g/dL) confirms compromised hepatic synthetic capacity, a crucial component of ALF diagnosis.

Imaging studies were essential for assessing structural integrity and disease burden. The abdominal ultrasound revealed generalized hepatomegaly coupled with the presence of multiple complex masses throughout the liver parenchyma. This finding strongly implicated widespread hepatic infiltration by the underlying lymphoma, shifting the diagnostic focus beyond isolated drug-induced injury (National Center for Biotechnology Information, 2020).

Diagnostic Challenges and Differential Diagnosis

The central diagnostic challenge in this case was accurately attributing the cause of ALF, which is crucial for determining appropriate antineoplastic management (Falcão et al., 2021). The main differential diagnoses included:

1. **Aggressive NKTCL Infiltration:** Rapid progression of the lymphoma directly destroying hepatic architecture, leading to failure.
2. **Chemotherapy-Induced DILI:** Specifically, severe toxicity related to Gemcitabine and/or Oxaliplatin.
3. **Synergistic Injury:** Malignant infiltration compromising liver function, making it susceptible to subsequent DILI.
4. **Paraneoplastic Syndromes:** Such as Hemophagocytic Lymphohistiocytosis (HLH), which can be associated with NKTCL and mimics ALF, characterized by fever and cytopenias.
5. **EBV Reactivation:** Since NKTCL is EBV-driven, chemotherapy may induce viral reactivation, leading to severe EBV-associated hepatitis or lymphoproliferative disorder.

The inability to perform a liver biopsy constituted the main diagnostic limitation (Falcão et al., 2021). Biopsy is generally considered indispensable in cases of ALF of unknown etiology in oncology patients, as it can definitively confirm malignant infiltration, differentiate it from DILI mechanisms (e.g., sinusoidal obstruction syndrome associated with oxaliplatin), or identify HLH features (MyLymphomaTeam, 2025). However, the patient's critical condition, evidenced by severe coagulopathy (bruising) and probable impaired International Normalized Ratio (INR), rendered the procedure critically high-risk (Falcão et al., 2021).

In the absence of histological confirmation, the diagnosis relied on the confluence of strong clinical evidence: the known aggressive nature of NKTCL, the confirmation of multiple complex hepatic masses on imaging (suggesting a large tumor burden), and the temporal relationship with the hepatotoxic Gemox regimen. The consensus diagnosis concluded a fatal synergistic injury.

Diagnosis and Prognosis

Diagnosis: Acute Liver Failure secondary to Nasal NK/T-cell Lymphoma hepatic infiltration critically exacerbated by Gemox chemotherapy-induced hepatotoxicity.

Prognosis: The prognosis for ALF secondary to hematologic malignancy is exceptionally poor. Published literature reports a mortality rate exceeding 90% for ALF caused by non-Hodgkin

lymphoma infiltration (Worapongpaiboon et al., 2019). Aggressive NKTCL itself carries a poor outlook, with five-year survival rates around 50%, even with the most effective therapies (Schmitz et al., 2021). When NKTCL progresses to ALF, the clinical trajectory is universally described as aggressive and rapidly fatal, often culminating in multi-organ failure shortly after symptom onset. Furthermore, the presence of active malignancy represents a contraindication to life-saving measures such as liver transplantation, eliminating the only potential curative option for refractory ALF.

Therapeutic Intervention

Prior Therapeutic Regimen

The patient was receiving the Gemox regimen, a combination of Gemcitabine and Oxaliplatin. This choice aligns with modern treatment strategies for NKTCL, which often favor non-anthracycline-containing regimens like GDP (Gemcitabine, Dexamethasone, Cisplatin) or P-GemOx (Pegaspargase, Gemcitabine, Oxaliplatin) (Wang et al., 2016). Oxaliplatin is known for its efficacy but carries a risk of sinusoidal obstruction syndrome (SOS) (Vincenzi et al., 2021), while Gemcitabine, though generally associated with mild aminotransferase elevations, can cause severe liver injury, especially cholestasis and failure, in patients with pre-existing hepatic disease (National Center for Biotechnology Information, 2020).

Intervention During ALF Crisis

Upon recognition of Grade 4 hepatotoxicity and the rapid decline toward ALF, all systemic chemotherapy was immediately suspended. The therapeutic approach shifted entirely to aggressive supportive care aimed at stabilizing the patient and managing the resultant complications.

Supportive measures included intensive neurological monitoring for the onset of hepatic encephalopathy, aggressive management of the severe coagulopathy (using fresh frozen plasma or Vitamin K to attempt correction of impaired synthetic function), and optimization of hemodynamic status. In cases of ALF of indeterminate etiology, standard protocols often dictate the empiric administration of N-acetylcysteine (NAC) and intravenous acyclovir to cover potential acetaminophen overdose or Herpes Simplex Virus (HSV) hepatitis, respectively, while definitive viral and serological workup is pending (American Association for the Study of Liver Diseases [AASLD], 2025a). Given the context of hematologic malignancy, treatment aimed at correcting electrolyte imbalances resulting from potential tumor lysis syndrome and broad-spectrum antibiotics to mitigate the high risk of infection associated with ALF and chemotherapy-induced immunosuppression were likely employed (American College of Clinical Pharmacy [ACCP], 2018; AASLD, 2025b).

Follow-up and Outcomes

The clinical course following the onset of ALF was characterized by relentless deterioration. Despite maximal supportive therapy, the patient showed no clinical or biochemical improvement. The liver injury progressed rapidly, leading to the failure of other organ systems. The persistent synthetic dysfunction, characterized by low albumin and severe coagulopathy,

combined with ongoing cytopenias (thrombocytopenia and anemia), created an environment conducive to multi-organ system collapse (Worapongpaiboon et al., 2019).

The ultimate and swift outcome was death due to refractory multi-organ failure. This fatal trajectory reinforces the consistent observation in the literature that ALF arising from direct malignant infiltration, especially in the context of aggressive high-grade lymphomas, is almost universally fatal, irrespective of early diagnosis and initiation of support.

Result and Discussion

Strengths and Limitations of the Case Report

A significant strength of this case report lies in highlighting a rare and lethal clinical intersection: acute liver failure superimposed on aggressive NK/T-cell lymphoma during cytotoxic chemotherapy. The temporal association between the third Gemox cycle and the onset of ALF provides a compelling opportunity to study synergistic organ toxicity.

The primary limitation, common to ALF patients presenting in extremis, was the inability to obtain a histological diagnosis via liver biopsy (Schmitz et al., 2021). Histopathology would have definitively quantified the extent of tumor cell infiltration, identified specific NK/T cell markers (e.g., CD56, Granzyme-1, EBV-EBER positivity) (Alexopoulou et al., 2006), and confirmed if DILI had manifested as SOS or severe cholestasis (Chavan et al., 2024). This histological absence requires the conclusion of multifactorial etiology to rely heavily on correlative evidence from imaging (multiple complex masses) and clinical context.

Review of Relevant Pathogenesis: NK/TCL, Hepatic Infiltration, and ALF

NK/T-cell lymphoma, especially the nasal type, is known for its highly aggressive nature and frequent extranodal involvement (Au et al., 2009). Hepatic involvement often takes two forms: diffuse infiltration (mimicking hepatitis or HLH) or focal lesions (masses). Diffuse infiltration of the liver by lymphoma cells (particularly T/NK cells) can mechanically compromise the hepatic microcirculation, leading to ischemia and subsequent hepatocyte necrosis, clinically manifesting as ALF (Worapongpaiboon et al., 2019).

Clinical reviews of non-Hodgkin lymphoma presenting as ALF describe a recognizable, albeit uncommon, syndrome often characterized by hepatomegaly and rapid death, sometimes associated with lactic acidosis (Worapongpaiboon et al., 2019). The presence of confirmed hepatomegaly and multiple complex masses in this patient's ultrasound strongly suggests the focal, large-scale infiltration mechanism, indicating a high tumor burden within the liver parenchyma. The rapid progression observed confirms the highly aggressive biological behavior typical of this specific presentation.

The Critical Role of Synergistic Toxicity (Malignant Infiltration + DILI)

The defining feature of this case is the timing of the ALF onset immediately following the administration of the third Gemox cycle. This temporal relationship suggests that the underlying malignancy, while severe, did not cause failure until a critical external insult was introduced.

1. **Pre-existing Vulnerability ("First Hit"):** The pre-existing NK/TCL hepatic infiltration,

confirmed by the complex masses, fundamentally compromised the liver's functional reserve. Lymphoma infiltration effectively creates a state analogous to pre-existing chronic liver disease (National Center for Biotechnology Information, 2020).

2. **Chemotherapy Overload ("Second Hit"):** Both components of Gemox contribute to hepatotoxicity. Gemcitabine is known to be associated with severe liver injury, specifically in patients with underlying hepatic pathology (National Center for Biotechnology Information, 2020). Oxaliplatin is well-documented to cause sinusoidal injury and SOS, which significantly impairs hepatic blood flow and can precipitate acute failure, especially in an already compromised liver (Robinson et al., 2013).

The patient's liver was already struggling under the massive tumor burden and likely subclinical damage from prior chemotherapy cycles. The cytotoxic load delivered in the third cycle overwhelmed the diminished capacity for metabolic clearance and cellular regeneration, pushing the liver past its functional threshold into irreversible failure. This synergistic mechanism explains the dramatic and rapid deterioration observed, distinguishing it from cases of primary DILI in a healthy liver or ALF caused solely by end-stage, untreated tumor burden (Falcão et al., 2021).

Differential Markers and Prognostic Indicators

Differentiating malignant infiltration from chemotherapy-induced injury is critical for treatment modification. While biopsy is the gold standard, non-invasive markers are sought. In NKTCL, monitoring plasma Epstein-Barr virus DNA (EBV-DNA) load is a vital prognostic tool and an indicator of tumor activity (Wang et al., 2018a). High pre-treatment EBV-DNA levels correlate strongly with poorer overall prognosis (Wang et al., 2018b). A dramatic increase in EBV-DNA during the ALF crisis could suggest widespread tumor cell death (lytic phase) or an EBV-driven HLH/reactivation component, which might require specific antiviral therapy (e.g., valganciclovir) (Kim et al., 2020).

The immediate implication of discovering malignant infiltration, even without biopsy (using strong imaging evidence and clinical context), is the absolute contraindication for urgent liver transplantation (Au et al., 2009). Since NKTCL is an aggressive, high-grade systemic disease, transplantation is rendered medically futile, locking the patient into palliative care (Worapongpaiboon et al., 2019).

Patient Perspective

Due to the critical and rapidly progressive nature of the illness and the subsequent fatal outcome, detailed retrospective documentation of the patient's perspective on the treatment and clinical course could not be obtained. However, the patient's immediate next-of-kin were actively involved in all medical decision-making regarding the supportive management provided during the final, critical days of the patient’s life.

Informed Consent

Informed consent for the preparation and publication of this case report was obtained from the patient's immediate next-of-kin. Care was taken to ensure that all patient-specific identifying

information remains de-identified, strictly adhering to ethical reporting guidelines.

CONCLUSION

This case report highlights acute liver failure as a lethal complication of aggressive NK/T-cell lymphoma (NKTCL), where hepatic infiltration—evident as multiple complex masses—creates a sensitized liver vulnerable to a "second hit" from hepatotoxic chemotherapy like Gemox, leading to synergistic collapse, rapid deterioration, and death despite intervention. Clinically, it emphasizes aggressive vigilance: clinicians should maintain a low threshold for discontinuing cytotoxic agents at moderate liver function test elevations in patients with suspected hepatic involvement, prioritize advanced imaging and histological diagnosis to differentiate drug-induced liver injury from malignant progression (despite coagulopathy risks), and pursue timely supportive care, though outcomes remain poor due to the disease's resistance. For future research, prospective studies should evaluate risk-stratification models integrating baseline hepatic imaging, biomarkers of infiltration, and pharmacogenomics to predict chemotherapy-induced failure, potentially guiding personalized de-escalation strategies or novel non-hepatotoxic therapies in high-risk NKTCL cohorts.

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