

ORIGINAL RESEARCH OPEN ACCESS

Hodgkin Lymphoma With Liver Involvement (Diagnostic, Therapeutic Difficulties, and Literature Review): A Retrospective Cohort Study

Fanni Borics^{1,2}  | Roxana Szabó³ | Sándor Barna⁴ | Judit Bedekovics⁵ | Boglárka Brúgós^{1,2} | Árpád Illés^{1,2} | Zsófia Miltényi^{1,2}

¹Division of Haematology, Department of Internal Medicine, University of Debrecen Faculty of Medicine, Debrecen, Hungary | ²Doctoral School of Clinical Medicine, University of Debrecen, Debrecen, Hungary | ³Hatvani Albert Schweitzer Kórház-Rendelőintézet Balassi Bálint u. 16, Hatvan, Hungary | ⁴ScanoMed Debrecen Nagyerdei krt. 98, Debrecen, Hungary | ⁵Department of Pathology, University of Debrecen Faculty of Medicine, Debrecen, Hungary

Correspondence: Fanni Borics (borics.fanni@med.unideb.hu)

Received: 6 February 2025 | **Revised:** 20 December 2025 | **Accepted:** 23 December 2025

Keywords: Hodgkin1 | liver3 | lymphoma2 | PET/CT4 | therapy5

ABSTRACT

Background and Aims: In classical Hodgkin lymphoma liver involvement occurs in 5%–8%, ranging from mild dysfunction to acute liver failure. Recognition and treatment of advanced cases are challenging due to rapid progression and limited use of therapies.

Methods: We analyzed the data of 250 Hodgkin lymphoma patients; 9 had liver involvement, one in the form of acute liver failure.

Results: Laboratory findings showed elevations of cholestatic enzymes, lactate dehydrogenase and haemostatic changes. PET/CT showed solo or multiple active areas in the liver and diffuse elevated standard uptake value in the patient with acute liver failure. In six cases ABVD/EBVD, in two brentuximab vedotin+AVD were used. Four patients achieved complete remission, four were relapsed or refractory, three of them died later. Brentuximab vedotin was started for the patient with acute liver failure, but she died in 2 days. Autopsy confirmed a Hodgkin-infiltrated liver structure.

Conclusion: Liver involvement has a negative impact on prognosis; however, early diagnosis and immediate initiation of therapy improve liver function. PET/CT can be a practical tool to support diagnosis and monitor response to therapy in patients where liver biopsy is not possible or does not contribute significantly to clinical management. With preserved liver function, ABVD is an effective treatment option, while with worsening liver function, brentuximab vedotin can be a safe alternative.

1 | Introduction

In classical Hodgkin lymphoma (HL), liver involvement is reported in 5%–8%. Its spectrum ranges from mild liver dysfunction to acute liver failure, which occurs in 0.44% of Hodgkin lymphoma cases [1]. It occurs mostly in patients with advanced-stage lymphoma, often in combination with splenic involvement. Usually, liver involvement is not associated with specific symptoms, laboratory or imaging abnormalities [2], therefore diagnosis and therapy are often delayed.

Early recognition of liver involvement is important, as in some cases the disease can follow a rapidly progressive clinical course with limited use of therapeutic options due to impaired liver function. Traditionally, confirmation of liver infiltration has relied on histopathological examination, liver biopsy. However, it is often technically challenging and contraindicated due to coagulopathy or rapidly deteriorating clinical status. These issues delay the diagnostic process and the start of appropriate therapy.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2026 The Author(s). *Health Science Reports* published by Wiley Periodicals LLC.

In this retrospective study, we investigated the prevalence and clinical course of liver involvement at our institution. Our aim was to characterize the diagnostic challenges, treatment outcomes and the potential value of PET/CT imaging. While PET/CT imaging is not a definitive diagnostic tool for liver infiltration, it may raise suspicion of hepatic involvement, particularly when histological confirmation is not possible due to clinical contraindications. By reviewing the symptoms, physical findings, imaging characteristics, and laboratory parameters of the patients we treated, we also aimed to identify patterns or features that might help define a severe disease course. These observations may support earlier recognition and intervention in this rare but severe form of HL.

2 | Patients and Methods

Between January 1, 2010, and December 31, 2023, we retrospectively reviewed the medical records of patients (≥ 18 years) diagnosed with classical Hodgkin lymphoma at the University of Debrecen.

Patients were included if both imaging (PET/CT) results and laboratory data (elevated liver enzymes and coagulation abnormalities) raised suspicion of liver involvement caused by Hodgkin lymphoma. Specifically, we selected cases where PET/CT scans showed hepatic abnormalities with increased [^{18}F]fluorodeoxyglucose (FDG) uptake, which were considered by a nuclear medicine specialist to be possible hepatic involvement of Hodgkin lymphoma. Laboratory parameters relevant to hepatic function were retrieved, including serum levels of alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total and direct bilirubin, aspartate aminotransferase (AST/GOT), alanine aminotransferase (ALT/GPT). Coagulation parameters, such as activated partial thromboplastin time (APTT), prothrombin index (PI), thrombin time (TT), and international normalized ratio (INR) were also recorded to assess haemostatic alterations. We also collected haematological (white blood cell count-WBC, haemoglobin-HGB, platelet count-PLT) and inflammatory (C-reactive protein-CRP) parameters.

For each included patient, we collected demographic data (age, sex), disease (Ann Arbor stage, histological subtype) and general condition characteristics (International Prognostic Score). Viral serology results for hepatitis B and C, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) were also recorded. We also collected data on first-line treatment decisions, dose modifications, the clinical response to therapy and long-term outcomes. We excluded patients with any form of pre-existing liver disease (autoimmune, infectious, alcohol-related or other non-lymphoma-associated etiologies) or with insufficient imaging and laboratory data.

Due to the relatively small number of patients, our analysis was limited to basic descriptive statistics. Continuous variables are presented as means and medians, while categorical data are shown as frequencies. No formal hypothesis testing was performed, as our primary aim was not to establish or verify statistical associations, but rather to highlight a clinically relevant and underreported observation.

The study protocol was approved by the Ethics Committee of the University of Debrecen (Approval No: 6477-2023, Date: 2023.06.21). All patient data were anonymized and handled according to the Declaration of Helsinki.

3 | Results

During the study period, we treated a total of 250 HL patients at our institution. Liver involvement was found in 9 patients (3.6%), in one case, hepatic involvement manifested as acute liver failure. Patient characteristics, laboratory and imaging findings are summarized in Table 1. In seven cases, the HL diagnosis was established by histological examination of peripheral lymph node. Two patients had no lymph nodes suitable for peripheral biopsy, and HL was confirmed by bone marrow examination. As for histological subtypes, mixed cellularity (MC) and nodular sclerosis (NS) were found in three patients, the lymphocyte-rich (LR) subtype in one patient, while in two cases the subtype was not defined (ND).

The mean age of patients (three women and six men) was 50.1 (range 24–71) years, with a median age of 55 years. All patients were diagnosed at Ann Arbor stage IV, while in 6 cases the International Prognostic Score (IPS) was ≥ 4 , indicating a high-risk disease.

On physical examination, lymphadenomegaly was confirmed in seven cases, and B symptoms were present in eight patients. In one patient, significant ascites was detected, while in the patient with acute liver failure, episodes of mental confusion and later jaundice were observed.

Laboratory tests revealed elevated ALP and LDH levels in 8 out of 9 patients, while GGT was increased in 7 cases. Mild elevations of transaminases (AST and ALT) were detected in two patients, while elevated bilirubin levels (TBIL, KBIL) were found in 3 cases. Haemostatic abnormalities were also common: prolonged APTT was present in five patients, and increased INR was observed in 4 cases. Reviewing the haematological and inflammatory parameters, neutropenia (WBC < 4.5 G/L) was present in 4, anemia (HGB < 115 g/L) in 8, and thrombocytopenia (PLT < 150 G/L) in 6 patients. Mild or moderate elevation of C-reactive protein (CRP > 4.6 mg/L) was observed in all 9 cases.

Serologic tests showed evidence of past EBV infection in 8 and CMV infection in 7 patients. None of the patients had a history of hepatitis in the past.

Conventional abdominal imaging (ultrasound and CT) did not reveal specific abnormalities in our cases, while PET/CT identified various hepatic findings. A solitary liver lesion was identified in 1, multiple active areas in the liver were found in 7 patients. On PET/CT, the patient with acute liver failure was found to have diffusely elevated standardized uptake value (SUV) in the liver (Table 1).

We started first-line ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) or EBVD (etoposide, bleomycin, vinblastine, dacarbazine) therapy in 6, brentuximab vedotin-AVD (adriamycin, vinblastine, dacarbazine) therapy in 2 cases. With the treatment applied, 4 patients achieved complete remission, while 4 patients relapsed or became refractory (R/R). A reduced dose of brentuximab vedotin was started for the patient with acute liver failure, which we planned to complement with AVD therapy later, but this was not possible due to her death 2 days later. Three patients from the R/R group died during following treatments.

Since the greatest differential diagnostic and therapeutic difficulty occurred with the patient presenting acute liver failure, we discuss her case below.

TABLE 1 | Details of our 9 Hodgkin lymphoma patients with liver involvement (PET/CT characteristics, therapy, outcome, laboratory parameters).

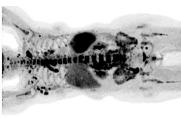
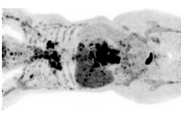
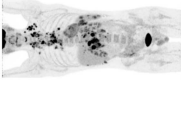
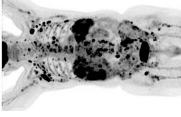
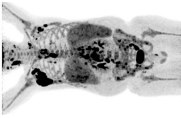
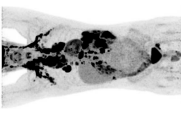
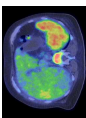
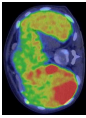
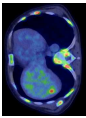
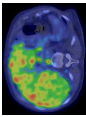
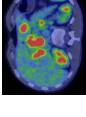
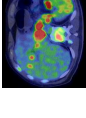
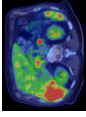
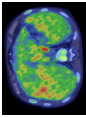
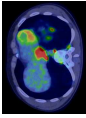
Patient	1	2	3	4	5	6	7	8	9
Whole body PET/CT images									
Cross-section PET/CT images of the liver									
Appearance of liver lesions	Multiple hypermetabolic lesions, large active areas								
Therapy	Diffusely elevated FDG uptake								
Outcome	Brentuximab vedotin Acute liver failure								
	Died during first-line therapy								
	Died during the following therapies								
	Currently under PD-1 inhibitor therapy								
ALP (U/L)	40–150	446	202	303	179	271	223	355	93
LDH (U/L)	135–220	437	270	1100	268	820	160	562	345
GGT (U/L)	7–50	250	121	36	114	91	256	355	37
AST/GOT (U/L)	< 40	102	29	9	28	52	24	27	15
ALT/GPT (U/L)	< 40	39	20	10	28	46	14	16	18
TBIL (μmol/L)	< 20	27.9	9.7	10.3	7.1	17	7.5	46.7	4.6
DBIL (μmol/L)	< 5	27	5.5	4.8	3.6	4	6.6	35.8	—
INR	0.8–1.2	1.93	1.76	1.35	1.02	1.08	—	1.08	—
APTT	25–35	42.7	41.9	37.4	30.8	35.6	—	33	—
WBC (Giga/L)	4.5–10.8	43.06	1.33	16.5	4.01	4.96	12.07	3.62	6.28
HGB (g/L)	115–150	83	97	98	99	152	85	79	100
PLT (Giga/L)	150–400	196	73	35	197	115	631	10	368
CRP (mg/L)	< 4.6	203	24	214	40	18.2	180	13	151

TABLE 2 | Laboratory findings of patient (Patient 1) with acute liver failure (values in red indicate results outside the normal range).

Days of admission	Day 1	Day 17
White blood cell (G/L)	2.95	1.99
Hemoglobin (g/L)	97	72
Platelet (G/L)	74	22
C-reactive protein (mg/L)	221	130
Procalcitonin (µg/L)	3.93	1.07
Alkaline phosphatase (U/L)	578	720
Lactate dehydrogenase (U/L)	296	236
Gamma-glutamyl transferase (U/L)	274	311
Total bilirubin (µmol/L)	28.7	157
Direct bilirubin (µmol/L)	25.1	153
Cholinesterase (kU/L)	—	2.03
Ammonia (µmol/L)	—	51
International normalized Ratio	1.27	1.32
Activated partial thromboplastin time	33.2	46.1

3.1 | Case Report

Our 59-year-old female patient had a history of thyroiditis with permanent hypothyroidism. In February 2022, she was admitted due to pancytopenia, B symptoms, weakness and mental confusion starting 2 months ago.

Laboratory findings (Table 2) included leukopenia, normocytic anaemia, thrombocytopenia, high inflammatory parameters and elevated liver enzymes. Chest X-ray showed no abnormalities, abdominal UH revealed asymptomatic cholelithiasis and larger retroperitoneal lymph nodes. COVID infection and other viral infections (human immunodeficiency virus (HIV), hepatitis A, B, C, EBV, CMV) were excluded, haemocultures were negative. Due to pancytopenia, bone marrow aspiration was performed; however, no pathological cells were detected. Flow cytometry could not confirm a definitive diagnosis either. As the axillary lymph nodes were unsuitable for core biopsy, a right parailiac lymph node was sampled under ultrasound guidance. At the time of the procedure, haemostasis parameters were within the normal range. From Day 12 after admission, jaundice was observed, increasing bilirubin and cholestatic enzymes were detected, and coagulation time prolonged. Two days after the core biopsy, the bone marrow biopsy confirmed classical Hodgkin lymphoma with not defined subtype. Staging PET/CT showed stage IV disease with diffuse elevated, inhomogeneous tracer uptake of liver (SUVmax: 5,4) and spleen involvement (Table 1). Overall, stage IV/B (liver, spleen, bone), Eastern Cooperative Oncology Group Performance Status (ECOG PS): 2, IPS: 4 was confirmed.

Due to the extensive disease and worsening liver function, brentuximab vedotin therapy and AVD treatment were planned. On Day 17 after admission, brentuximab vedotin was started at a reduced dose (1.2 mg/kg); however, treatment with chemotherapy (AVD) could not be added due to severe laboratory abnormalities (Table 2). On the 20th day of hospitalization, the patient had sudden respiratory and circulatory failure. Although reanimation was successful, after 1 day intensive care management, she eventually passed away.

Autopsy confirmed that the lobular structure of the liver was preserved macroscopically (Figure 1), however, microscopic examination revealed a completely remodelled structure with diffuse infiltration by Hodgkin lymphoma (Figure 2). Eventually, liver failure due to the underlying lymphoma was identified as the main cause of death, with no evidence of infection.

4 | Discussion

Neoplasms are often associated with liver involvement; however, most of the cases metastatic lesions do not affect liver function. In some cases, diffuse metastatic infiltration of the liver can cause severe liver damage, even acute liver failure via hepatocellular necrosis. This occurs mostly due to pressure atrophy or interference of vascular supply [3]. Liver involvement is observed in 15%–22% of haematological malignancies, but it is less common in HL, occurring in 5%–8% [1, 4].

In a study in Barcelona between 1972 and 1995, 6 out of 421 HL patients (1.4%) with clinical or analytical liver abnormalities and in the absence of peripheral lymphadenomegaly underwent liver biopsy. The histopathological examination confirmed HL. Retroperitoneal lymphadenomegaly and/or bone marrow involvement was observed in three patients, while the other three had liver involvement only. Staging tests revealed further 25 patients with hepatic abnormality, resulting a total of 7.4% cases [5].

Out of 250 patients treated at our institute, we found 9 patients (36%) with liver involvement. In less severe cases, there was no significant clinical benefit from liver biopsy during the diagnostic procedure, since the presence of liver involvement (based on PET/CT and laboratory findings) did not significantly influence the therapeutic choices. In our patient with acute liver failure, liver involvement was confirmed post-mortem. Rapid progression and worsening haemostasis parameters precluded liver biopsy during life.

According to literature, several underlying mechanisms could cause liver involvement [1, 6]:

- HL infiltrates the liver parenchyma, bile ducts and liver vasculature leading to necrosis, fibrosis.
- Vanishing bile duct syndrome (VBDS) can be caused by HL-induced cytokine release, which destroys interlobular bile ducts and causes portal fibrosis.
- Extrahepatic bile ducts can be infiltrated by HL, leading to biliary obstruction.
- Parenchyma destruction without hepatic infiltration of the HL has been described in some cases, caused by paraneoplastic mechanisms [3, 7].

The definition of acute liver failure is not consistent in the literature. According to the widely accepted definition [8], acute liver failure is defined as coagulopathy and encephalopathy within 26 weeks after the onset of icterus, without a history of previous chronic liver disease or cirrhosis. It is also referred to in the medical terminology as fulminant hepatic failure, fulminant hepatitis or fulminant hepatic necrosis. Based on the onset of encephalopathy, liver failure can be classified as

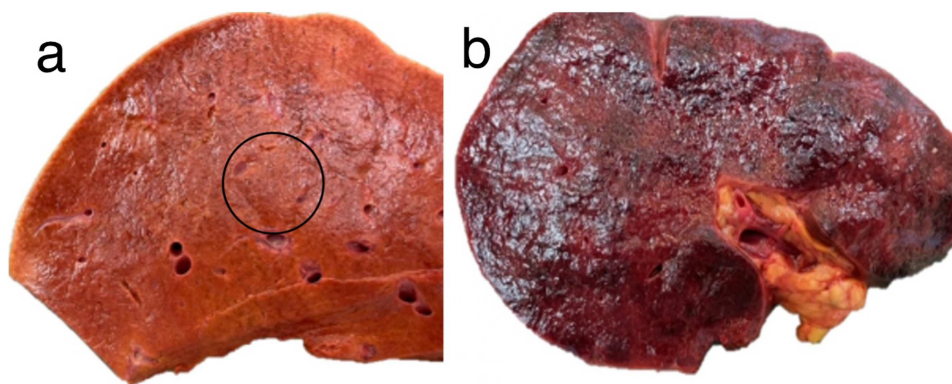


FIGURE 1 | Macroscopic image of the liver in acute liver failure (Patient 1). (a) The lobular structure of liver is preserved. (b) The liver shows increased density.

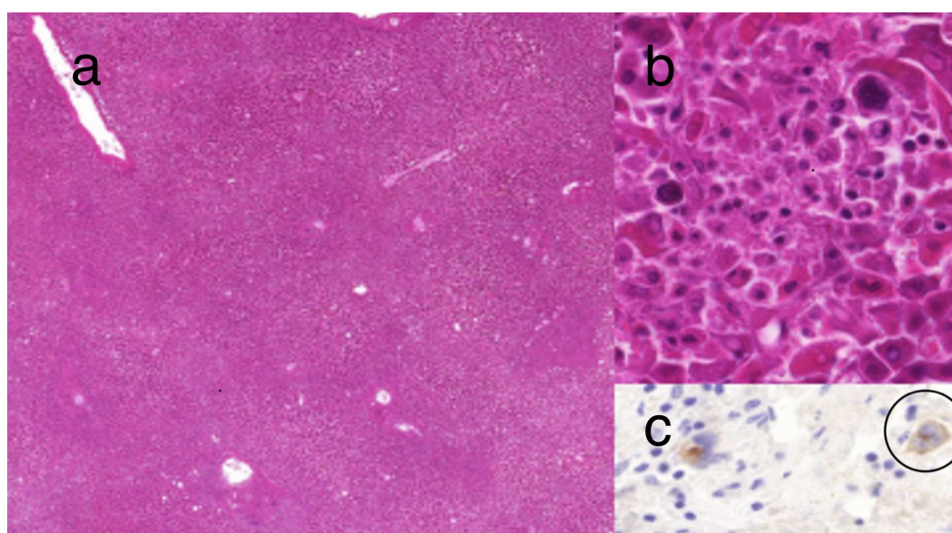


FIGURE 2 | Microscopic and immunohistochemical features of the liver in acute liver failure (Patient 1). (a) Histology of the liver with hematoxylin and eosin staining. (b) Sternberg-Reed cell with histiocytes. (c) Immunohistochemistry showing strong CD30 positivity in Sternberg-Reed cells.

hyperacute (less than 1 week), acute (7–21 days) and subacute (after 21 days) liver failure [8, 9]. Haematological malignancies are not the leading cause; more frequent reasons are liver damage caused by toxins, drugs, viruses, Budd–Chiari syndrome, ischaemia, autoimmune disorders and acute flare-ups of chronic liver diseases [1, 8].

Although it was not present among the group of patients treated at our institute, we should mention primary hepatic Hodgkin lymphoma. It is an extranodal lymphoma of the liver with or without regional lymph node involvement. According to scientific publications, primary hepatic Hodgkin lymphoma occurs in 0.4%–0.7% of Hodgkin lymphoma cases, and its incidence is increased after previous EBV, HIV, and hepatitis C infection [6, 10–12]. In most publications describing primary hepatic Hodgkin lymphoma, PET-CT was not available, in the presence of liver abnormalities (without lymphadenopathy), liver biopsy was performed confirming HL [5, 10]. In one case, the diagnosis was established by a PET-CT scan, the images revealed higher FDG uptake only in the hepatic lesions and the surrounding portal lymph nodes. The subsequent liver biopsy confirmed Hodgkin lymphoma [11].

4.1 | Diagnostic Difficulties (Clinical Signs, Laboratory Results, PET/CT, Biopsy)

According to literature, in the presence of liver involvement, physical examination often reveals hepatomegaly, while jaundice, ascites, and changes in mental status can be observed in advanced cases [5, 13]. In our study, we predominantly observed clinical findings commonly associated with Hodgkin lymphoma (B signs, lymphadenomegaly), while clinical signs specifically suggestive of liver involvement were identified in only two cases. In one patient (who was later successfully treated with ABVD), significant ascites was detected, while in the patient with acute liver failure, episodes of mental confusion were noted. In her case, jaundice became apparent only later, during the diagnostic procedures.

Abdominal ultrasound and CT scans often reveal no abnormalities, since conventional imaging modalities often fail to detect smaller, metabolically active lymphomatous infiltration in the liver [14]. In most publications, hepatomegaly, splenomegaly, steatosis, increased echogenicity of the liver, lymphadenomegaly or ascites is confirmed [3, 5, 6, 13]. Among the patients we studied, abdominal ultrasound revealed

lymphadenomegaly in all 9 patients. Hepatomegaly was described in 3 cases and splenomegaly in 4 cases, while ascites was detected in 2 patients. Focal hepatic abnormalities were identified by abdominal ultrasound in only 3 cases.

In most publications addressing hepatic involvement, PET-CT was not performed. In those reports including PET/CT imaging, solitary lesions are observed in two-thirds, while multiple lesions are observed in one-third of cases [15]. In publications of Ortin et al. and Gota et al., increased FDG uptake was observed in a solitary liver lesion and its surrounding portal lymph nodes, while Wang et al. described a case with multiple hypermetabolic lesions in the liver [4, 11, 16]. Diffuse infiltration of the liver, with diffusely elevated SUV on PET-CT, is extremely rare, with only one case described so far [15]. According to our PET-CT images, one of our patients with liver involvement had a solitary, while seven had multiple lesions. In the patient with acute liver failure, diffuse FDG uptake of the liver was confirmed.

Laboratory findings are mainly liver enzyme abnormalities, cytopenia and high inflammatory markers. In cases of liver failure, changes in haemostasis can be detected, while other causes (microbiological, viral and immunological issues) are excluded [5, 13]. As in literature, laboratory parameters predominantly showed an increase in cholestatic enzymes (GGT: 7 patients, ALP: 8 patients) and LDH (8 patients), while mild elevations of transaminases were observed only in 2 cases [5]. Three patients had elevated bilirubin levels, two of them, the most severely affected, died within a few days. Reviewing haemostasis changes, we found that elevated INR levels (4 patients) and prolonged APTI (5 patients) were present in the patient with acute liver failure and in those 3 R/R patients who later died during subsequent treatment (Table 1).

Interpreting the laboratory findings in relation to the PET-CT results, we found no significant abnormalities, apart from a slightly elevated LDH level in the patient with a small solitary liver lesion. Patients with multiple hepatic lesions showed variable laboratory changes, but no clear correlation between the size or number of lesions and the severity of the laboratory abnormalities. In our patient with acute liver failure (Patient I), although diffuse liver involvement was described on PET/CT scan, at this stage, liver enzyme abnormalities were not markedly increased. However, her clinical condition and laboratory abnormalities (unlike the other patients) rapidly progressed to acute liver failure leading to death within a few days.

Previous publications have suggested that liver biopsy was necessary to establish an accurate diagnosis, but with the widespread use of PET/CT, in some cases, the necessity of histological sampling has been questioned. Due to the focal abnormalities and the frequent presence of small lesions, false negative results are common [2], with only 10% of cases being histologically confirmed. Moreover, in advanced cases of acute liver failure, the fulminant progression and coagulation abnormalities often preclude biopsy, and the diagnosis is frequently established only at autopsy [1].

Although liver biopsies were not performed during staging in the patients we treated, autopsy results of the two most severe cases are available. In our patient with acute liver failure, large, atypical cells were found in several areas of the liver, Hodgkin-infiltrated structure was confirmed. In one of our R/R patients, multiple extensive focal lesions with atypical cells were detected.

There are conflicting findings examining the relationship between histological subgroups and the incidence of liver involvement. In some observations, liver involvement occurs mostly in lymphocyte-depleted (LD) subtype [1], while others describe it is more common in MC and LR subtypes [5]. Ma et al. discovered liver involvement mainly in NS and MC Hodgkin lymphoma [10]. In the present study, we also observed a higher prevalence of NS and MC subtypes, but we did not find a connection between the subtype and pattern of hepatic involvement.

4.2 | Therapy

Most chemotherapy options currently used to treat Hodgkin lymphoma are known to have hepatotoxic side effects, so choosing the right therapy in the presence of liver involvement is challenging. The anthracycline and vinca alkaloid components of first-line ABVD therapy are metabolized in the liver, so in case of liver dysfunction, other therapies should be considered [15]. DHAP has been shown in publications to be a safe and effective alternative without dose reduction in cases of poor liver function [1]. Several publications report the use of so-called bridge therapy in the presence of liver dysfunction. In these cases, brentuximab vedotin (BV) may be a good option alone, or in combination with steroids and chemotherapy, until liver function improves. Treatment with ABVD can be continued afterwards [16, 17].

Improvement in liver function may be achieved using radiotherapy according to some publications, particularly in cases of vanishing bile duct syndrome and primary hepatic HL [1, 12]. Despite the fact, that it may have a positive effect on prognosis, the use of radiotherapy in advanced disease has not been studied, no real conclusion on its benefits can be drawn [18].

Since the prognosis in the presence of acute liver failure is very poor, with an average survival of 6 days (1–51 days), deciding on the most appropriate treatment is extremely difficult [1]. In several cases, the patients have died before the start of therapy or a few days after, mainly due to sepsis and multi-organ failure [4, 13, 19].

The possibility of liver transplantation in the presence of irreversible liver failure is controversial in the literature. Some publications report significant improvement after liver transplantation for HL limited to the liver only [6]. Other reviews suggest that liver transplantation is contraindicated in cases with haematological malignancy, as lymphoma may recur in the transplanted liver. These studies suggest that only early diagnosis and immediate initiation of chemotherapy can influence the outcome positively [1].

Among the new innovative therapies, brentuximab vedotin may be a good therapeutic alternative in cases with liver dysfunction. In the available publications, the disappearance of liver lesions on PET-CT images and normalization of liver enzyme levels were observed in 4 cases after administration of BV at a reduced dose (1.2 mg/kg) [17, 20]. In one patient treated with BV progression of Hodgkin lymphoma occurred later, but no liver involvement was observed again [17]. In the publication of Ishitsuka et al., BV given in the presence of vanishing bile duct syndrome resulted in a partial therapeutic response. Although

progression of HL was observed during the treatment, the biopsy showed a slight improvement of biliary status [18]. The use of PD-1 inhibitor after progression with BV has been discussed [17], but there is no available literature on the administration of PD-1 inhibitor in HL with liver involvement.

In our cohort, therapeutic decisions were made individually, based on the clinical status, liver function, comorbidities of each patient, and were analysed retrospectively. In 8 of our treated patients, liver function was not substantially impaired, full dose (6 cycles) ABVD/EBVD was administered in six cases, while in two cases brentuximab vedotin and AVD therapy were used as first-line treatment. In the patient with acute liver failure, we started reduced dose brentuximab vedotin therapy (1.2 mg/kg), however our plan to supplement it with AVD therapy after liver function improved could not be realized due to her sudden death.

Regarding clinical outcomes, four of our patients (Patients 6–9) achieved complete remission following first-line treatment. Among these four patients, in two cases six cycles of EBVD were used due to concerns regarding anthracycline cardiotoxicity, while two patients were treated with six cycles of A + AVD, since this regimen was already available at that time.

In contrast, four patients (Patient 2–5) became R/R following six cycles of ABVD therapy. Patient 2 received one cycle of DHAP followed by one cycle of brentuximab vedotin, but progressed rapidly and died of septic shock. Patient 3 received two cycles of DHAP followed by three cycles of brentuximab vedotin, and due to persistent relapse was treated for 1 year with PD-1 inhibitor (pembrolizumab) before his death. Patient 4, due to advanced age, was treated in second line with brentuximab vedotin-bendamustine, followed by PD-1 inhibition (nivolumab), but also died from infectious complications. Since the liver function remained preserved in the R/R group, consistent with previous publications, these therapies were administered without dose reduction. In these cases (Patient 2–4), even in the presence of liver lesions and disease progression, treatment could be used under close monitoring without deterioration in liver function or further rise in hepatic enzyme levels.

Although Patient 5 (the fourth R/R patient) remains under treatment, liver lesions were no longer described on repeated PET/CT after two cycles of DHAP and third-line brentuximab vedotin therapy. He has been receiving PD-1 inhibitor therapy for over a year for suspected relapse following autologous stem cell transplantation, without recurrence of liver involvement.

5 | Conclusion

In this retrospective cohort, we described the clinical features, diagnostic difficulties, and therapeutic challenges of Hodgkin lymphoma patients with hepatic involvement treated at our institution.

Unlike most previous reports that relied primarily on liver biopsy for confirmation (often delaying diagnosis or being unfeasible) our study illustrates the potential practical value of PET/CT detecting liver involvement. While conventional imaging modalities (ultrasound, CT, MR) often fail to detect subtle or diffuse lymphomatous infiltration in the liver, PET/CT showed higher sensitivity for extranodal disease assessment. It provides metabolic information, which allows the detection of metabolically

active small lesions and diffuse hepatic involvement that may not yet cause structural abnormalities. Our experience suggests that the number and size of liver lesions observed on PET/CT do not correlate well with the clinical picture and subsequent outcome. However, in the presence of diffuse liver involvement confirmed by PET/CT, there is an increased suspicion of severe liver dysfunction, requiring close attention and prompt initiation of appropriate therapy. The most consistent indicators of clinical deterioration were laboratory abnormalities and their dynamic changes over time. Careful monitoring of these laboratory parameters proved more reflective of disease course and guiding therapeutic decisions.

Although there are no guidelines yet for the treatment of Hodgkin lymphoma patients with liver involvement, available publications and our clinical experience suggest that ABVD remains a good choice for patients in case of preserved liver function with close control of liver abnormalities. Despite a very poor prognosis, in the presence of worsening liver dysfunction and liver failure, BV therapy may be a safe alternative, but early recognition and prompt treatment initiation remain crucial.

Our study is limited by the small sample size and its retrospective nature, which preclude statistical analysis or definitive conclusions. Although further multicenter studies are needed to optimize diagnostic pathways, and find evidence-based therapeutic strategies, our aim was to highlight the potentially fulminant course of liver involvement and the need for recognition and intervention as early as possible.

Author Contributions

Fanni Borics: conceptualization, data curation, investigation, writing – original draft. **Roxana Szabó:** investigation. **Sándor Barna:** investigation, visualization. **Judit Bedekovics:** investigation, visualization. **Boglárka Brúgós:** investigation. **Árpád Illés:** investigation, supervision, writing – review and editing. **Zsófia Miltényi:** conceptualization, investigation, supervision, writing – review and editing.

Funding

The authors received no specific funding for this work.

Ethics Statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Debrecen (Date: 2023.06.21/No: 6477-2023).

Consent

Informed consent was obtained from all individual participants included in the study.

The authors affirm that human research participants provided informed consent for publication of the images in Table 1, Figure 1a,b, Figure 2a-c.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Transparency Statement

The lead author, Fanni Borics affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. P. Karmacharya, N. Bhandari, M. R. Aryal, et al., "Before It Crumbles: Fulminant Hepatic Failure Secondary to Hodgkin's Lymphoma," *Journal of Community Hospital Internal Medicine Perspectives* 4, no. 5 (2014): 25821, <https://doi.org/10.3402/jchimp.v4.25821>.
2. L. Zhang, H. Shao, and S. Alkan, ed., *Diagnostic Pathology of Hematopoietic Disorders of Spleen and Liver* (Springer International Publishing, 2020), <https://doi.org/10.1007/978-3-030-37708-3>.
3. A. J. Deacon, N. N. Goetz, N. Weber, et al., "Relapsed Nodular Lymphocyte-Predominant Hodgkin Lymphoma Presenting as Severe Paraneoplastic Hepatitis: A Case Report," *Journal of Medical Case Reports* 17, no. 1 (2023): 269, <https://doi.org/10.1186/s13256-023-04014-9>.
4. X. Ortín, M. Rodríguez-Luaces, R. Bosch, M. Lejeune, and L. Font, "Acute Liver Failure as the First Manifestation of Very Late Relapsing of Hodgkin's Disease," *Hematology Reports* 2, no. 1 (2010): e5, <https://doi.org/10.4081/hr.2010.e5>.
5. F. Cervantes, J. Briones, M. Bruguera, et al., "Hodgkin's Disease Presenting as a Cholestatic Febrile Illness: Incidence and Main Characteristics in a Series of 421 Patients," *Annals of Hematology* 72, no. 6 (1996): 357–360, <https://doi.org/10.1007/s002770050186>.
6. F. S. Hong, C. L. Smith, P. W. Angus, P. Crowley, and W. K. Ho, "Hodgkin Lymphoma and Fulminant Hepatic Failure," *Leukemia & Lymphoma* 51, no. 5 (2010): 947–951, <https://doi.org/10.3109/10428191003699571>.
7. S. P. Dourakis, E. Tzemanakis, M. Deutsch, G. Kafiri, and S. J. Hadziyannis, "Fulminant Hepatic Failure as a Presenting Paraneoplastic Manifestation of Hodgkin's Disease," *European Journal of Gastroenterology & Hepatology* 11, no. 9 (1999): 1055–1058, <https://doi.org/10.1097/00042737-199909000-00019>.
8. J. Polson and W. M. Lee, "AASLD Position Paper: The Management of Acute Liver Failure," *Hepatology* 41, no. 5 (2005): 1179–1197, <https://doi.org/10.1002/hep.20703>.
9. N. B. Ozturk, E. Herdan, F. H. Saner, and A. Gurakar, "A Comprehensive Review of the Diagnosis and Management of Acute Liver Failure," *Journal of Clinical Medicine* 12, no. 23 (2023): 7451, <https://doi.org/10.3390/jcm12237451>.
10. J. Ma, Y. Wang, H. Zhao, et al., "Clinical Characteristics of 26 Patients With Primary Extranodal Hodgkin Lymphoma," *International Journal of Clinical and Experimental Pathology* 7, no. 8 (2014): 5045–5050.
11. V. Gota, N. Purandare, S. Gujral, S. Shah, R. Nair, and V. Rangarajan, "Positron Emission Tomography/Computerized Tomography Evaluation of Primary Hodgkin's Disease of Liver," *Indian Journal of Cancer* 46, no. 3 (2009): 237, <https://doi.org/10.4103/0019-509x.52960>.
12. A. M. Nasiri, M. Alshammari, A. Ahmed, Ahmed B. Elsir, and H. Alghethber, "Primary Hepatic Hodgkin's Lymphoma: A Case Report," *Journal of Family Medicine and Primary Care* 11, no. 3 (2022): 1184–1187, https://doi.org/10.4103/jfmpe.jfmpe.1116_21.
13. E. Vardareli, E. Dünder, V. Aslan, and Z. Gülbaş, "Acute Liver Failure due to Hodgkin's Lymphoma," *Medical Principles and Practice* 13, no. 6 (2004): 372–374, <https://doi.org/10.1159/000080477>.
14. D. Ippolito, M. Porta, C. Maino, et al., "Diagnostic Approach in Hepatic Lymphoma: Radiological Imaging Findings and Literature Review," *Journal of Cancer Research and Clinical Oncology* 146, no. 6 (2020): 1545–1558, <https://doi.org/10.1007/s00432-020-03205-x>.
15. L. You, X. Zhuang, H. Liu, and W. Qian, "Case Report Hodgkin Lymphoma Presenting With Diffuse Liver Involvement: A Rare Case Report," *International Journal of Clinical and Experimental Medicine* 9, no. 3 (2016): 6947–6950.
16. R. G. Mihăilă, "Liver Involvement in Hodgkin's Lymphoma: Types of Injuries and Therapeutic Implications," *International Journal of Pharmacology, Phytochemistry and Ethnomedicine* 8 (2017): 1–15, https://www.academia.edu/80185601/Liver_Involvement_in_Hodgkins_Lymphoma_Types_of_Injuries_and_Therapeutic_Implications.
17. N. Spathas, M. Belia, T. Giannikos, et al., "Successful Reversal of Severe Liver Function Impairment With Brentuximab Vedotin in Multiply Relapsed/Refractory Classical Hodgkin Lymphoma," *Journal of BUON: Official Journal of the Balkan Union of Oncology* 24, no. 6 (2019): 2483–2489.
18. K. Ishitsuka, Y. Yokoyama, N. Baba, et al., "Administration of Brentuximab Vedotin to a Hodgkin Lymphoma Patient With Liver Dysfunction due to Vanishing Bile Duct Syndrome Resulting in a Partial Response Without Any Severe Adverse Events," *Journal of Clinical and Experimental Hematopathology* 62, no. 3 (2022): 154–157, <https://doi.org/10.3960/jslr.21035>.
19. M. Schindler, N. Kreplak, L. Acevedo, H. Damis, G. Márquez, and C. Del, "Ictericia Febril Colestásica Como Forma de Presentación de Linfoma de Hodgkin," *Medicina (Buenos Aires)* 74 (2014): 60–61.
20. Y. Wang, Z. Wang, C. Wei, et al., "Single-Agent Brentuximab Vedotin as Frontline Therapy for Hodgkin Lymphoma Patients With Severe Hepatic Impairment: A Report of Two Cases," *Annals of Hematology* 102, no. 10 (2023): 2973–2975, <https://doi.org/10.1007/s00277-023-05390-4>.