Liver Involvement in Hodgkin's Lymphoma: Types of Injuries and Therapeutic Implications

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Abstract. The hepatocytolysis raises questions on following therapeutic conduct when it occurs during chemotherapy for Hodgkin's lymphoma, expression of its liver toxicity. But the onset of primary liver Hodgkin's lymphoma, including the form manifested by acute liver failure, poses even greater problems, as in the case of occurrence of vanishing bile duct syndrome - expression of a paraneoplastic syndrome, hemophagocytic lymphohistiocytosis, peliosis hepatis or association of lymphoma with infection with hepatitis viruses or human immunodeficiency virus or different autoimmune diseases. This review summarizes the clinical experience acquired on the relationship between Hodgkin's lymphoma and liver, from the point of view of clinical manifestations, used treatments and clinical evolution. Suggestions on the course of treatment in patients with Hodgkin's lymphoma and liver damage have been formulated starting from the metabolism and elimination of chemotherapy drugs and taking into account the clinical experience of published clinical trials and cases. This review is a synthesis of knowledge obtained in this field, during the time, of therapeutic possibilities and limits, and formulates potential future milestones for research.

Introduction

Around 66,000 peoples were newly diagnosed with Hodgkin's lymphoma (HL) worldwide, and around 17,600 in Europe in 2012 [1,2]. The highest world age-standardised incidence rate for HL was in Croatia, and the highest incidence rate was in Northern America in the same year [3,4]. In 2012, the 5-year prevalence of HL was estimated to be 59,817/100,000 inhabitants in Europe [4]. It is assessed that 9,050 new cases of HL were diagnosed in the USA only in 2015 and the number of deaths due to HL was estimated at 1,150 in the same year [5]. HL represented 32.7% of all cases of lymphoma diagnosed in Lebanon in 2007. In most patients IgG anti-Epstein-Barr virus were present, but serology for hepatitis C virus (HCV) was negative in 122 tested cases [6].

In general, the chemotherapy for HL is well tolerated. Last year, I was surprised to detect that a young patient with mediastinal onset of HL, having an ECOG performance status of 1, without notable comorbidities, with any liver disease in his history, and with no clinical or biological arguments for any liver disease at that moment, developed hepatic cytolysis after the first application of ABVD regimen. The cytolysis increased after the next two applications (with maximum values of 360 IU/L for AST and 280 IU/L for ALT) and decreased until the next round of chemotherapy. This adverse effect required to leave the ABVD regimen. We continued with 5 courses of ICE regimen, which were well tolerated, followed by complete response (the PET/CT scan did not show any uptake in wasted lymph nodes).

Starting from this rare experience of an acute hepatitis induced by chemotherapy, I decided to make a literature review on liver involvement in HL. I selected the articles published in PubMed from 2004 until today, using the terms "Hodgkin's lymphoma," "hepatitis", "liver", "ALT", "ABVD" "BEACOPP", "Stanford V". The research objectives were: 1) to realize a synthesis of liver side effects induced by chemotherapy, 2) to assess other possible etiologies of liver injuries in Hodgkin's lymphoma patients (as the hepatic lesions due to Hodgkin's lymphoma, the relationship with liver
transplantation, the link between Hodgkin’s lymphoma and hemophagocytic lymphohistiocytosis, peliosis hepatis, the association of lymphoma with hepatitis viruses infection and autoimmune hepatitis), and 3) to establish the best therapeutic conduct in front of a Hodgkin's lymphoma patient with liver damage.

Liver damage in Hodgkin’s lymphoma

A hematological neoplasm can be suspected in a young patient, without cancer history, having fever with unexplained etiology and/or night sweats, who has pathological bone marrow aspect. This clinical picture is supported by the following imaging features: polyadenopathies located above and below the diaphragm, hepatosplenomegaly or splenic lesions, an infiltrating tumor at the liver hilum without biliary obstruction, and a vascular encasement by a mass which do not produces thrombosis or occlusion. A core needle biopsy is frequently useful for the diagnosis [7].

HL can produce liver damage in various ways: hepatitis, liver infiltration, biliary obstruction by lymphomatous compressions, sepsis, vanishing bile duct syndrome [8], hemophagocytic lymphohistiocytosis [9], postransplant lymphoproliferative disorders [7], liver adverse effect of chemotherapy [8] or peliosis hepatis [10]. After serum ferritin, serum alkaline phosphatase and alanine aminotransferase (ALT) are two parameters that can make the best prediction on treatment response of HL (according to the results of a study which investigated 35 clinical and biological parameters at the time of HL diagnosis, prior any therapy), which stresses the importance of liver damage in this type of lymphoma. These three variables suggest a pathogenic relationship between inflammation, iron overload (which has liver toxicity), liver damage and disease extension size [11].

The selection of an optimal graft conditioning therapy for lymphomas is a challenge for haematologists. BEAM graft conditioning regimen which consists in carmustine, etoposide, cytarabine and melphalan had less liver toxicity compared to busulfan, etoposide and melphalan (BuEM), but after BuEM progression free survival and overall survival of patients with HL was marginally significantly improved [12].

Liver dysfunctions

Theoretically speaking, if the patient has liver involvement at the diagnosis of HL, ABVD regimen can increase the liver toxicity. Such a case with adenomegalies and jaundice, due to an obstructive biliary disease diagnosed by magnetic resonance imaging, received a bridge therapy which consisted in dexamethasone, gemcitabine and cisplatin (GDP). The functional liver tests were improved enough after 4 cycles, so the patient continued with ABVD regimen. GDP is a useful salvage therapy in these situations [13].

Sometimes, the initial therapy with ABVD regimen can also not be used in patients with atypical and extranodal presentations of HL, particularly in those with liver or renal failure, due to the potential liver toxicity of anthracyclines. Two such HL patients with severe liver dysfunctions were successfully treated with cyclophosphamide, etoposide, procarbazine and prednisone [14]. Another HL patient who had severe liver dysfunction with hyperbilirubinemia was treated with dexamethasone, high-dose cytarabine, and cisplatin regimen (DHAP) until liver dysfunction disappeared. The treatment was completed with ABVD cures, followed by complete remission obtaining [15].

An obstructive jaundice associated with enlarged lymph nodes was empirically treated as tuberculosis. After HL recognition ABVD protocol was used with dose adjustments according to the values of liver function tests. The liver answer was quick, with the normalization of liver function tests after the first cycle of chemotherapy [16].

The presence of liver dysfunction in HL patients limits especially the use of anthracyclines and vinca alkaloids, both present in ABVD regimen. A solution can be the use of corticotherapy in association with mechlorethamine until liver function will be improved. Then, the transition to the ideal HL therapy can be made. In the absence of mechlorethamine, some patients were treated with gemcitabine/cisplatin, ifosfamide/carboplatin [17], or gemcitabine/steroids with good results
[17,18], followed in the last drug association by ABVD regimen, after the improvement of liver biochemical tests [18]. A similar experience was communicated by Mayo Clinic researchers, where between 41 patients with lymphoma at diagnosis, 4 had HL. All of them had cholestasis, with a median serum total bilirubin level of 10.7 mg/dL. Mechlorethamine, in some patients along with high-dose corticosteroids, contributed to a sufficient improvement in liver function so that the patients can further be treated with standard chemotherapy. The serum bilirubin reduction and the possibility to continue with standard therapy were contributing factors to overall survival improvement [19].

It is also possible that a long recurrent intrahepatic cholestasis (7 months in a published case [20]) precedes the diagnosis of HL. The liver biopsy that was done showed a deficiency in some export pumps expression (that of bile salt and gamma-glutamyl transpeptidase). Interesting was that cholestasis disappeared 7 months before HL diagnosis. This patient had some polymorphisms in ATP8B1 and ABCB11 which are risk factors for intrahepatic cholestasis development in HL patients, due, probably, to the presence of abnormal pro-inflammatory cytokine environment of lymphoma. A close monitoring of patients with cholestasis of undetermined etiology can sometimes contribute to an early detection of a HL [20].

Liver failure is a characteristic of end-stage disease of lymphomas (stage IV). Therefore, the liver primary presentation with acute liver failure is exceptionally rare. Such a HL case relapsed very late (20 years after the date on which it was initially diagnosed), as an acute liver failure [21].

Liver infiltration

In a study realized by Ma J et al., the liver is the 4th extranodal sites of HL in frequency, after the lung, stomach, and gut [22]. In another Chinese study, extranodal involvement was present in 22 of 250 untreated HL patients, and the most frequent sites were the liver and lung [23]. In order to establish the presence of liver involvement it is recommended to use at least two diagnosis procedures, as liver scanning and computed tomography [24]. HL with primary liver involvement manifests most often with dissemination-related liver lesions, while the dissemination of the relapsed HL appears frequently as focal and diffuse liver involvement [24]. The prognostic of those 26 patients with primary extranodal HL included in the study of Ma J et al. was good, but their survival did not correlate with the international prognostic score [22], neither in patients with different extranodal sites [23].

A febrile cholestasis is an infrequent debut of liver HL. In the absence of adenomegalies, the liver biopsy established the diagnosis in such a case, who had a fast, severe and multisystemic disease dissemination [25].

A lymphomatous liver infiltrate was frequently observed in patients with diffuse large B cell non-Hodgkin’s lymphoma, appeared as a result of a nodular lymphocyte predominant HL transformation (which occurred in 17% of patients during a monitoring period of 30 years). This high-grade lymphoma (including its liver involvement) responded well to antracycline-based therapy in induction, platinum-based regimen as consolidation, and stem cell harvesting followed by BEAM conditioning and autograft [26].

A diffuse lymphomatous infiltration of the liver parenchyma can occur in HL and a liver biopsy is needed to confirm the diagnosis. This liver malignanat involvement can induce fulminant hepatic failure (if the diagnosis is not made early), which is a contraindication for chemotherapy. The prognostic of such patients is very poor [27]. Such a liver failure initial presentation was found in an explanted liver from a patient with clinical diagnosed alcoholic cirrhosis. It had nodular regenerative hyperplasia and portal infiltrate with Reed-Sternberg cells (CD15+, CD30+), and hilar adenopathies. Liver biopsy can be useful to establish the correct diagnosis [28]. Another patient, aged just seven years, also came with fulminant liver failure. Periportal lymph nodes were found during liver transplantation. Their histopathological examination and that of the liver found the same lymphomatous clone. The diagnosis was nodular lymphocyte-predominant HL, which was the cause of liver failure [29].
Chemo- and radiotherapy induced liver toxicity

Drug metabolism and excretion

| Main Route of Excretion | Kidney                     | Biliary                        |
|-------------------------|----------------------------|--------------------------------|
| Drug                    | Bleomycin                  | Anthracyclines                 |
|                         | Carboplatin                | Vinca alkaloids                |
|                         | Cisplatin                  |                                |
|                         | Cytarabine                 |                                |
|                         | Dacarbazine                |                                |
|                         | Dexamethasone              |                                |
|                         | Etoposide                  |                                |
|                         | Gemcytabine                |                                |
|                         | Ifosfamide                 |                                |
| Chemotherapy Regimen    | ABVD                       | ABVD                           |
|                         | BEACOPP                    | BEACOPP                        |
|                         | DHAP                       | Stanford V                     |
|                         | GDP                        |                                |
|                         | ICE                        |                                |
|                         | Stanford V                 |                                |

ABVD regimen: As doxorubicin is predominantly eliminated in the bile, liver function may be damaged in patients who have hepatic insufficiency or cholestasis. So, it is contraindicated in severe hepatic insufficiency, while in cholestasis a dose reduction by half is recommended if the bilirubin is between 20-50 micromol/L and by a quarter - if total bilirubin is > 50 micromol/L [30]. Bleomycin biotransformation occurs in plasma, liver and other organs. Its excretion take place via the kidneys and 2/3 of administered amount is eliminated unchanged [31]. The predominant metabolism and excretion of vinblastine is hepatic, too, so that in case of hyperbilirubinemia between 20-50 micromol/L it is recommended to reduce the dose to a half, and at higher values - stopping the vinblastine, due to the risk of worsening the liver disease [32]. The main place of dacarbazine metabolism is the liver, and its elimination is performed by the kidneys; 20-50% of its initial amount - in unchanged form. Liver toxicity of dacarbazine is uncommon (the frequency is ≥1/1000 and <1/100) and consists in an increase of serum ALT, aspartat aminotransferase (AST), lactic dehydrogenase, alkaline phosphatase, liver necrosis produced by veno-occlusive disease, hepatic vein thrombosis, and potentially fatal Budd-Chiari syndrome [33].

Gemcitabine is rapidly metabolized in the liver, kidney, blood and other tissues. Its excretion is 99% in the urine. Caution is also advised in the use of gemcitabine in patients with hepatic impairment. Results of clinical trials are insufficient to allow a clear dose recommendation in these patients. In patients with liver diseases, gemcitabine can exacerbate pre-existing hepatic impairment. During gemcitabine therapy liver function tests should be monitored [34].

DHAP regimen: Dexamethasone metabolism take place mainly in the liver, and less in the kidneys and its excretion is produced via the kidneys, in unconjugated form. In case of liver dysfunction drug metabolism decreases, which leads to drug accumulation [35]. Cytarabine metabolism occurs in the liver and partly in the kidneys and its excretion - primarily by the kidneys. It is recommended to monitor the liver and renal function during the treatment with cytarabine. In case of liver failure, the dose may be reduced. Liver abscesses were rarely reported after cytarabine [36]. Peak concentrations following i.v. administration of cisplatin occur in the liver, kidney and prostate, and its excretion occurs mainly via the kidneys; only small amounts can be found in the gall bladder and intestine. Transaminases rarely can increase and the process is reversible [37].

ICE regimen: The metabolism of ifosfamide is made in the liver and the drug and its metabolism products are eliminated predominantly by urine. Ifosfamide can rarely induce liver
function abnormalities (cytolysis and / or cholestasis) [38]. Carboplatin is eliminated mainly by the kidneys. In rare cases it can cause increasing gamma glutamyl transpeptidase (24%), AST (15%), or bilirubin (5%) in patients with normal baseline values of liver function tests. These dysfunctions were generally mild and reversible in about half of patients. Some cases with acute, fulminant liver cell necrosis were reported after high doses of drug administration [39]. Etoposide is eliminated by renal and non-renal way, but only 6% of the drug administered i.v. can be found in the bile. Liver dysfunctions may occur in below 3% of cases. High doses can induce elevations in bilirubin, serum alkaline phosphatase and AST [40].

Aside from the adverse effects that may occur after each drug use, their combination (and possibly also with other drugs used for related diseases) increases the risk of toxicity, particularly when they are metabolized through the same pathways (Table 1) and leads to their serum concentration (and, consequently, their toxicity) increase.

Findings of evidence-based medicine

Only a case of HL patients who developed liver toxicity (fulminant hepatitis and then hepatic coma) after chemotherapy was published until 2004 [41].

A single-center study included 119 children diagnosed with HL. Toxic hepatitis or liver cell failure was more frequently observed in the children treated with OAP protocol (20%), versus those who received COMP protocol (5%). In addition, the use of COMP protocol led to a better response, but the survival and the relapse rate were similar or almost the same [42]. Patients with HL and liver impairment can be treated with brentuximab vedotin (BV) as single agent until liver biochemical tests become normal [43], then specific HL treatment can be done. BV can be given together with chloromethine hydrochloride (CH), as in a study which included 6 cases of relapsed and refractory HL after failure of monotherapy with BV. A course of chemotherapy consists in BV (1.2-1.8 mg/kg, iv. gtt, in day 1) and CH (6 mg/m², iv. gtt, in day 1) and lasts 3 weeks. All patients responded to those 3-8 courses of chemotherapy (with 2 complete responses) and only one presented a grade I hepatocytolysis [44].

Between 20 HL patients (found in stage IIB of the disease or higher) included in a German multicentre study, only 2 patients developed non-hematologic toxicities of grade 3 or higher, including one with an increase of transaminases, after BEACOPP regimen, which however led to very good hematological results [45].

It is good to know that gemcitabine can also (but rarely) have adverse liver effects. The first case of severe hepatotoxicity associated with gemcitabine was published in 2010. It was a patient with a stage 4 lymphoma treated during 5 months with gemcitabine. He developed an acute worsening of liver function tests and hepatic encephalopathy, which completely disappeared after the drug stopping [46].

Methotrexate is frequently used for the treatment of rheumatoid arthritis. In such a case, it was associated with nonsteroidal anti-inflammatory drugs, prednisolone, and biological drugs. Adenomegalies and hepatosplenomegaly which arised, spontaneously disappeared after stopping the drug. In time, the female patient developed HL with many adenomegalies and multiple tumoral liver involvement (their etiology was clarified by liver biopsy), which produced liver failure. The evolution was to disseminated intravascular coagulation and death, before the start of chemotherapy [47].

Proton therapy is a solution to reduce the liver irradiation in HL patients compared with intensity-modulated radiotherapy or three-dimensional conformal photon radiotherapy, with a theoretical potential to decrease the risk of secondary malignancies and other late consequences of radiation [48].

Liver dysfunctions along with renal and gastrointestinal toxicity were reported to be the main non-hematological toxicities after autologous stem cell transplantation in 44 patients with lymphomas (including HL). In the study made by Kumar L et al. the graft conditioning was realized especially with high dose chemotherapy which consisted of cyclophosphamide, BCNU and
etoposide, and more rarely of etoposide, cytosine arabinoside and melphalan +/- BCNU, or melphalan in monotherapy [49].

The association of bortezomib and gemcitabine is less active and has higher toxicity in relapsed HL as against other current regimens. It can produce severe liver toxicity: a grade III transaminase increasing was showed in 3 of 18 patients [50].

A rare case of primary biliary cirrhosis occurred in a HL patient after chemotherapy [51].

**Hodgkin’s lymphoma and vanishing bile duct syndrome**

Hepatic lesions due to LH are relatively frequent but only a few patients have jaundice. Causes of jaundice in HL patients are: lymphomatous liver invasion, obstructive adenomegalies, hemolysis, chemotherapy adverse effects, or, in rare cases, VBDS [52].

The vanishing bile duct syndrome (VBDS) consists in a gradual destruction and disappearance of intrahepatic bile ducts (ductopenia) [52], and progressive liver failure [53]. Ductopenia means a loss of interlobular bile ducts in over a half of portal tracts, as a result of a disequilibrium between cell apoptosis and regeneration [54]. The cholestasis can progress to biliary cirrhosis and liver failure [55]. VBDS can be found in autoimmune diseases, adverse drug reactions, graft versus host disease, and malignancies [56].

VBDS is manifested by cholestatic jaundice [8,54,56] increased aminotransferases, and an histological aspect of bile duct loss [56] in the absence of liver infiltration by lymphoma cells [8,54,56] or obstructive adenopathies [54], so that it is believed to be the expression of a paraneoplastic syndrome [8,54,56], consequence of cytokine release from lymphoma cells [54]. HL occurrence may be preceded by a VBDS [53,57] even by several months [53]. The period of time until HL appearance was 18 months in 75-year-old patient who also had a pre-existent unexplained immunodeficiency [57].

The treatment is difficult due to the potential liver toxicity of many chemotherapy regimens, which may aggravate cholestasis or also induce hepatic cytolysis. Even if the treatment is appropriate, many patients experience progressive disease or liver failure, which can lead to death [8,56]. An exception is a 17-year-old man who was successfully treated with chemotherapy, after which the initial greatly increased serum bilirubin level normalized and he had a good clinical outcome [8]. Other authors also consider that full dose chemotherapy associated with ursodeoxycholic acid and prednisone could restore the liver function, with a resolution of VBDS, and contribute to HL complete remission [56]. Good results have also been obtained with MOPP-ABV regimen, however the transplant represents the only curative treatment in cases with progressive liver disease [53].

But there are also authors who recommend a good differential diagnosis between VBDS and idiopathic cholestasis, which implies the absence of ductopenia and where the liver function improves after treatment. Made this difference is essential in their view, as VBDS is generally considered to be irreversible. A female patient with VBDS had jaundice, distributive shock, high white cell count, cholestasis, and mild transaminase increase. Liver dysfunction worsened and liver failure occurred, despite the chemotherapy [54]. To another HL patient who at presentation also had VBDS, the chemotherapy allowed to obtain complete hematological response, but the cholestasis worsened progressively and fatal liver failure occurred [55].

This viewpoint was contradicted by Wong KM et al, who presented a patient having HL associated with VBDS. Not only lymphoma responded to 8 cycles of ABVD regimen followed by autologous hematopoietic stem cell transplantation, but also VBDS disappeared. The repeated liver biopsy at the moment of lymphoma complete remission found interlobular bile ducts regeneration, an argument for the reversibility of bile duct injury in VBDS [58]. Such isolated cases do not allow us to draw any definite conclusion on the general reversibility of VBDS.

A literature search found 37 cases of HL-related idiopathic cholestasis and VBDS. The death rate was 65% after a median follow-up of 7 months. The disease stage I or II, obtaining of complete response, and accomplishment of radiotherapy significantly contributed to an improved survival
without liver failure. The authors concluded that idiopathic cholestasis and VBDS due to HL are potentially reversible entities, with a good liver and lymphoma outcomes noticed in 30% of patients. But the restoration of liver function depends on obtaining complete response to HL therapy, which should be done as soon as possible [59].

**The relationship with liver transplantation**

If HL is the cause of acute liver failure, either at diagnosis or at relapse, liver transplant could be a solution for these patients [60].

Early liver transplantation could also be a therapeutic option in patients with unfavorable VBDS evolution [55].

Not only HL can conduce to liver involvement or damage. There is also the possibility to lymphoproliferative disease de novo occurrence after orthotopic liver transplantation (OLT). A very interesting study was realized in this regard in Italy: during a median follow-up of 5.2 years, 98 of those 1675 patients developed a primary cancer; a number of 22 were lymphoproliferative diseases, including 2 HL. A close surveillance after OLT is needed in order to improve their early detection [61]. In a series of 10 consecutive cases with lymphoproliferative diseases (including one with HL), which was also published, the median time from transplantation to lymphoma diagnosis was 5 years. This lymphoproliferative neoplasm was often extranodal and involved the received liver. If the reduction of immunosuppression do not conduces to complete response (50-77%), the patients have indication for chemotherapy (as in 8 patients from the study of Marino D et al). This conduct allowed to obtain a disease free survival in 6 of those 10 patients, after a median follow-up of 25 months [62].

**Hodgkin’s lymphoma and hemophagocytic lymphohistiocytosis**

HL may be one of the causes of hemophagocytic lymphohistiocytosis. Such a patient had at the diagnosis jaundice, fever, anasarca, encephalopathy, acute liver failure, and lymphadenopathy (due to a mixed cellularity type of HL). Hemophagocytic lymphohistiocytosis diagnosis was supported, apart from fever, by the bicytopenia, increased serum levels of bilirubin, lactic dehydrogenase, ferritin, INR, and the presence of hemophagocytic phenomena in ascites [9]. This condition associated to HL, which may have liver involvement (even severe liver damage), should be suspected and recognized in time, so that it can be treated promptly in order to avoid an unfavorable outcome.

The haemophagocytic syndrome, a type of hemophagocytic lymphohistiocytosis with infectious etiology, can occur in HL patients [63] found in all stages of HIV infection [64] having a positive Epstein Barr virus (EBV) viremia or with EBV RNA present in the lymphomatous cells. A recent literature review identified 6 such articles. Most patients were men aged under 50 years, with a very low CD4 count (under 100 cells/µL), even found under HAART treatment, and with a high EBV viremia. Despite the cortico- and chemotherapy +/- etoposide, they frequently evolved to death. In such a case with fever, pancytopenia, high serum level of ferritin, lactate dehydrogenase, and soluble IL2 receptor (CD25), EBV was high and liver biopsies showed haemophagocytosis phenomenon and lymphocyte depleted form of HL. He received etoposide, corticotherapy and R-ABVD (6 cycles). This complex immunological reaction initiated by the double viral infection and HL has an unclear pathogenesis [63].

**Peliosis hepatis**

Peliosis hepatis implies the presence of multiple irregularly distributed blood-filled cavities along the liver, which are irregular and diffusely broadened liver sinusoids. It may be the result of toxic, infectious or neoplastic liver damage. A patient came for asthenia, weight loss, anemia, increased serum level of liver enzymes and mediastinal tumor (which according to a CT scan guided biopsy was classical HL). He was undergone to a liver biopsy as he has multiple spots of livid color diffusely distributed over the liver at mini-laparoscopy. This biopsy allowed to establish the
diagnosis of peliosis hepatis, which was a rare manifestation of HL at diagnosis. The symptomatology and lab tests were improved quickly after the first cycle of BEACOPP regimen [10].

**The link between Hodgkin’s lymphoma and liver virus infections**

It is known that Epstein-Barr virus (EBV) infection is involved in some cases of HL etiopathogenesis. Some viruses (as human herpesvirus 8 or EBV) have the ability to directly infect and transform lymphocytes, some of them (as human immunodeficiency virus) have immunosuppressive effect and others (as hepatitis C virus) produce chronic immune stimulation [65], mechanisms that can contribute to lymphomagenesis.

**Hepatitis B virus (HBV)**

A nested case-control study was realized in 8 European countries which participated in European Prospective Investigation into Cancer and Nutrition study in order to investigate the possible involvement of hepatitis B and C viruses as risk factors in lymphoid malignancies occurrence. Between those 739 patients with lymphoid malignancies, 46 had HL. They were compared with 2028 witnesses from the point of view of the presence of serological markers of hepatitis B and C viruses. The authors concluded that chronic HBV infection may be a risk factor for malignant lymphoid proliferations [66].

The possible involvement of HBV in HL occurrence was studied in a recent meta-analysis which included 10 studies. The authors concluded that HBV seropositivity is a factor that increases the risk of HL (and multiple myeloma) occurrence. The odds ratio of developing HL in these subjects was 1.54 [67]. Studying the relationship between the stage of HBV infection and the lymphoma development the researchers of First Hospital of Jilin University found that lymphoma patients had serum markers found in the early stage and intermediate stage of HBV infection [HBsAg(+), respectively HbsAg and HbsAb negative but other positive HBV markers] [68].

Among 120 HL patients included in a single-center study from China 18 (15.0%) were HBsAg-positive. This incidence of HBV infection was similar with those of normal Chinese population. The 5-year survival rate was significantly lower in the HBsAg-positive patients with HL in stage I and II, compared with those HBsAg-negative (64.8% versus 96.0%) [69].

On the other hand, it is regrettable that not everywhere HL patients with HBV infection are verified before starting chemotherapy. Excepting the patients who were treated with allogeneic stem cell transplantation, who were tested in 100% of cases, only 5 of 11 patients with HL requiring chemotherapy were screened at baseline in the study made by Borde JP et al. [70]. A definite exclusion of a viral infection in immunosuppressed patients should only be made after virological analysis by molecular biology. A hepatitis E virus (HEV) infection was discovered in this way in a patient with HL (HEV-RNA was positive at PCR). The molecular diagnosis is useful especially in patients with strong clinical suspicion and negative serological results (the patient was from India, where HEV is endemic, and had prolonged jaundice after resolving his leptospirosis) [71]. But this behavior is also indicated in patients with HL suspected to be infected with other hepatitis viruses, including HBV.

The chemotherapy used for HL treatment can favor the occurrence of a liver virus infection. Such a patient with HL developed a severe acute HBV infection after chemotherapy performing and before beginning the radiotherapy. Biochemical and virological response was obtained with entecavir, condition which allowed him to resume the treatment, followed by obtaining complete hematological response [72].

European Conference on Infections in Leukemia considered that routine monitoring of CMV infection in patients treated by autologous peripheral stem cell transplantation (ASCT) is important, as the progression probability from infection to disease is low, excepting the patients receiving CD34-selected grafts [73]. A new risk factor for this disease after ASCT was proposed based on a study that included 128 lymphoma patients treated by ASCT of which 36 (28,1%) had HL. The
incidence of CMV infection and disease it all these lymphoma patients was about 12%, important as this can be a possible life-threatening complication. The authors suggested that a pre-transplant HBcIgG seropositivity could represent an independent predictor of a clinically relevant CMV infection after ASCT [74].

It is known that the treatment of HL including with BV can contribute to HBV reactivation [75]. If the chemotherapy of lymphomas is made without anti-HBV prophylaxis it can conduce to functional liver impairment, fulminant liver failure (sometimes), and to an overall liver-related mortality exceeding 5% [76].

**Hepatitis C virus**

In a large research, 2,819 lymphoma patients were compared with a large number of witnesses, in a region with a low incidence of HCV infection, in order to study a possible association between HCV and the risk of lymphomas development. In contrast to a possible association between HCV infection and the risk of non-Hodgkin’s lymphoma, no HL patient was HCV-positive [77].

A patient affected by war stress developed a HL (found in clinical stage IIIIB) one year after he was diagnosed with chronic hepatitis C. The treatment consisted in 6 cycles of ABVD regimen, which were very well tolerated (without any hepatitis flare either during or after them), and followed by complete hematological response [41]. This is a happy case, as theoretically, chemotherapy may worsen liver function. However, the treatment responses of patients are extremely varied, and in the literature there are no studies that include a large number of HL patients infected with hepatitis viruses and treated in order to draw conclusions based on evidence.

A marked regression of a HL present in a HCV-infected patient was observed after interferon-based antiviral treatment [78].

The hepatic damage due to the chemotherapy used for HL treatment is one of the cause of liver graft-failure after OLT for end-stage-liver-disease in patients with human-immunodeficiency-virus (HIV) infection, beside hepatitis due to HCV infection and recurrent hepatic-artery thrombosis. Such a patient had undetectable HIV viremia and a stable number of CD4 T-cells during a period of 20 months after OLT. But portal fibrosis was detected to him 18 month after OLT, and hepatic failure progressed, so that HAART had to be stopped. Afterwards, HIV infection progressed fast and the patient died 31 months after OLT as he had graft failure following liver chemotherapic toxicity and chronic liver disease due to HCV progressive infection [79].

**Hodgkin’s lymphoma associated with hepatitis virus infections**

Patients with HL often have concomitant infections with hepatitis viruses. Between 41 patients with chronic lymphoproliferative diseases and hepatitis B, C, or D viral infection, 2 (4.87%) had HL, in a single-center study performed during 2 years. This is a low proportion comparing to those having B-cell non-Hodgkin’s lymphoma - 28 patients (68.29%). These patients require clinical and biological monitoring throughout chemotherapy and antiviral treatment [80].

**Hodgkin’s lymphoma and autoimmune hepatitis**

Immunomodulatory treatment for autoimmune hepatitis and other autoimmune diseases (azathioprine, methotrexate, thalidomide, and tumor necrosis factor-α inhibitors, used as single drug therapy or in various combinations) may also favor the occurrence of classic HL, according to a study published by Loo EY et al, realized on 10 patients with iatrogenic immunodeficiency, including 1 with autoimmune hepatitis. In most of these patients who developed HL, Epstein-Barr virus RNA was present in their Reed-Sternberg cells. Stopping immunomodulatory therapy and performing adequate HL treatment was frequently followed by a favorable evolution [81]. It follows that the evolution of patients with autoimmune hepatitis should also be monitored to discover a possible lymphoma development.

Sometimes HL coexists with autoimmune hepatitis since the diagnosis. Such a case also had Hashimoto’s thyroiditis and was treated with ABVD protocol, which was well tolerated. HL
relapsed after one year at the level of cervical lymph nodes, when the patient developed 2 other autoimmune disorders: hemolytic anemia and thrombocytopenia [82]. This can be an argument for the involvement of autoimmunity in HL pathway.

**Associated diseases**

A HL patient can also develop liver dysfunctions as a result of its associated diseases or secondary to the treatment for these. Such a case of HL patient treated with a thiazolidinedione - rosiglitazone (4 mg/day, during 11 months) for his type 2 diabetes developed cholestasis and liver cytolysis, which progressed to acute liver failure, despite the discontinuation of rosiglitazone. Liver imaging and biopsy were used to exclude HL direct involvement in the etiology of liver complication [83].

**What is the best conduct in front of a Hodgkin’s lymphoma patient with liver damage?**

All chemotherapy drugs are metabolized in the liver or also in the liver. Therefore, it is not easy to find the ideal medication in case of liver damage.

Studying the main regimens recommended by current guidelines for HL therapy (ABVD, BEACOPP, Stanford V) it can be observed that they have at least two drugs that are eliminated mainly through the bile: an anthracycline and a vinca alkaloid. If cholestasis is present, they could worsen it. It follows that these regimens are not the most appropriate in case of the presence of liver dysfunctions.

BV (a chimeric monoclonal antibody anti-CD30 – drug conjugate) is used today for the treatment of refractory HL after failure of at least 2 types of chemotherapy regimens or after autograft failure. It can also be used as consolidation treatment after autograft in HL patients at high risk of relapse or progression. But if it is available, as it is expensive, it could also be a good bridge therapeutic option in HL patients with liver damage, alone or in combination with CH. This combination could especially be useful in patients found in intermediate or advanced stage of HL, as other bridge therapy, too: dexamethasone, gemcitabine and cisplatin, or cyclophosphamide, etoposide, procarbazine and prednisone. After improving liver function tests the patients can be treated with the classical regimens indicated in HL. For patients with an aggressive HL disease (advanced stages, relapsed or refractory disease) a salvage chemotherapy regimen (as ICE or DHAP) could be indicated - a therapeutic conduct which are not completely devoid of liver toxicity, given that the drugs are metabolized in the liver. Hepatic and renal function should be carefully monitored in patients during and after therapy. Liver transplantation is indicated for patients with severe hepatic impairment (Table 2). If liver dysfunction occurs during or after a particular chemotherapy regimen, it would be indicated not to use the above mentioned regimen again after a bridge or other type of chemotherapy.

If HL patient is infected with hepatitis B or C virus, the antiviral treatment is necessary during chemotherapy.

**Table 2. A Possible Conduct in HL Patient with Liver Damage.**

| HL Severity | +   | ++  | +++ | ++++ |
|-------------|-----|-----|-----|------|
| Suggested Conduct | BV as bridge therapy until liver functional test improving; then – ABVD, BEACOPP or Stanford V regimen | BV + chlormethine hydrochloride, or dexamethasone + gemcitabine + cisplatin, or cyclophosphamide, etoposide, procarbazine and prednisone as bridge therapy until liver functional test improving; then – ABVD, BEACOPP or Stanford V regimen | ICE or DHAP | Liver transplantation |
From present to future research directions

Any abnormality of liver function tests requires to be quickly investigated in terms of etiology by noninvasive means and, if it is not followed by results, also by liver biopsy. Otherwise, it can advance, even fast, towards liver failure.

If HL is the cause of liver damage, its treatment is required in order to reestablish the liver function (in combination with antivirus therapy, if any infection with hepatitis viruses is associated). Clinical experience of the physician will establish the most appropriate chemotherapy regimen depending on the severity of HL and liver damage.

It would be ideal that future pharmacological research find drugs with no liver toxicity or, if they have it, at least without liver metabolization and without biliary excretion, even when their serum concentration increases. Monoclonal antibodies toward several antigens of the lymphoma cell surface could be such a drug category, in combination or not with different chemotherapy agents. As the knowledge of HL pathophysiology gets deeper, it may offer new therapeutic targets that could contribute to improve the therapeutic outcomes, including that of liver damage.

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