Primary lymphoma of the liver – morphological and clinical analysis of 6 cases. Success of aggressive treatment

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Histological, clinical and immunohistochemical analysis of 6 cases of primary liver lymphomas (PLL) are presented. PLL represents 4.3% of primary malignant liver tumors diagnosed in our department. The patients were relatively young people, who despite the presence of a large tumor, were in good general health status. There were no signs of scirrhosis, and cancer markers were normal. All lymphomas were CD20, CD79a, BAX positive, CD3, CD30, EMA, CD10, CD5, CD59, c-myc, Bcl2, EBV(LMP), CK negative. The proliferation index (Ki67) was high, ranging from 50–100%. In two cases positive staining for Bcl6 and in another one for cyclin D1 was obtained.

The major histological type of the tumor was diffuse large B-cell lymphoma. Positive immunohistochemical results with BAX and the lack of Bcl2, c-myc and CD59 are associated with better prognosis. We have not confirmed the value of Bcl6 and CD10 stains as a predictor of poor outcome. Despite clinically advanced stage at the time of diagnosis, if treated appropriately, the primary lymphoma of the liver has relatively good prognosis (five of our patients are alive).

Key words: liver lymphoma, extranodal DLBCL, immunohistochemistry

Primary extranodal lymphomas comprise up to 40% of all lymphomas [23], their location within the liver is infrequent. However, due to the overall increase in incidence of lymphomas, and, in particular, of those arising in extranodal sites, now it appears necessary to include this disease in differential diagnosis of primary hepatic tumors [28]. Fast and precise diagnosis of hepatic lymphoma is important, since even if being in advanced stage of the disease, the patients still have a chance to be cured [23, 28, 35].

During the years 2000–2002, among 116 patients with primary malignant tumors of the liver treated surgically in our hospital there were 5 cases of malignant lymphoproliferative disease (4.3%). Here we present those 5 cases, as well as one additional patient, who was operated for lymphoma of the liver in 1996.

Material and methods

All clinical data concerning preoperative period and early postoperative course are presented in Table 1. Four patients, in addition to surgical treatment were treated with chemotherapy or chemoimmunotherapy (CHOP/R-CHOP – Vincristin, Adriamycin, Cyclophosphamide, Prednisone and Rituximab). In one case (no. 4) autologous peripheral blood stem cells transplantation (autoPBSCT) was performed. The data concerning patients treatment are presented in Table 2. One of the patient (no. 1) was lost in observation.

Histological procedures. In all cases complete surgical specimens were available for morphologic examinations – the tumor with adjacent normal parenchyma (excised anatomically) and, depending on the extent of the procedure, gallbladder, regional lymph nodes and, in one case (no. 5) right adrenal gland. The tissues were fixed in 10% formalin and processed routinely for paraffin embedding. 5-μm-thick sections were stained with hematoxylin and eosin, and with Gomori stain for reticulin fibers. The following broad panel of immunohistochemical stainings was applied: CD20, CD3, CD79a, CD30, CD10, CD5, CD59, EMA, CK, Ki67, c-myc, Bcl6, Bcl2, BAX, cyclin D1, CD68, VS38c, EBV (LMP). In addition to the surgical material, in 5 cases a trephine biopsy

Table 1. Clinical characteristics of cases

Patient	1	2	3	4	5	6
Age	66	42	17	28	31	42
Sex	F	M	M	F	M	M
Clinical signs	Abdominal pain, nausea, vomiting	Fever, weakness	Weak abdominal pain	None	None	Abdominal pain, jaundice
Laboratory abnormalities	Normal values	LDH, ALT, AST, bilirubine	LDH, GGT	LDH, GGT	LDH, GGT, ALT, bilirubine	LDH, GGT, alkaline phosphatase, ALT, AST, bilirubine
HBV/HCV	Negative	Negative	Negative	Negative	HBVnegative HCVpositive	Negative
AFP, CEA, Ca19-9	Not performed	Not elevated	Not elevated	Not elevated	Not elevated	Not elevated
Postoperative course	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful	Leak of transsudate after drain removal, early abscesses

F – female, M – male, – slight elevation HBV/HCV results of serologic tests for viral B and C infections.

Table 2. Additional therapy

Patient	1	2	3	4	5	6
Time from surgery to additional treatment	None	5 weeks	12 weeks	6 weeks	None	3 weeks
Cycles of CHOP therapy	–	7	6	8	–	6
Duration of therapy	–	8 months	6 months	7 months	–	7 months
Rituximab	–	–	–	375mg/m^2	–	375mg/m^2
Stem cells transplantation	None	None	None	15 months after the onset of chemotherapy	None	None
Complete remission	Lost in follow up	28 months	34 months	14 months	27 month	11 months

was performed and evaluated. The latter material was fixed in Oxford fluid and processed routinely.

The mobilizing chemotherapy consisted of the following regimen – etoposide 200 mg (days 1–3), iphosphamide 8 g (day 2) and carboplatin 750 mg (day 2). As *in vivo* purging anti-CD20 monoclonal antibody (Mabthera, Roche) was used (375 mg/m^2). From day +7 until last leucopheresis, granulocyte colony-stimulating factor (G-CSF) was administered subcutaneously (15 μg/kg/day). 7.1x10^6 CD34/kg positive cells were collected. Prophylaxis against Pneumocystis carinii and fungal infections was used. The conditioning for autologous peripheral blood stem cells transplantation (autoPBSCT) consisted of BCNU (170 mg/m^2) on days –8, –7, –6, etoposide 670 mg/m^2 on days –8, –7, –6 and cyclophosphamide 1460 mg/m^2 on days –5, –4, –3, –2. Unmodified PBSC were infused on day "0". 4.9x10^8 nucleated cells/kg recipient weight and 3.8x10^6/kg peripheral blood stem cells were infused. G-CSF was injected on days 5–12, 5 mg/kg/day s.c. and on day +14 monoclonal antibody anti-CD20 was administered (375 mg/m^2). Prophylaxis against Pneumocystis carini and fungal infections was used.

Bone marrow function recovered on +16 day after autoPBSCT.

Results

Morphological characteristics are presented in Table 3.

All liver specimens contained single large tumors (all but one above 10 cm), four of which were located in the right lobe, one was centrally located, and one was confined to the left lobe. Macroscopically the tumors appeared similar to other primary hepatic tumors – not encapsulated, beige and hard on palpation. In two cases (no. 3 and 4), some satellite foci were found in the vicinity of the main tumor, in two other cases (no. 2 and 5), the tumors invaded (from outside) the gallbladder and the adrenal gland, respectively. On microscopic examination all tumors were composed of large lymphoid cells having vesicular nuclei with 1–3 nucleoli, and abundant cytoplasm, resembling centroblasts. The cells resembling immunoblasts were infrequent. The tumors grew in the form of solid fields, and focally, nests surrounded by reticulin fibers were found. All tumors had high degree of atypia with frequent bizarre cells. In two cases (no. 3 and 4) there were foci of necrosis. All cases were diagnosed as being diffuse large B-cell lymphomas (DLBCL), centroblastic variants. The results of immunohistochemical reactions are shown in Table 4. The VS38c and CD68 stains were positive in plasmacytes and histiocytes, but negative in neoplastic cells. In all cases, the structure of the liver parenchyma apart from the tumor was normal. Lymphoma cells were not detected either in normal sinusoids or in regional lymph nodes. In one case (no. 2), microscopic examination confirmed invasion of the gallbladder wall, in other case (no. 5), the tumor cells were found in the capsule of adrenal gland. In only one (no. 4) of the trephine biopsies examined, the bone marrow was invaded by lymphoma.

Table 3. Cases descriptions – morphological characteristics

Patient	1	2	3	4	5	6
Clinical stage (Ann-Arbor classification)	IEA	IVB	IVA	IVA	I EA	I EB
Localization in liver segments	V,VI,VII	IV,V	IV, VIII	I,II,III	VI	IV, inferior segments of right lobe
Infiltration of adjacent structures	–	Gallbladder wall	–	–	Capsule of right adrenal gland	–
Tumor size (cm)	10x10x10	13x10x9	14x10x7	14x9x11	7x7x7	16x13x10
Satellite foci	–	–	+	+	–	–
Infiltration of regional lymph nodes	–	–	–	–	–	–
Infiltration of bone marrow	–	–	–	+	–	–
Liver cirrhosis	–	–	–	–	–	–

Table 4. Immunohistochemical data

	1	2	3	4	5	6
CD20	+	+	+	+	+	+
CD79a	+	+	+	+	+	+
CD3	–	–	–	–	–	–
CD30	–	–	–	–	–	–
EMA	–	–	–	–	–	–
CD10	–	–	–	–	–	–
CD5	–	–	–	–	–	–
CKMNF	-	-	-	-	-	-
CD59	–	–	–	–	–	–
Ki67	60%	50%	100%	80%	60%	70%
c-myc	–	–	–	–	–	–
Bcl6	–	-	–	+	+	–
Bcl2	–	–	–	–	–	–
BAX	+	+	+	+	+	+
EBV(LMP)	–	–	–	–	–	–
Cykl D1	+ cytopl	–	–	–	–	–

Discussion

Although the liver is very often secondarily involved in clinically advanced lymphomas, primary involvement of this organ is rare, being estimated as less than 1% of cases of all extranodal lymphoid malignancies [3, 9, 26]. Primary lymphoma of the liver is defined as malignant lymphoproliferation arising in, and limited (at least for some time) to the liver [28]. At early stages of this disease there should be no involvement of lymph nodes, spleen or bone marrow. Nevertheless, in practice, at the time of diagnosis, primary lymphoma of the liver is often being detected in the spleen, as well.

Although hepatic lymphomas typically occur in men about the age of 50, the range of patients' age is in fact very broad [23, 26, 28, 30]. In our group of patients there were 4 men, aged 17–42, and 2 women aged 28 and 66. The mean age in the group (38) was lesser than the typical age of onset of primary lymphoma of the liver.

Various authors have claimed an association between hepatic lymphomas and hepatitis B and C, especially in case of diffuse large B-cell lymphomas [2, 7, 9, 15, 26, 31, 32]. Among our patients, only one (no. 5) had confirmed HCV infection (and was anti-HCV seropositive). Some authors found an association between primary lymphoma of the liver and autoimmune diseases or industrial toxins [23, 28]. Among our patients none of such risk factors was found.

Primary hepatic lymphomas more often arise in patients having prior liver transplantation, as a form of posttransplant lymphoproliferative disease, due to standard immunosuppressive treatment and/or Epstein-Barr virus infection [12]. By immunohistochemistry, we did not find the evidence of EBV infection in any of our patients. It is possible that the causative role of EBV is limited to those hepatic lymphomas that arise in conditions of severe immunodeficiency, including AIDS [3, 28, 38].

Similarly to other liver tumors, the symptoms caused by primary lymphomas result from their effect on liver parenchyma due to location and/or size (cholestasis, abdominal pain, maldigestion) [15], rather than from specific features of the cancer. In addition, so called B-symptoms, found frequently in patients suffering from B-cell lymphomas, can be present, including fever, night sweats and loss of weight [26, 28]. Accordingly, one of our patients had jaundice and three had general unspecific complaints. Two patients were free of complaints. None of the patients was suspected to have lymphoma prior to the surgery.

Similarly to other authors, among our cases we found neither scirrhosis nor elevation of cancer markers (AFP, CEA, Ca19-9) [3, 26, 30, 34]. As reported [3, 6, 26, 30], a consistent finding was increased LDH. The latter however, similarly to mildly increased transaminases, bilirubin or GGT is not a specific marker of the disease.

Histological features of primary hepatic lymphomas are indistinct. Most often these are B-cell lymphomas, growing as a single tumor or in multiple nodules, or (infrequently) diffusely [15, 26]. T-cell lymphomas are very rare, and have usually diffuse type of growth [1]. All our patients had single focal lesions, of the size more than 10 cm (except one case).

According to the literature, more than 50% of the cases of primary lymphoma of the liver are DLBCL [6, 15, 25–28, 30]. Less frequent are MALT lymphoma [22, 29], mantle

cell- or anaplastic lymphoma [27], plasmacytoma [28], and peripheral T-cell neoplasms, including hepatosplenic T-cell lymphoma [27, 28, 41]. BORGONOVO et al have described primary lymphoplasmacytic lymphoma of the liver in 38 years old man with no underlying disease [6].

All our patients have been diagnosed as having diffuse large B-cell lymphoma, centroblastic variant with typical immunophenotype; positive for B-cell markers (CD20, CD79a) and negative for CD3, CD30, EMA, CK. The proliferation index (Ki67) was always high, ranging from 50 to 100%. There was no association between proliferative activity and tumor size, node involvement or large vessel/neighbouring organs invasion.

An important prognostic value in lymphomas has recently been ascribed to the origin and stage of differentiation of neoplastic B-cells [14]. Based on immunohistochemical and genetic studies, two subgroups of lymphomas can be distinguished: a) those arising from germinal center-cells, and b) those arising from mature effector B lymphocytes – postgerminal center cells. The former, being positive for Bcl6 and often for CD10, have better prognosis, are more sensitive to chemotherapy, and are less prone to relapse [5, 11]. ROSENWALD et al identified also the third group (unclassifiable), which probably contains several subgroups of DLBCL [40]. Among our 6 patients, 2 had positive staining for Bcl6 (however none was CD10-positive). Thus, our 4 Bcl6-negative cases possibly belong to the group of aggressive postgerminal-center-cell-derived lymphomas, whereas the two others represent more benign germinal-center-cell derived neoplasms of better prognosis. Follow up 11 to 34 months (mean 21 months), has not confirmed these results; 3 of them (the fourth was lost in observation) are alive without disease.

Unfortunately, due to unspecific mild complaints or even lack of complaints in our patients, we cannot adequately assess at which stage of the disease-progression they actually were at the time of surgery. It is possible, that the period of occult disease could have been quite variable, since the diagnostic process was initiated only after the tumors reached large sizes.

All our cases occurred to be BAX-positive. BAX protein belongs to the family of Bcl2-related proteins, but unlike the prototype family member, it is a pro-apoptotic caspase activator. There have been several reports published on the expression of BAX in DLBCL. Some authors found an association between positive BAX immunostaining and worse prognosis, others did not find such an association, whereas some claimed BAX-negativity to be unfavorable prognostic factor [4, 13, 36]. According to GASCONE et al [13] this is the combination of BAX-positive- with Bcl2 negative staining that gives the best prognosis in aggressive lymphoma. As indicated in Table 4, such a combination was found in all our cases. Thus, in spite of being in advanced stage of the disease, our patients**,** who are all, except the woman no. 1**,** relatively young and in good general health status, hopefully have chances either for complete cure or at least for considerable life prolongation. The prognosis may be especially good for those that have DLBCL derived from germinal-center cells (Bcl6 positive, patients no. 3 and 5).

Aberrant expression of c-myc that results from chromosomal translocations have been described in a proportion of DLBCL cases [8, 33, 42]. According to CHANG et al [8] c-myc expression correlates with advanced disease and worse prognosis. ZHANG et al [42] do not support a significance of c-myc overexpression as a diagnostic/prognostic factor in DLBCL. In our cases, we found no c-myc expression, what, in connection with no disease relapses in our five patients**,** may support CHANG's et al results**.**

Cyclin D1 is an essential regulatory component of cyclin-dependent kinase complexes (containing CDK4/ /CDK6 as catalytic components), which by phosphorylation of various proteins, drives the cells from G0 to S phases of the cell-cycle [10]. The intracellular distribution of cyclin D1 varies, depending on the phase of the cell-cycle, being nuclear in G1 and cytoplasmic in S phase [24]. In tumors, the most frequent is the intranuclear pattern of cyclin D1 expression, whereas the cytoplasmic staining is rare [18, 39]. In DLBCL, cyclin D1 immunoreactivity is most often negative [21]. According to ZHANG et al [42], those rare cases that do have cyclin D1 overexpression have unfavorable prognosis. We found positive cytoplasmic staining for cyclin D1 in one of our patients (no. 1 – unfortunately lost in follow up). Although possible, it is rather unlikely, that this DLBCL arose secondarily from mantle-cell lymphoma, since CD5 immunoreactivity was negative.

Recently, immunotherapy with anti-CD20 monoclonal antibody Rituximab combined with chemotherapy, has become a standard treatment option for patients with various B-cell lymphomas, including DLBCL [20]. The mechanism of Rituximab action is based, at least in part, on complement-dependent cytotoxicity, and the major factors limiting the efficacy of such a treatment include the expression of complement inhibitors in cancer cells [16, 17]. CD59 (protectin) is the most potent membrane-bound complement inhibitor [19]. The lack of CD59 expression in all our patients may indicate potential feasibility of the use of Rituximab, along with surgery and/or traditional chemo/radiotherapy, to treat primary hepatic lymphoma. Interestingly, encouraging results have recently been obtained with such a treatment in some cases of gastrointestinal B-cell lymphoma [37].

Conclusions

1. The major histological tumor type was diffuse large B-cell lymphoma, which, in 4 cases, appeared to be derived from postgerminal-center cells. 2. The immunohistochemical analysis of our cases may the view support that the positive result with BAX and the lack of Bcl2, c-myc and CD59 are associated with better prognosis. We have not confirmed the

value of Bcl6 and CD10 stains as a predictor of poor outcome. 3. Despite being clinically advanced at the time of diagnosis, if treated appropriately, primary lymphoma of the liver has relatively good prognosis (five of our patients are alive). Thus, prompt and precise diagnosis of this disease, including histopathology, is of utmost importance.

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