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Role of Fine Needle Aspiration Cytology in Management of Hepatocellular Carcinoma: A Single Centre Experience

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A B S T R A C T

Hepatocellular carcinoma (HCC) mostly occurs in chronic liver disease and cirrhosis. Liver resection and liver transplantation (LT) represent potentially curative treatments of choice and if not feasible, palliative strategies such as percutaneous interventional techniques (PITs) and chemotherapy (ChT) are considered. Elevated alfa-fetoprotein, typical imaging pattern, needle core biopsy (NCB) and fine needle aspiration cytology (FNAC) complement diagnostic assessment of HCC. We have retrospectively analyzed all patients with contraindications for NCB in which HCC was diagnosed by FNAC during consecutive 5 years in our hospital. Ultrasound guided FNAC provided a safe method of approach and, except for mild transitory discomfort at the site of puncture, no complications were documented. The diagnosis was established on May-Grünwald-Giemsa (MGG) stained aspirates and additional immunocytochemistry. Of our 62 patients, HCC developed in 61.3% cirrhotic and 38.7% non-cirrhotic livers. In the setting of cirrhosis 18.4% of patients underwent LT, 15.8% PITs, 26.3% ChT and 39.5% symptomatic therapy. In non-cirrhotic setting 46% of patients underwent liver resection, and PIT, ChT, and symptomatic therapy were applied in 4%, 25%, 25% of cases, respectively. Pathohistology of resected and explanted livers (18 cases) confirmed the initial diagnosis made on FNAC. Since only early stage of HCC has a better prognosis, every effort should be made to establish prompt and accurate diagnosis. Our observations demonstrate that FNAC offers minimally invasive, rapid and uncomplicated diagnostic approach, with sensitivity from 67% to 93% and specificity from 96% to 100%. FNAC, is of utmost importance in the setting of abnormal coagulation tests and ascites commonly seen in advanced liver disease, facilitating diagnostic workup and treatment decisions.

***Key words**: hepatocellular carcinoma (HCC), fine needle aspiration cytology (FNCA), treatment*

Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer in the world and its incidence is still rising. It accounts for about 90% of all primary liver cancers and mostly occurs in the setting of chronic liver disease and cirrhosis. Several important risk factors for HCC have been identified: male gender (3.7:1 men to women)[1], higher age (mean age at presentation between 50 and 60 years)[2], chronic liver disease (chronic hepatitis or cirrhosis) of any cause[3–5], hepatitis B virus (HBV) infection – (chronic HBV infection is the predominant global environmental cause of chronic hepatitis or cirrhosis, whereas 25% of infected or more will develop HCC)[6,7], hepatitis C virus (HCV) infection (80% of acutely infected become chronic carriers, and about 60% develop chronic hepatitis of which 20% progress to cirrhosis over a period of 20–25 years, and a proportion of these develop HCC)[8,9], iron overload: hereditary hemochromatosis (HH) and dietary iron overload (with a relative risk of greater than 200)[10], aflatoxin (mycotoxin produced by the fungi Aspergillus flavis), nonalcoholic fatty liver disease (NASH) and diabetes mellitus (DM)[11], inherited metabolic disorders: alpha-1 antitrypsin (α1AT) deficien-

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cy, hereditary tyrosinemia type 1 (HT1), glycogen storage diseases and Wilson's disease[12–15].

Although elevated level of serum alpha-fetoprotein and a typical imaging pattern (demonstrated by ultrasound, computer tomography – CT, magnetic resonance – MR and angiography) may be sufficient for diagnosis, in inconclusive cases tissue diagnosis is mandatory. Needle core biopsy (NCB) and fine needle aspiration cytology (FNAC) both can provide definitive morphological assessment. HCC is typically diagnosed late in its course, and the median survival following diagnosis is approximately 6 to 20 months[16]. Treatment strategies, depending on tumor extent and underlying liver dysfunction, include liver resection or transplantation, percutaneous interventional techniques (PITs), chemotherapy (ChT) and symptomatic therapy.

Materials and Methods

This study was carried out by the multidisciplinary team of tertiary Gastroenterology centre from »Merkur« University Hospital. We retrospectively identified all HCC patients diagnosed only by FNAC at our institution in the period from January 2004 to July 2009. Data collected from patients' medical records specified clinical, laboratory, imaging and cytological results. Diagnostic assessment included imaging studies (ultrasound, CT or MR imaging) and serum alpha-fetoprotein level. Ultrasound guided FNAC with the CHIBA needle of 0.7 mm (22 gauge) was performed in patients with clinical suggestion of HCC with contraindications for NCB; abnormal coagulation parameters, refractory ascites or lack of a safe access. The cytological smears were stained by the standard May-Grünwald-Giemsa method (MGG) (Figure 1a and b). Immunocytochemical staining was performed by LSAB method with monoclonal antibodies (DAKO), applying a panel of α-fetoprotein (Figure 1c), BerEP4, CD31, CK8, CK18 (Figure1d), and in selected cases, CK 5/6, CK7, CK 19, CK 20, CD117, desmin, SMA, chromogranin, synaptophysin, thyroid transcription factor-1 (TTF-1), Ca19,9, CEA etc. for the diagnosis of HCC and distinction of HCC from metastatic tumors (MC) or to identify the primary tumor site of MC. Statistical analyses were performed using MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium). Data were analyzed with Mann Whitney test, χ^2-test and Fisher's exact test. Differences were considered significant when two sided $p<0.05$.

Results

In period from 2004 to 2009, all patients with contraindications for NCB in which HCC was diagnosed by FNAC are analyzed. FNAC was performed under the guidance of ultrasound. No serious post-procedural complications were documented, except for mild transitory discomfort at the site of puncture. Summarized data of all our patients are presented in Table 1. 62 patients were included, mean age of 63 years (range 47–86, SD 13). The majority of patients (61.3%) developed HCC in cirrhotic liver, whereas 38.7% in non-cirrhotic form of parenchymal liver disease. Dominant gender in both groups was men: 81.6% in cirrhotic group (CG) and 83.3% in non-cirrhotic group (NCG). HCC developed in significantly earlier age in CG (mean age 62±9.1) than in NCG (mean age 70±9.3, Mann Whitney, $p<0.02$). In the majority of patients in CG (63.2%) the etiology of underlying liver disease was known; alcohol in 47.4% and viral diseases (HBV and HCV) in 15.8% of cases. In comparison, in 83.3% of cases in NCG, the etiology of the liver disease remained unknown and in only 8.3% it was alco-

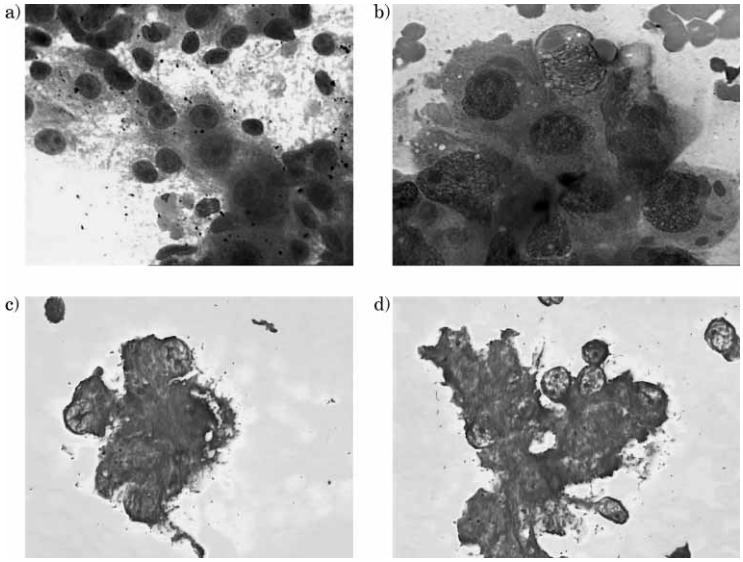

Figure 1. Fine needle aspiration cytology of hepatocellular carcinoma: a) well-differentiated (MGG, 1000x), b) poorly differentiated (MGG, x1000), c) α-feto protein positive cells (immunocytochemistry, LSAB, 1000x), d) Cytokeratin 18 positive cells (immunocytochemistry, LSAB, x1000).

TABLE 1
DATA FOR PATIENTS WITH HEPATOCELULLAR CARCINOMA

Characteristics	Cirrhotic group % (n)	Non-cirrhotic group % (n)	p-value
Patients	61.3% (38)	38.7% (24)	
Female	18.4% (7)	16.7% (4)	0.89
Male	81.6% (31)	83.3% (20)	
Age, mean±SD,	62±9.1	70±9.3	<0.002*
Etiology			
Alcohol	47.4% (18)	8.3% (2)	0.004*
Viruses (HBV+HCV)	15.8% (6)	8.3% (2)	0.64
Undetermined	36.8% (14)	83.3% (20)	<0.001*
Tumor presentation			
Mutifocal	52.6% (20)	41.7% (10)	0.56
Solitary	47.4% (18)	58.3% (14)	
Therapy			
Hepatic resection	0	45.8% (11)	
OLT	18.4% (7)	0	
PITs	15.8% (6)	4.2% (1)	0.32
Chemotherapy	26.3% (10)	25% (6)	0.86
Symptomatic therapy	39.5% (15)	25% (6)	0.34

*statistically significant, OLT – orthotopic liver transplantation, PIT – percutaneous interventional techniques

hol and 8.3% viral infection. There was no statistically significant difference between the groups regarding tumor presentation (multifocal or solitary) at the time of diagnosis (χ^2, p=0.56).

In the setting of decompensated cirrhosis, 18.4% of patients which met Milan criteria, underwent liver transplantation, 15.8% underwent PIT, 26.3% were treated with chemotherapy and 39.5% with symptomatic therapy. In non-cirrhotic group HCC was treated in 45.8% of cases by liver resection, in 25% with chemotherapy, in 25% with symptomatic therapy and in 4% by PIT. Pathohistological analysis of resected (11 cases) and explanted livers (seven cases) confirmed the initial diagnosis made on FNA specimens.

Discussion

There is a general consensus that periodic abdominal ultrasound (every six months) and the measurement of serum AFP level in surveillance of high risk groups can detect HCC in its early stage, which is associated with better prognosis[17]. However, significant proportion of HCC lesions are not associated with elevated AFP and although imaging methods show a typical imaging pattern, that finding is not always patognomonic, especially for small and hypovascular tumors[18–20]. Therefore, additional morphological assessment should be made either by FNAC or NCB. Although NCB is considered a gold standard for identification of HCC, in the clinical practice, especially in the setting of advanced parenchymal liver disease, it is not always a feasible method. Major obstacles for its use are: low platelet count, abnormal coagulation parameters, refractory ascites or localisation of lesion with no safe access route. Limited by aforementioned parameters, diagnostic workup may be delayed or interrupted enabling further progression of malignant disease and restraining treatment options. FNAC results in a little liver damage and has a high safety. The occurrence rate of complications ranges from 0.05% to 0.16% and includes bleeding, bile leakage, infection and death[21]. In theory, pulling out the needle after aspiration procedure may result in further seeding of the tumor cells. None of these complications were observed in our survey. The specificity and positive predictive value of FNAC is ranges from 96% to 100% and its sensitivity ranges from 67 to 93%[22–24]. These results are comparable to the accuracy of NCB (sensitivity range 61 to 94%)[25,26].

Liver resection is the treatment of choice for HCC in non-cirrhotic and Child A cirrhotic patients, but in the setting of decompensated liver disease, liver transplantation (LT) represents an effective treatment as it simultaneously treats the tumor and the underlying liver disease. If not feasible, percutaneous interventional techniques (PITs); percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), selected transcatheter arterial chemoembolization (TACE) provide optional choices of treatment. Liver resection or LT are considered best treatment options for HCC because of potential complete recovery. However these procedures are mainly limited by the size of tumor and the possibility of disease dissemination. Therefore every effort should be made to enable the accurate diagnosis in the early stage of the

disease. Postponing or interrupting the diagnostic process due to contraindication for certain methods restricts treatment to palliative modalities such as chemotherapy and symptomatic therapy. HCC is a chemotherapy-refractory tumor and cytotoxic effect is modest in patients with HCC. No single regimen has emerged as superior to any other (doxorubicin, mitoxantrone, cisplatin-based and gemcitabine-based combination regimens) and in general, the duration of benefit is limited. Although molecular pathogenesis of HCC remains still poorly understood, molecularly targeted therapy (sorafenib) has emerged in recent years for treatment of advanced stage of the disease.

Out of 62 HCC patients with contraindications for NCB, detection of HCC by FNAC in 64.2% (18.4% CG and 45.8% NGC) of patients still in early stage of the malignant disease allowed application of potentially curative treatment options (LT and resection). Our observations demonstrate that in spite of obstacles in advanced liver disease, FNAC offers safe and effective diagnostic approach steering the treatment to more beneficial prognosis.

Therefore since only early stage of the disease offers potentially curative treatment options it is imperative, especially in high risk group patients, to perform intensive screening for HCC and, if suspected, every effort should be made to establish early and accurate diagnosis.

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ULOGA CITOLOŠKE PUNKCIJE U STRATEGIJI HEPATOCELULARNOG KARCINOMA – ISKUSTVO JEDNOG CENTRA

SAŽETAK

Hepatocelularni karcinom (HCC) se razvija uglavnom u kroničnoj bolesti jetre ili cirozi. Resekcija i transplantacija jetre (LT) su potencijalne metode izlječenja HCC, no ukoliko nisu primjenjive, dolaze u obzir palijativne strategije poput perkutane interventne tehnike (PITs) i kemoterapije (ChT). Povišeni alfa-fetoprotein; tipični morfološki prikaz, iglena biopsija (core needle biopsy – NCB) i citološka punkcija (fine needle aspiration cytology – FNAC) komplementarne su metode u dijagnostici HCC. Analizirali smo sve bolesnike s kontaindikacijom za NCB kod kojih je HCC dijagnosticiran citološkom punkcijom u razdoblju od 2004.–2009. godine u našoj ustanovi. Citološka punkcija učinjena je pod kontrolom ultrazvuka te osim prolazne nelagode na mjestu punkcije nisu opažene druge komplikacije. Dijagnoza je postavljena na citološkim razmazima obojenim May-Grunwald-Giemsa bojenjem i imunocitokemijski. Od ukupno 62 bolesnika, HCC se razvio u 61,3% bolesnika s cirozom jetre te u 38,7% bolesnika bez ciroze jetre. Kod ciroze jetre u 18,4% bolesnika izvršena je LT, 15,8% PITs, 26,3% ChT te je u 39,5% provedena simptomatska terapija. U skupini bolesnika bez

ciroze, kod 46% bolesnika je izvršena resekcija, u 4% primjenjen je PITs, u 25% ChT i u 25% simptomatska terapija. Patohistološka analiza reseciranih i eksplantirannih jetri (18 slučajeva) potvrdila je citološku dijagnozu. Budući rani stadiji bolesti imaju bolju prognozu, potrebna je brza i točna dijagnostika. Naša zapažanja ukazuju da je FNAC minimalno invazivna, brza i jednostavna dijanostička metoda sa osjetljivošću od 67% do 93% i specifičnošću od 96% do 100. Citološka punkcija, naročito u slučajevima uzapredovale bolesti jetre s komplikacijama (loša koagulacija i ascites) omogućuje rano postavljanje dijagnoze, te time i raniji početak liječenja.