·临床病理讨论·

Clinicopathological Conference

Hepatic cirrhosis and hepatocellular carcinoma in a patient with drug-induced hepatitis

(The 14th case)

Department of Geriatric Gastroenterology, Chinese PLA General Hospital

Case Presentation

The patient, male, 79 years old, was admitted with a history of abnormal hepatic function for longer than 20 years and a history of systemic aching for 2 weeks. Tuberculosis was first found in biliary duct in 1982 when the cystectomy was performed because of cholecystolithiasis, and treated with anti-tuberculotic drugs such as isoniazid and streptomycin. GPT increased 3 months after therapy of tuberculosis and reduced to normal level after drugs withdrawal. Abdominal ultrasonograms displayed multiple angiomas of liver in 1983. Tuberculosis occurred in the lymph nodes at the right side of neck in 1986 and treated for over 1 year. Liver aminotransferases were elevated progressively but with negative serologic markers of viral hepatitis and immunology(IgA, IgG, IgM, ANA, AMA). GPT and GOT fluctuated between 50 to 110 U/L after the treatment of tuberculosis was discontinued and the drugs for protection of liver was administrated intermittently. The patient was diagnosed as decompensated liver cirrhosis in May 1999 when GPT increased to 1100 U/L, abdominal ultrasonograms displayed cirrhosis, splenomegalia and ascites, and gastroscopy revealed esophageal varices. Symptoms disappeared by way of diuretic and supportive treatment. In June 2001, CT displayed a space-occupying lesion with a size of 7.2×5.3 cm in left lobe of liver, in which the midium-low density area was larger than before and presented stria intensification in arterial phase, corresponding to the image display of hepatocellular carinoma (HCC). However B-type ultrasonograms and MRI didn't support this diagnosis but rather the diagnosis of fibrosis and organized hemangioma. The diagnosis of HCC was reconfirmed by abdominal image finding, multiple lesions and portal vein tumor embolus as displayed by abdominal ultrasonograms, CT and MRI in September, 2003. Treatment with liver-protecting measures, nutritional support and immunotherapy were given to the patient. He was admitted to this hospital because of aching for 2 weeks but no fever, nausea, vomiting, black stool.

The patient had a history of malaria, hypertension and vertebrobasilar arterial insufficiency. There were no coronary heart disease, diabetes and drug hypersensitivity in his past medical history.

Physical examination: T: 37.0℃, P:76/min, BR: 18/min, BP: 125/70 mmHg. He was conscious and in automatic body position and had facies hepatica, jaundice, spider telangiectasia and liver palm. No swelling of superficial lymph nodes was found. Breath sound was clear, without bubble and wheezing sound in both lung fields . The heart rate was 76/min, cardiac rhythm was regular and no murmur at any valve auscultation field was heard. Abdomen was flat and soft, there were no subcutaneous varicose veins of abdominal wall and no peristaltic wave. There was tenderness under the costal margin at right midclavicular line, but no rebounding tenderness and no abdominal mass. Liver and spleen were not palpable with no percussion pain in hepatic region and bowel sounds were normal. Shifting dullness was present. Backbones and limbs had no abnormalities, tenderness and no pitting edema. Arteriopalmus of both dorsum pedis were normal. Physiological reflexes existed, pathologic reflex was absent. Laboratory examination: WBC: 5.9×10^9/L, N: 0.85, RBC: 3.23×10^{12}/L, PLT: 70×10^9/L. GPT: 23.5 U/L, GOT: 39.0 U/L, Alb: 25.4 g/L, TBil: 148.1 μmol/L, DBil: 109.8 μmol/L. AFP: 3.52 μg/L.

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Symptomatic and supportive treatment such as liver protectives, albumin replenishing, diuretic, analgesics were given after admission. Blood NH_3 concentration increased to 107 μg/dl, accompanied with dullness in response and abnormal electroencephalogram on 3, April 2004, which supported the diagnosis of hepatic encephalopathy. Blood NH_3 gradually decreased and returned to normal level after intravenous administration of arginine and branched-chain amino acid and oral administration of Duphalac and metronidazole. Ten days later, pain in chest and waist was aggravated. X ray examination of the chest showed infectious signs in the lower lungs on the both sides and compressed fracture in the 10th thoracic vertebra and the 1st, 4th, 5th lumbar vertebrae. Body bone scanning suggested that osseous metastasis could not be excluded because of the gathering of nuclide in ribs and thoracic vertebrae. MRI of thoracicolumbar vertebrae revealed metastasis and pathological fracture in vertebral bodies of T10 and L1 – L3. Antibiotics and analgesics such as bolin, morphine and Durogesic were given. On 26 May, 2004, intermittent asthma started, accompanied with quick heart rate and moist rales at the bases of lung on both sides. Two days later, X-ray of chest displayed infection in both lungs, pleural effusion bilaterally and fracture of the 6th and 7th left ribs. Antibiotic and analgesic management were continued and sometimes cardiotonic and diuretic treatment were also given. The patient died of the deterioration of the general conditions on 3, Oct. 2004.

Clinicopathological Discussion

Dr. Liu Aijun (*pathologist*): Autopsy findings were as follows: (1) Liver weighed 1280 g (normal, 1300 – 1500 g) and had multiple tumors, with the largest one 9 × 8 × 8 cm and the smallest 2 × 2 × 1.7 cm. The tumors were hepatic cellular cancer confirmed by histological examination, only the one (4 × 3 × 2.5 cm) in square lobe was spongy hemangioma. Other features included congestion, cholestasis, chronic inflammatory cell infiltration in portal triad and fibrous hyperplasia. (2) Splenomegaly, the spleen weighed 302 g (normal, 110 – 200 g) and congestion was seen in the histological examination. (3) Significant adherence of both lungs to thoracic wall. Histological examination revealed fibrous hyperplasia in pleura and congestion in lungs with local edema and inflammatory cell infiltration. (4) Pleural effusion with 500 ml in the left cavity and 550 ml in the right. No tumor was found in bones and pleura.

Dr. Xu Shiping: Drugs account for 20% of causes of liver injury in the old patients. The diagnosis of drug-induced hepatitis was explicit in the patient because he had a history of liver injury following the medication for tuberculosis and negative serologic markers of viral hepatitis and immunity which excluded virus hepatitis and autoimmune hepatitis. It is uncommon that the drug-related hepatotoxicity developes progressively to form cirrhosis, even HCC in our case, since this kind of hepatotoxicity is generally reversible if the drug is discontinued. It was possible that he was infected with other unknown hepatitis virus.

Dr. Wu Benyan: Multiple masses in the liver were considered as hemangioma by abdominal ultrasonograms and CT in 1983, but suspected to be HCC by CT in 2001 and confirmed in 2003 and at autopsy. There was no evidence that HCC originated from hemangioma because of the tissue origin difference between hemangioma and HCC. The patient had no gold standard of liver pathological diagnosis before death, and final diagnosis could not only depend on various imaging display. It was supposed that HCC developed from hepatic adenoma or focal nodular hyperplasia.

Dr. Yang Shaobo: Whether there are differences in cell types of HCC between those induced by drug and by viral hepatitis is yet to be determined. In this patient with histologically confirmed HCC, AFP was not increased, which is uncommon in HCC patients. Due to the limitation of the sample taken at autopsy, multiple osseous metastasis and portal vein tumor embolus demonstrated by image analysis were not verified by autopsy. Bone tuberculosis could not be excluded according to the patient's history of tuberculosis.

Dr. Cai Changhao: The patient missed the chance to receive any surgical intervenition treatment because of

multiple large tumors complicated by metastasis and liver dysfunction, and could not recover by medical management during the course of hospitalisation. The cause of his death can be inferred as circulatory and respiratory failure resulting from liver dysfunction due to HCC and cirrhosis, hypertension, chronic pulmonary infection, and pleural effusion.

(Translator: LIU Jing, WU Benyan, CAI Changhao, et al)

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药物性肝炎后肝硬化、肝癌1例

1 病历摘要

患者,男性,79岁,主因"肝功能异常20余年,全身酸痛2周"于2004年3月16日入院。患者缘于1982年因胆囊结石行胆囊切除术中发现胆管结核,术后予以抗结核药物(雷米封、链霉素)治疗3个月后出现GPT升高,停药后肝功恢复正常。1983年始腹部B超检查提示肝脏多发性血管瘤。1986年再次出现右颈部淋巴结结核,给予抗结核药物治疗1年余,发现转氨酶进行性升高,多次行肝炎病毒血清学检查,HBVAg、HCVAb、HAVAb均阴性,免疫指标:IgA、IgG、IgM均在正常范围,抗核抗体、抗线粒体抗体均阴性。停用抗结核药物,间断口服保肝药物治疗,GPT、GOT波动于50~110 U/L。1999年5月GPT升至1100 U/L,腹部B超提示:肝硬化、脾大、腹水,胃镜检查示食管静脉曲张。诊断为:肝硬化肝功能失代偿期。予以保肝、利尿等对症治疗。2001年6月肝脏CT平扫+增强提示肝左外叶7.2 cm×5.3 cm不均匀中强回声团块较前增大,其中中低密度区较前明显增多,动脉期呈线条样增强,部分符合肝癌影像学表现,但结合B超、MRI影象学检查,确诊为血管瘤纤维化、机化。2003年9月腹部B超、CT及MRI均提示:肝脏多发占位病变、门脉瘤栓,诊断为原发性肝癌。给予保肝、对症、营养支持、免疫等治疗。2周前出现腰痛及全身酸痛,无发热、恶心、呕吐、呕血、黑便等,为进一步诊治入我科。

既往患者有疟疾(已治愈)、高血压、椎基底动脉供血不足等病史。无冠心病,糖尿病等史;无药物过敏史。

体格检查:体温:37.0℃ 脉搏:76次/min 呼吸:18次/min 血压:125/70 mmHg。意识清楚,肝病面容,自动体位。皮肤黄染,可见面部毛细血管扩张及肝掌。浅表淋巴结无肿大。双肺呼吸音清晰,无干湿啰音。心率76次/min,律齐,各瓣膜听诊区无杂音。腹部平坦,未见腹壁静脉曲张,未见蠕动波及肠型,右锁骨中线肋缘下有压痛,无反跳痛,肝脾肋下未触及,未及腹部肿块,肝区无叩击痛,移动性浊音阳性,肠鸣音正常。脊柱及四肢无畸形、变形及压痛,双下肢无浮肿,双足背动脉搏动正常。生理反射存在,病理反射未引出。辅助检查:血常规:WBC 5.9×10^9/L, N:0.85, RBC 3.23×10^{12}/L, PLT: 70×10^9/L。肝功:GPT:23.5 U/L, GOT:39.0 U/L, Alb:25.4 g/L, TBil: 148.1 μmol/L, DBil: 109.8 μmol/L。AFP: 3.52 μg/L。

入院后给予保肝、补蛋白、利尿、止痛、对症、支持治疗。4月3日出现反应迟钝,血氨浓度:107μg/dl,脑电图异常,支持肝性脑病诊断,给予静滴精氨酸、支链氨基酸,口服杜秘克、甲硝唑治疗,血氨恢复正常。10 d后,胸部、腰部疼痛明显加重,胸片回报,双下肺感染,T10压缩改变。L1、4、5压缩改变。全身骨扫描结果:肋骨、胸椎浓聚,不除外骨转移。胸腰段MR平扫:T10、L1~L3椎体转移瘤伴病理性骨折。给予抗感染治疗,应用博宁、吗啡、多瑞吉等止痛治疗,5月26日始间断出现憋喘症状,心率增快,双肺底可闻及湿性啰音。5月28日胸片回报:双肺感染、双侧胸腔积液,左6、7肋骨骨折。继续给予抗感染、止痛治疗,间断予以毛花甙丙、呋塞米、乙胺碘呋酮等药物强心、利尿治疗。2004年10月3日19:50突然出现血压、心率下降,陈施呼吸,给予气管插管,肾上腺素、多巴胺、洛贝林等药物强心、升压等治疗,抢救无效,患者临床死亡。

2 临床病理讨论

尸检解剖主要所见:(1)肝脏重1280 g(正常为1300~1500 g),肝实质内多个肿瘤结节,大者9 cm×8 cm×8 cm,小者2 cm×2 cm×1.7 cm,光镜下为肝细胞癌;于肝方叶见一海绵状肿物,大小为4 cm×

3 cm×2.5 cm,光镜下为肝海绵状血管瘤。此外肝脏淤血、淤胆明显,汇管区慢性炎细胞浸润,纤维组织增生。(2)脾增大,重量为302 g,(正常为110～200 g)镜下有明显淤血现象。(3)双肺与胸壁粘连明显,光镜下见胸膜纤维组织增生明显、肺淤血,局部水肿伴炎细胞浸润。(4)胸腔积液,左侧500 ml,右侧550 ml,虽然影像学检查提示肿瘤骨转移和胸膜转移,但尸检发现胸膜以炎性纤维组织增生为主要病变,并未发现肿瘤。此外,由于限于尸检标本中骨组织取材的局限,双侧胸部第4、5肋骨多处取材,未发现肿瘤组织。

老年肝功能损害20%与治疗用药有关,患者有应用抗结核药(雷米封、链霉素)后肝功受损病史,多次肝炎病毒血清学检查及免疫指标检查均为阴性,基本排除病毒性肝炎、免疫性肝炎,药物性肝炎诊断明确。药物性肝损害一般是可逆的,停药后可自动恢复,但该患者的药物对肝脏的损伤是不可逆的,并逐渐发展成肝硬化、肝癌,较少见,不排除存在其他未知类型肝炎病毒感染的可能。患者1983年始B超、CT等影像学诊断提示肝脏多发血管瘤,直至2001年6月肝脏CT提示肝左外叶7.2 cm×5.3 cm占位性病变影像学表现部分符合肝细胞癌,但结合B超、MRI影象学检查,确诊为血管瘤纤维化、机化。2年后肝内多发占位明确诊断为肝癌,且有门脉癌栓、多发骨转移,已为肝癌晚期。尸检亦证明肝内多个肿瘤结节,仅于方叶见一海绵状血管瘤。因肝血管瘤与肝细胞癌组织来源不同,肝细胞癌不会由肝血管瘤发展而来。由于患者自发病以来,始终未行肝穿活检,缺乏病理诊断金标准,而各种影像学检查不能作为确诊的绝对依据,考虑最初肝内多发占位为肝腺瘤或局灶性增生可能性大。此外,原发性肝细胞癌通常为单发且伴有AFP的升高,该患者为多灶性病变且AFP始终在正常范围。药物性肝炎引起的硬化及肝癌在细胞类型上与病毒性肝炎引起的上述病变有何不同,尚待进一步研究。虽然病程中多次影像学检查提示多处骨转移及门脉癌栓,但尸检并未证实,可能与尸检取材的局限性有关,因患者结核病史多年,不排除骨结核的可能。

因患者肝脏肿瘤病灶大、多发,伴多处转移,全身情况及肝功差,已不适合行积极手术及各种介入治疗。在院期间主要以对症、支持治疗为主,不能逆转病情的发展。死亡原因为原发性多结节肝细胞癌伴肝硬化,肝功能失代偿,加之高血压及慢性肺部感染及胸腔积液,最终导致循环、呼吸多器官功能衰竭。

(参加讨论医师:刘爱军 徐世平 吴本俨 蔡昌豪 杨少波)

(刘婧 吴本俨 蔡昌豪 等整理)

·消 息·

欢迎订阅《中华老年心脑血管病杂志》

《中华老年心脑血管病杂志》是由解放军总医院主管、主办的医学专业学术期刊。1999年12月创刊,2000年纳入国家科技统计源期刊。2004年4月确定为中国医药卫生核心期刊。同年10月获全军期刊优秀学术质量奖。主要报道老年心脏、脑部疾病、血管系统疾病的临床诊断及治疗等相关内容,包括临床研究、基础研究、影像学、遗传学、流行病学、临床生化检验与药物、手术和介入治疗以及有关预防、康复等。主要栏目:专家论坛、述评、临床研究、基础研究、循证医学荟萃、继续教育园地、保健与康复、综述、讲座、病例报告、论著摘要、读者·作者·编者等。是一本具有可读性和指导性的杂志。

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