·临床病理讨论·

Clincopathological Conference (the 55th case)

An old patient with primary systemic amyloidosis

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Case presentation

A male patient, 75 years old, was admitted to Shandong Provincial Hospital on August 2, 2011, because of decreased appetite, body mass loss with fatigue for 8 months. Since the onset, there was no abdominal pain, nausea, vomit, block feeling when eating, abnormal feces, or joint pain. The body mass gradually decreased 15kg in 8 months. In the past history, because of ache, the patient underwent biopsy on iliac bone and suspected amyloidosis. Five years ago, the patient underwent a surgery on the left neck for subcutaneous tissue amyloidosis. There was no history of coronary artery disease, diabetes, hepatitis, tuberculosis, or nephritis. And there was also no history of trauma or drug allergy. There was an infusion of albumin 1 week ago.

Physical examination: BP 150/90mmHg (1mmHg=0.133kPa), lean, no superficial lymph node was touched, also no edema of eyelids, but the sclerals were yellow dyed lightly. His cardiac rhythm was regular at 62 beats per minute, and no obvious pathological murmur was heard in the valve auscultation areas. The abdomen was soft with no tenderness or rebound tenderness. The liver was 6cm below ribs and 10cm below xiphoid process, with hard quality and clear boundary. The Murphy's sign was negative. And there was no knocked pain on the liver or renal area. There was mild edema in both ankles. But there was no swelling or deformity in the limbs.

Accessory examination: Red blood cells (RBC) 3.03×10^{12}/L, hemoglobin (HGB) 102 g/L; urine protein 1 + , urobilinogen 1 + , 24h urine protein 2.26 g/24h; liver and renal function test: aspartate aminotransferase (AST)63 U/L, γ -glutamyl transferase(GGT)437 U/L, alkaline phosphatase(ALP)551 U/L, albumin 22.4 g/L, and total bilirubin 38.2 μmol/L, direct bilirubin 14.5 μmol/L, indirect bilirubin 23.7 μmol/L, blood urea nitrogen(BUN)16.1 mmol/L, serum creatinine (CR) 151.9 μmol/L; C-reactive protein(CRP) 11.2 mg/L; thyroid function test: free triiodothyronine (FT3) 2.55 pmol/L, thyroid stimulating hormone(TSH) 8.11 mUI/L; coagulation function test: prothrombin time(PT)18.2s, International Normalized Ratio (INR) 1.5, activated partial thromboplastin time(APTT) 40.6 s, thrombin time 31.4 s, D-dimer 922 ug/L, fibrinogen 0.82 g/L; tumor markers: carbohydrate antigen 125 (CA125) 105.8 kU/L, alpha fetoprotein (AFP), carcinoembryonic antigen(CEA), prostate-specific antigen(PSA), carbohydrate antigen 153(CA 153), carbohydrate antigen 199(CA199), and carbohydrate antigen724(CA724) were normal; The hepatitis B, hepatitis C and HIV were rejected by viral test; Anti-nuclear antibody(ANA),anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody-M2 (AMA-M2) were negative; Abdominal ultrasound show enlarged liver, spleen and the gallbladder, as well as a damaged sign of kidney; The enlarged liver, spleen and gallbladder were also found in abdominal MRI.

Diagnosis and treatment process: After the above examinations, we employed polyene phosphatidylcholine to protect impaired liver function. We also used amino acids and vitamins to improve his appetite and fatigue, as well as the levorotatory thyroid tablets to improve thyroid function. After treatment, his symptoms were improved. Taking into account the history of amyloidosis of the subcutaneous tissue and bone, in combination of damage in multiple organs, such as liver, spleen and kidney, we highly doubt the possibility of multiple amyloidosis. The doctor in liver department suggested liver biopsy. After injection of vitamin K1 and fresh plasma , the patient′s abnormal liver and coagulation function were improved. Five days later, we took a strip of hepatic tissue from the left lobe under the B ultrasound. Pathology: liver tissue's plate intervals were widened, there was also some pink staining and homogeneous materials deposited in the hepatic sinusoids. Immunohistochemistry: Congo red (+), PAS (+), Ki-67 <1%. The pathological diagnosis is hepatic amyloidosis (Figure 1). The patient was eventually diagnosed as primary systemic amyloidosis.

Clinical discussion

***Dr. Zhou Jie*:** Obvious fatigue, loss of appetite and body mass were the main reasons for treatment. Atypical clinical manifestations are rare, including

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enlarged liver accompanied by liver and kidney dysfunction. After admission, we excluded schistosomiasis japonica, primary biliary cirrhosis, primary liver cancer, non-alcoholic fatty liver disease and other diseases which commonly induced hepatomegaly. Then we knew that the patient was detected amyloidosis in the bone and subcutaneous tissue previously. And it has been reported that the unexplained hepatomegaly with normal or a slight change of liver function, which was out of proportion, may indicate hepatic amyloidosis. So after liver protection treatment, nutritional support, and improvement of coagulation function, we took liver tissue for biopsy, the pathology confirmed the presence of hepatic amyloidosis. In this case we can also rule out tuberculosis, cancer, connective tissue disease which lead to secondary amyloidosis, so the case can be diagnosed as primary systemic amyloidosis.

***Dr. Chen Haiyan*:** Hepatomegaly can be found in 40%–50% of patients with common systemic amyloidosis. Common abnormal laboratory tests in these patients include moderately elevated serum alkaline phosphatase level, low albumin, and prothrombin time may be abnormal. But abnormal serum transaminase level is less seen, high serum bilirubin level is very rare. There's no correlation between the degree of abnormal liver function and the severity of hepatic amyloidosis. In this case there are obvious fatigue, loss of body mass, enlarged liver, moderately elevated ALP, hypoalbuminemia, coagulation abnormality, abnormal renal function, mild abnormality with serum bilirubin and transaminase, which are consistent with the literature. The liver, kidney, bone and subcutaneous tissue are typical of multiple organs involved. Furthermore the amyloidosis was confirmed in the biopsies of liver, bone and subcutaneous tissue. Moreover, we can exclude diseases which may cause secondary amyloidosis. Taken together, this case can be diagnosed as primary systemic amyloidosis.

***Dr. Li Minglong*:** Primary amyloidosis is a clinical syndrome which has no clear causes or coexisting disease. Its mechanism is unknown. The clinical manifestations of this disease are lack of specificity, the main of them are fatigue, body mass loss and edema. Approximately 25% of patients with systemic amyloidosis appear paresthesia and other secondary organs involvement. But the symptoms of liver involvement are not common. Due to diverse clinical manifestations, and it's a rare disease, the early diagnosis of this disease is very difficult. It needs to be confirmed by biopsy and pathological examination. The multiple organs damage which cannot be explained in clinical work, we should consider the possibility of this disease. Generally, systemic amyloidosis is an incurable, progressive disease. Cardiac and renal function impairments induced by amyloidosis are the major cause of death in these patients. However, the fatality rate and morbidity rarely depend on the extent of liver involvement. Although patients with severe cardiac or renal involvement have very poor prognosis, patients with liver involvement as the first manifestation can live longer. At present there is no effective treatment. The MP program (joint application of melphalan and prednisone) is conventional treatment method. And symptomatic and supportive therapies are helpful to prolong the survival time.

Since the patient presented with non-specific clinical signs, we first considered diseases that may lead to appetite and body mass loss and fatigue. We mainly excluded malignant tumors. According to the laboratory and image examination, we can rule out primary liver cancer which is considered as the most likely disease. After analysis of laboratory examination, we found the patient had multiple systems damage. So it should convert single system disease to systematic disease. This requires comprehensive analysis of the patient's clinical manifestations, examinations, medical history, and other relevant information, particularly should not miss any meaningful clinical data. From these data, we found that the patient′s multiple organ lesions, including liver and kidney damage, as well as splenomegaly, could not be explained with common disease. We should consider the diagnosis of rare disease. While the patient suffered from bone and cervical subcutaneous tissue amyloidosis, which belonged to the rare disease. The literatures revealed that this disease can affect almost all organs except brain, leading to multiple organs damage. And liver involvement is very common, the ratio can be high up to 97%. This patient just has the most significant liver enlargement, with liver and kidney damage, we highly suspected amyloidosis. In order to verify the diagnosis, we performed liver biopsy, the result also confirmed this diagnosis. At the same time we also excluded diseases that may cause secondary amyloidosis. So this case can be diagnosed as primary systemic amyloidosis. The successful diagnosis of this patient may due to abundant clinical experience and clear diagnostic mentality. When one orientation is denied, we should decisively change it. Only in this way can we get a definite diagnosis in a relatively short time .

Postscript: After the patient left our hospital, edema appeared in both lower limbs. Then he was admitted to a local hospital. Eventually he died of heart failure. The prognosis of amyloidosis with cardiac involvement is very poor. Regarding the cause of the patient′s death, cardiac amyloidosis may not be excluded.

(Translator: Zhang Rongrong)

老年原发性系统性淀粉样变 1 例

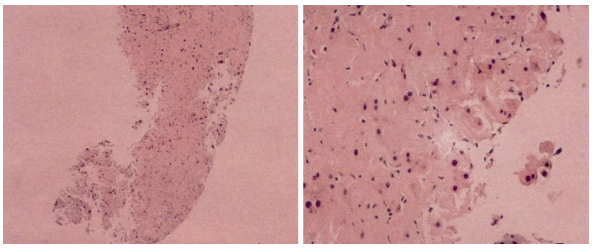
1 病例摘要

患者，男性，75 岁，因“食欲下降、体质量减轻伴乏力 8 个月”于 2011 年 8 月 2 日入院。发病以来，患者无腹痛、恶心、呕吐，无进食阻挡感及大便性状改变，无四肢关节疼痛。体质量逐渐下降，8 个月内消瘦约 15kg。患者既往因骨痛行髂骨活检疑淀粉样变，5 年前又因“左颈部皮下组织淀粉样变”行手术治疗。无冠心病和糖尿病史，否认肝炎、结核、肾炎史，无外伤和药物过敏史。1 周前输白蛋白一次。

入院查体：血压 150/90mmHg（1mmHg=0.133kPa），形体消瘦，浅表肿大淋巴结未触及，眼睑无水肿，巩膜轻度黄染。心率 62 次/min，A2 > P2，心音无异常，未闻及杂音。腹软，全腹无压痛、反跳痛，肝脏肋下 6cm，剑下 10cm，质较硬，边界清，Murphy 征阴性，肝区及肾区无叩击痛。双踝部轻度凹陷性水肿，四肢关节无红肿及畸形。

辅助检查：红细胞 3.03×10^{12}/L，血红蛋白 102g/L；尿蛋白（+），尿胆原（+）；24h 尿蛋白定量：2.26 g/24 h；肝肾功能：天冬氨酸转氨酶 63 U/L，γ-谷氨酸转肽酶 437 U/L，碱性磷酸酶 551U/L，白蛋白22.4g/L，总胆红素38.2μmol/L，直接胆红素 14.5μmol/L，间接胆红素 23.7μmol/L，血尿素氮 16.1 mmol/L，血肌酐 151.9 μmol/L；C 反应蛋白 11.2 mg/L；甲状腺功能：游离 T_3 2.55 pmol/L，促甲状腺激素 8.11 mIU/L；凝血检查：凝血酶原时间 18.2 s，国际标准化比率 1.5，活化部分凝血激酶时间 40.6s,凝血酶时间 31.4s，D-二聚体 922μg/L，纤维蛋白原 0.82 g/L；肿瘤标志物：CA125 105.8kU/L，甲胎蛋白、癌胚抗原、前列腺特异性抗原、癌抗原 153、癌抗原 199、癌抗原 724 均正常；病毒系列排除乙肝、丙肝、HIV；抗核抗体、抗平滑肌抗体、抗线粒体抗体-M2 均阴性；腹部超声示肝脾增大，胆囊增大，双肾实质损害声像图；腹部 MRI 符合肝脏、脾脏肿大、胆囊扩张表现。

诊疗经过：经上述检查后，因肝功能损害，予多烯磷脂酰胆碱针保肝，因食欲差和乏力，给予输注氨基酸、维生素营养支持，因甲状腺机能异常给予左旋甲状腺素片等。治疗后，患者乏力有所减轻，食欲亦有所改善。考虑到患者既往有皮下组织、骨骼淀粉样改变，结合肝脾肾多发脏器损害，高度怀疑多发淀粉样变的可能。遂请肝病科会诊，建议行肝脏穿刺活检。因患者存在肝功能和凝血指标异常，给予维生素 K_1 和新鲜血浆输注，5d 后在 B 超引导下取肝左叶组织一条，送检。病理显示：肝组织细胞板间隔增宽，肝窦内较多淡红染均质物质沉积。免疫组化：刚果红（+），PAS（+），Ki-67 < 1%。病理诊断肝淀粉样变（图 1）。该患者最终确诊为原发性系统性淀粉样变。



A B

图 1 肝淀粉样变病理图

Figure 1 Pathological picture of hepatic amyloidosis (HE)
A: 40 ×; B: 200 ×

2 临床病例讨论

周洁主治医师：该患者以“明显乏力、食欲及体质量下降”为主要就诊原因，临床表现不典型，出现肝脏重度肿大，同时伴有肝肾功能损害，也较为少见。入院检查排除血吸虫性肝病、原发性胆汁性肝硬化、原发性肝癌、非酒精性脂肪性肝病等常见致肝肿大的疾病之后，了解到患者既往检出骨及皮下组织淀粉样变。有文献报道，不明原因的肝肿大而肝功能正常或改变轻微，二者不成比例，可考虑肝脏淀粉样变的可能。于是在保肝、营养支持以及改善凝血等治疗后，行肝穿刺活检，病理报告证实存在肝淀粉样变。本例亦可排除结核病、肿瘤、结缔组织病等所致的继发性淀粉样变，此例可诊断为原发性系统性淀粉样变。

陈海燕副主任医师：较常见的系统性淀粉样变性中 40%～50%的患者可发现肝脏肿大。肝脏淀粉样变性患者中常见的异常实验室检查有血清碱性磷酸酶水平中度升高、低蛋白血症等，凝血酶原时间可有异常；而血清转氨酶水平异常较少见，血清胆红素水平升高则非常罕见，肝功能试验异常的程度与肝脏淀粉样物质沉积的严重程度之间无相关性。

本例患者存在明显乏力、体质量下降，肝脏肿大，碱性磷酸酶中度升高，低蛋白血症，凝血功能异常，肾功异常，血清胆红素及转氨酶轻度异常，均与文献报道相符。该患者累及肝脏、肾脏、骨、皮下组织，为典型的多器官组织受累，加上肝脏、骨及皮下组织活检证实为淀粉样变，且可除外引起继发性淀粉样变的疾病，因此本例可确诊为原发性系统性淀粉样变。

李明龙主任医师：原发性淀粉样变性是一种没有明确原发或共存疾病的临床综合征，促使原发性系统性淀粉样变发生的机制尚不明了。本病临床表现缺乏特异性，主要有乏力、体质量下降、水肿，大约 25%的系统性淀粉样变性患者出现感觉异常以及继发于其他脏器受累的表现，而肝脏受累所致的症状并不常见。由于临床表现多样，且为少见病，致使本病早期诊断非常困难，确诊依靠活检病理学检查，对于临床上不能解释的多器官组织损害应考虑发生本病的可能。系统性淀粉样变性通常是一种不可治愈的持续进展的疾病。淀粉样变所致心功能不全和肾功能损害是患者病死的主要原因，淀粉样变性的致病率和病死率极少决定于肝脏受累的程度；而且，虽然严重心脏或肾脏受累患者的预后非常差，但以肝脏受累为首发表现的患者可以生存较长时间。本病目前尚无有效治疗方法，常规治疗方法为 MP 方案（联合应用马法兰，泼尼松），对症支持治疗有助于延长存活时间。

本例患者临床表现不具特异性，我们首先考虑可能导致食欲体质量下降及乏力的疾病，主要排除恶性肿瘤。根据化验及影像学检查，我们可排除原发性肝癌等最有可能的疾病。之后分析化验检查，患者存在多系统器官的损害，所以应该从单一系统疾病转为从整体考虑。这就需要把患者所有的临床表现、化验检查以及病史等每个有关的信息联系起来综合分析，不放过任何一个有意义的临床资料。从这些临床资料里，我们发现患者的肝肾损害以及脾大等多器官的病变不能以常见病来解释，我们可以将思路延伸至少见病。而患者既往确实患过骨及颈部皮下组织的淀粉样变，属于少见病，通过查阅文献发现，本病可累及除大脑外的几乎所有脏器，导致多器官系统的损害，累及肝脏非常常见，其比率可高达 97%。本例恰巧以肝脏肿大最为显著，且存在肝肾损害，我们高度怀疑淀粉样变。为验证此诊断，我们进行了肝穿刺活检，结果也证实了此诊断。同时我们也排除了导致继发性淀粉样变的疾病，所以此病例可确诊为原发性系统性淀粉样变。此患者的成功诊断，得益于丰富的临床经验以及明确的诊断思路。在一种思路被否定之后我们要果断改变诊断方向，才可使疾病在较短的时间内得到明确诊断。

后记：患者出院后出现双下肢水肿，入住当地医院后，发生心力衰竭死亡。因淀粉样变累及心脏者预后非常差，所以分析该患者死因不排除心脏淀粉样变的可能。

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