Liver transplantation for treating idiopathic adulthood ductopenia☆

One case report and literature review

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Abstract: To summarize and explore the etiopathogenisis, clinical characteristics, diagnosis and treatment and prognosis of idiopathic adulthood ductopenia. We described a 27-year-old Chinese female initially manifested with jaundice, pruritus, dark urine, and pallor of the stools in October, 2002. Symptoms occurred repetitively and severed progressively, and she received therapy at the General Hospital of Chinese People's Armed Police Forces. B-ultrasound demonstrated that hepatic lesion and slightly swelling spleen. Pathological diagnosis of liver biopsy showed that she affected idiopathic adulthood ductopenia. The outcome of treatment of ursodeoxycholic acid and adrenal cortical hormone was not significant. She received orthotopic liver transplantation on June 24th, 2005. After liver transplantation, pruritus and jaundice were promptly disappeared. Each index of hepatic function recovered to a normal level. In March 2007, decreased dose of hormone induced an abnormal hepatic function, with mildly acute rejection. Drug dose was regulated, and hepatic function gradually returned to normal. During follow-up 51 months after the operation, she was doing well and was free of symptoms with normal liver function and no evidence of allograft dysfunction. The pathogenesis of idiopathic adulthood ductopenia is still unknown. There are still no precise and effective drugs for treatment of idiopathic adulthood ductopenia. Liver transplantation offers an effective therapy for end-stage patients with idiopathic adulthood ductopenia.

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INTRODUCTION

Idiopathic adulthood ductopenia (IAD) is a chronic cholestatic liver disease with unclear causes and characterized by the loss of interlobular and septal bile ducts[1]. It is a very rare disease in the entire world. In this study, we described a patient with IAD rescued by liver transplantation at the Organ Transplantation Institution, General Hospital of Chinese People's Armed Police Forces, and reviewed the literature to date about this uncommon hepatobiliary disorder.

CLINICAL DATA

A 27-year-old Chinese female initially manifested with jaundice, pruritus, dark urine, and pallor of the stools. The symptoms were gradually progressive and severe since October 2002. Laboratory results showed normal white and red blood cell numbers. Serum biochemical tests of liver function of our hospital showed a predominantly cholestatic pattern: total bilirubin (TBIL) level 344 μmol/L, direct bilirubin (DBIL) level 274.2 μmol/L, γ-glutamyltransferase (GGT) level 374 IU/L, alkaline phosphatase (ALP) level 679 IU/L, alanine aminotransferase (ALT) level 157 IU/L, aspartate aminotransferase (AST) level 202 IU/L. Viral hepatitis and other virus infection markers were absent. antimitochondrial autoantibody (AMA) was slight positive. Assay for other autoantibodies was negative. Ultrasound of the abdomen demonstrated liver damage and mild spleen enlargement. Histological examination of a liver specimen showed severe cholestasis and absence of interlobular bile ducts, diagnosed Idiopathic adulthood ductopenia. She had not neonatal or childhood jaundice, viral hepatitis, other previous liver disease, alcohol or other drug abuse, or transfusions of blood products. She had no relevant family or social history. She had no response to ursodeoxycholic acid and steroid. Jaundice and itch worsened. Therefore, orthotopic liver transplantation was performed on June 24th 2005. Liver pathology showed, absence of interlobular bile ducts in the portal area and severe cholestasis were observed, a portal tract confirming the absence of bile ducts and the presence of a mild chronic inflammatory infiltrate that included lymphocytes, plasma cells and neutrophils. IAD was diagnosed. After liver transplantation, the jaundice and itch disappeared gradually. Serum biochemical tests of liver function turn to be normal. She used tacrolimus (4 mg once per 12 hours), mycophenolate (MMF) (500 mg once per 12 hours) and methylprednisolone (16 mg once a day) for immune inhibiting treatment. One episode of acute cellular rejection occurred in March 2007 after orthotropic liver transplantation (OLT) for decrease of steroid (methylprednisolone from 4 mg to 2 mg once a day). Serum biochemical tests of liver function showed a abnormal pattern: ALT level 187 IU/L, AST level 307 IU/L, GGT level 302 IU/L, ALP level 162 IU/L, TBIL level 23.3 μmol/L, DBIL level 8.1 μmol/L. Liver biopsy specimen showed mild acute cellular rejection. With increase of tacrolimus and sterol (methylprednisolone 4 mg once a day), and combined with MMF (750 mg once per 12 hours), liver function turn to be normal in short time. She still used tacrolimus, MMF and methylprednisolone for immune inhibiting treatment now. At follow-up 51 months after transplantation, she was doing well and was free of symptoms, with normal liver function and no evidence of allograft dysfunction.

DISCUSSION

Since the first description by Ludwig[1-2] in 1988,

several cases of IAD have been reported abroad, and this is the first case reported in China.

Etiology of IAD

Numerous previous studies have been implicated in the pathogenesis of intrahepatic biliary destruction, including develop-mental biliary atresia (secondary to infection or α1-antitrypsin deficiency), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), graft versus. host disease, ischemia, infection, sarcoidosis, lymphoma, chemical injuries (such as injection of scolicidal solution or formaldehyde), as well as a variety of therapeutic drugs (including chlorpromazine, prochlorperazine, organic arsenicals, and tolbutamide). If these causes are systematically excluded, IAD should be considered as the possible diagnosis in young to middle-aged adults, who manifest cholestatic liver disease without history of infantile cholangiopathy. Ludwig[1-2] reported the causes of small duct biliary diseases in 2082 cases diagnosed between 1988 and 1994. These were: 65% PBC; 28% PSC; 3% chronic ductopenic rejection; 1.6% paucity of intrahepatic bile ducts; 1.2% idiopathic adult ductopenia; 0.7% chronic cholestasis of sarcoidosis, and 0.5% drug-induced ductopenia.

Although a distinct cause of IAD has not been determined, several hypotheses have been raised. ①IAD may be related to the late expression of a nonsyndromic form of Alagille syndrome[3-7]: infantile scarcity of interlobular bile ducts, sharing few characteristics with the nonsyndromic form of Alagille syndrome and lacking the relatively poor prognosis; ②Small-duct PSC, without large duct involvement and without evidence of inflammatory bowel disease. The clinical appearance of patients with IAD bears similarities to that of patients with PSC. In fact, pericholangitis is frequently observed surrounding the remaining bile ducts in liver biopsy specimens from patients with IAD. Patients with Alagille's syndrome have cholestasis that is most severe in infancy and tends to improve as they grow, it is conceivable that IAD could be considered a form of isolated, atypical, or limited variant of small-duct PSC; ③Nonsuppurative viral cholangitis, some viral hepatitis may cause nonsuppurative viral cholangitis, leading to disappearance of interlobular. Dural *et al*[8] reported an old hepatitis C virus (HCV) patient without clinical characters was diagnosed as IAD; ④PBC, in the absence of typical autoantibodies (cryptogenic chronic hepatitis), which is a normal cholangiogram and no evidence of inflammatory bowel disease; ⑤Genes: Garcia studied 22 Caucasian patients with mild idiopathic adulthood ductopenia (MIAD), found that a different pattern of HLA-DRB1 increased in MIAD, and positions 25 and 32 of the beta chain of the HLA- DR associated with MIAD respectively[8-10]. Kelly *et al*[9] reported five cases in three generations with one IAD Family, suggesting that genetic factors may play an important role in IAD.

Clinical characteristics of IAD

Nearly one third of the IAD patients started with jaundice, pruritus, which attacked recurrently and were gradually progressive and severe; A few patients, first manifested esophageal varices resulted from portal hypertension or upper gastrointestinal bleeding; some had no symptoms, and only serum biochemical tests of liver function showed a predominantly cholestatic pattern. Medical check-up found xanthochromia, pigmentation and splenohepatomegalia in various degrees. Laboratory studies showed GGT level and ALP level increased, simultaneously with hyperbilirubinemia and hypercholesteremia, which manifested bilirubin rising up mostly. In addition, for most patients AST level and ALT level were abnormal too, in advanced stage, hypoproteinemia happened probably. Imageology-scopy: retrogressive pancreatocholangiography showed intrahepatic and extrahepatic biliary ducts were normal, and normal colonoscopy excluding inflammatory bowel disease-related cholangiopathy, which would help to distinct to IAD and PSC[1-5, 11-15].

Diagnosis of IAD

Diagnostic criteria of IAD was proposed by Ludwig *et al*[1-2]: ① Entity in adults, including anaphase of puberty; ② Biochemical tests of liver function showed a predominantly cholestatic pattern, and ALP level increased; ③Showed the disappearance of interlobular and septal bile ducts in at least 50% of the portal tracts; ④Cholangiography and duplex contrasting retrogressive colon opacification or colonoscope had no abnormality seen. Exclusion criteria: ①History of infantile cholangiopathy, contacting history of drug or poison and evidence of inflammatory bowel disease; ②Serum AMA was positive; ③Having granulomatous cholangitis, neutrophilia purulent cholangitis or non-neutrophilia cholangitis, histiocytosis X, lymphoma or neoplasmin liver biopsy specimens; ④Imageology-scopy found small bile duct associated big bile duct abnormality and/or inflammatory bowel disease signs. However, the criteria needed to be modified further more. First, the diagnosed age had to be debated. Some scholars proposed whether to include adolescence. Second, some documents indicated when most of the intrahepatic biliary ducts injured, having inflammation, and the rest of small biliary ducts disappeared absolutely, appearing destructive biliary ducts injuring, though disappearance of interlobular bile ducts was not up to the index (≥50%), it could also diagnose IAD; Besides, disappearance of interlobular bile ducts less than 50% was definite mild IAD in some documents[16-21]. The third, the author presumed, although serum positive AMA was the exclusive criteria of IAD, for it is conceivable that IAD could be considered a form of isolated, atypical, or limited variant of primary sclerosing cholangitis, positive AMA could not exclude IAD. Our documents showed, though AMA was slight positive, liver biopsy specimens before and after operation all confirmed IAD.

Pathematology diagnostic criteria: Absence of interlobular bile ducts in at least 50% of small portal tracts on an adequatesized liver biopsy specimen. Microscope-scopy found destructive cholangeitis, biliary tract piecemeal necrosis, cholestasis, canals of Hering accrementition, portal areas inflammation and secondary primary biliary fibrosis, cirrhosis[1-5].

Treatment and prognosis of IAD

So far no medicine can be used to treat IAD. Since the etiological factors of IAD were not definite yet, patients can be

only given palliative treatments. Many groups[9, 12] proposed that adrenal cortex steroid, ursodeoxycholic acid could obtain satisfying effects (mainly for inchoate longitudinalcholestasis), such as improvement of liver function and decrease of the clinical symptoms. However, large-sample random investigation is lacking. The effects of ursodeoxycholic acid to the progression of disease are unclear. The patients in our team had already used adrenal cortex steroid, ursodeoxycholic acid, and the effect was not significant. Asymptomatic IAD progressed slowly, and the prognosis was better. Whether liver transplantation is needed for treatment needs further investigation. Some documents represented giving supportive treatment and monitoring biochemical indicator carefully[5], others claimed liver transplantation in nonage was more effective[17]. When patients with IAD appeared to liver failure, or severe intractable cholestatic symptoms such as refractory severe pruritus, OLT is an only effective therapeutics approach[16]. The symptoms and biochemical indexes were improved in short time. Summarizing the documents, there were 8 patients of IAD accepting liver transplantation so far, in which 4 cases survived more than 1 year. Sherlock[11] and Burak[10] respectively reported 1 patient survived for 7 years and the other survived for 12 years after liver transplantation. Both of them were fine. The patient in our group, at follow-up 51 months after transplantation, was doing well with normal results of liver function studies and no evidence of recurrence. For patients of IAD after liver transplantation，there was no standard immunodepressive treatment. Numerical documents manifested that the patients often needed combination with low dose steroid for immunodepressive treatment in long term. Sherlock[11] reported 1 case, who took ciclosporin azathiopurine and radiosone, emerged rapid rejection on day 5 after liver transplantation. When steroid impulsing treatment was carried, liver function reversed in short time. Then low doses steroid was used continuously until 5 years after liver transplantation. During follow-up 7 years after transplantation, she was doing well with normal liver function and no evidence of recurrence. The patient from our report, who used tacrolimus, MMF and methylprednisolone for immunodepressive treatment, had one episode of acute cellular rejection 21 months after liver transplantation because of lower steroid doses. But when she got higher sterol doses, liver function recovered quickly. Up to now, During follow-up, 51 months after transplantation, she had been doing well with low doses steroid therapy. The effect of sterol is still unknown, but many groups showed that combination with low doses sterol for immunodepressive treatment could reduce the danger of rejection.

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肝移植治疗特发性成人肝内胆管缺失症1例并文献复习☆

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摘要：总结并探讨特发性成人肝内胆管缺失症的发病原因、临床特征、诊治及预后。27岁女性患者，2002-10无明显诱因出现巩膜黄染，皮肤瘙痒，伴尿颜色加深、便灰白色，症状反复出现并进行性加重入住武装警察部队总医院接受治疗。B超提示，肝损害，脾脏轻度肿大。肝穿病理诊断为特发性成人肝内胆管缺失症。给予熊去氧胆酸、肾上腺皮质激素治疗，效果均不明显。于2005-06-24行原位肝移植。肝移植后患者黄疸、瘙痒症状迅速消失，肝功能各项指标恢复正常。2007-03因激素减量出现肝功能异常，出现轻度急性排异反应，调整用药剂量，并辅以保肝治疗，肝功能逐渐降至正常。术后随访51个月，患者及移植物功能均正常，未出现原发病的复发。提示特发性成人肝内胆管缺失症的病因及发病机制尚不明确，属于一种以组织学特征为主的排除诊断性疾病，且目前尚无治疗特发性成人肝内胆管缺失症确切、有效的药物。肝移植是治疗终末期特发性成人肝内胆管缺失症惟一有效的方法。

关键词：特发性；成人肝内胆管缺失症；肝移植；治疗

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肾移植排斥反应中特异性抗体及细胞因子的作用
（本刊中文部）

1 慢性移植肾肾病肾组织中转化生长因子β1、金属蛋白酶2、金属蛋白酶组织抑制剂1的表达及意义

2009年5期821页。

推荐理由：慢性移植肾肾病是造成肾移植后期移植肾丢失的主要原因，其发病原因包括免疫因素和非免疫性等多种因素，这些因素最终都造成移植肾的纤维化并引起移植肾功能的丧失，而细胞外基质积聚则是肾纤维化的主要病理基础和特征。

转化生长因子β1是重要的致纤维化因子，转化生长因子β1能刺激成纤维细胞增加大部分基质蛋白的合成，包括胶原、纤维连接蛋白和蛋白多糖的合成。另外转化生长因子β1能减少基质蛋白水解酶的表达并且上调它们的特异性抑制物，因而加重基质的积聚。

实验应用免疫组织化学SP法检测慢性移植肾肾病患者的移植肾组织中转化生长因子β1，金属蛋白酶2及其主要抑制物金属蛋白酶组织抑制剂1的表达，以探讨它们在移植肾肾病病理生理过程中的关系及作用。实验表明可以将转化生长因子β1，金属蛋白酶组织抑制剂1，金属蛋白酶2作为移植肾活检时判断移植肾小球及小管间质损害程度的判断量化指标；有利于慢性移植肾肾病的早期诊断，对疾病进展及预后作出评估；同时为进一步阐明慢性移植肾肾病的发生、发展机制提供线索，为治疗提供可能的方向及作用靶点。

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2 肾移植亚临床排斥反应患者血清细胞因子水平变化及干预

2009年44期8618页。

推荐理由：由于采用组织病理活检来诊断肾移植亚临床排斥反应对移植肾具有创伤性，不利于临床推广，尽管亚临床排斥反应发生时没有临床表现，隐蔽性强，但通过对患者手术前后外周血中细胞因子水平的变化，可发现其相关证据，不仅有利于肾移植亚临床排斥反应的早期诊断，而且有利于肾移植亚临床排斥反应干预治疗效果的评估，该方法简便、属无创性，便于临床应用。

本次实验通过对68例肾移植后肾功能恢复正常住院或出院的患者进行至少1年的随访，根据临床症状及实验室生化免疫指标，以彩色多普勒超声检查结果为基础，以移植肾病理活检为诊断依据，将随访者分为亚临床排斥组和正常组，观察两组血清白细胞介素2，6，8，10的表达，结果显示出细胞因子在肾移植术后随访中具有很好的临床应用价值。

3 细胞间黏附分子1与移植肾急性排斥反应

2009年5期862页。

推荐理由：近年来有研究表明，在急性排斥反应发生的同时，移植肾组织中细胞间黏附分子1表达水平增高，由此推测细胞间黏附分子1表达增高，应该较病理诊断提前数天。因此，细胞间黏附分子1更能早期，客观地反映移植肾在不同状况下局部免疫变化特点。

文章采用免疫组化图像半定量分析法，检测正常、急性排斥及非排斥情况下移植肾穿刺组织中细胞间黏附分子1的表达水平，以分析其表达与肾移植急性排斥反应的关系，旨在寻找一种及时、敏感、准确的诊断肾移植排斥反应的方法。结果证实免疫组化图像半定量法应用于肾移植排斥时细胞间黏附分子1表达水平的检测可行，且具有客观、准确、便于统计分析的优点。

基金资助：福建省科技计划重点项目资助（2005Y017）。

4 肾移植后急性排斥中sCD30表达意义

2009年18期3421页。

5 溶解性CD30水平检测在肾移植中的应用

2009年53期10553页。

6 移植肾C4d的表达及体视学测定

2009年5期853页。

7 抗HLA和MICA抗体与移植肾慢性排斥反应的关系

2009年5期845页。

8 特异性抗体与肾移植急性排斥反应的关系

2009年18期3417页。

9 体液免疫在移植肾慢性排斥反应中的作用

2009年18期3437页。

10 人类白细胞抗原配型及其抗体监测在亲属活体供肾移植中的应用价值

2009年44期8623页。

全文详见：http://www.crter.org/Html/2010_01_18/2_64027_2010_01_18_91278.html