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述评 EDITORIAL

IgG4相关硬化性胆管炎的研究进展

黄颖秋

■背景资料
1995年, 日本学者Yoshida首次报道了以血清免疫球蛋白(IgG4)水平升高、胰腺肿大及IgG4阳性淋巴浆细胞组织浸润为特征的一种慢性纤维炎症性疾病, 即自身免疫性胰腺炎(AIP). 随后的多项研究显示, AIP常伴肝内外胆道狭窄及胆管内大量的IgG4阳性浆细胞浸润, 2007年Bjornsso建议称其为IgG4相关性胆管炎(IAC), 因其主要表现为胆管弥漫性或局限性纤维化, 与原发性硬化性胆管炎(PSC)酷似, 现称为IgG4相关硬化性胆管炎(IgG4-SC).

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Recent advances in research of immunoglobulin G4-related sclerosing cholangitis

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Abstract
Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is a recently defined disease entity characterized by elevated serum IgG4, chronic progressive obstructive jaundice, and diffuse or mass-forming inflammatory reaction rich in IgG4-positive plasma cells and lymphocytes associated with fibrosclerosis and obliterative phlebitis, which shares a number of clinical, biochemical, and radiological features with primary sclerosing cholangitis (PSC) or cholangiocarcinoma (CC). IgG4-SC is commonly associated with autoimmune pancreatitis (AIP). Steroid therapy comprises the mainstay of treatment for IgG4-SC patients. However, liver transplantation is the only useful treatment for PSC patients, and CC patients require surgical therapy. Therefore, the accurate discrimination between IgG4-SC and PSC or CC is a very important issue. In this article, we will review the features and role of immunoglobulin G4 (IgG4), the diagnosis and therapy of IgG4-SC, and the relations between IgG4-SC and AIP, PSC or CC.

Key Words: Immunoglobulin G4; Immunoglobulin G4-related sclerosing cholangitis; Immunoglobulin G4-related sclerosing disease

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摘要
免疫球蛋白G4相关硬化性胆管炎(immunoglobulin G4-related sclerosing cholangitis, IgG4-SC)是一种新近认识的以血清IgG4升高、慢性进行性阻塞性黄疸、弥漫性或局限性IgG4阳性浆细胞和淋巴细胞组织浸润、纤维化及闭塞性静脉炎为特征的慢性炎症性疾病, 常并发自身免疫性胰腺炎(autoimmune pancreatitis, AIP), 其临床、生化及影像学特征与原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)或胆管癌(cholangiocarcinoma, CC)相似. 类固醇激素是IgG4-SC的主要治疗手段, 而肝移植是PSC唯一的有效治疗方法, CC则需外科手术治疗. 因此, IgG4-SC与PSC或CC间的准确鉴别是目前面临的一个十分重要的课题. 本文详尽地阐述了免疫球蛋白G4(immunoglobulin G4, IgG4)的特征和功能, IgG4-SC的诊断和治疗, IgG4-SC与AIP、PSC及CC之间关系等研究进展, 为IgG4-SC的精确诊断和治疗提供了新的思路.

关键词: 免疫球蛋白G4; IgG4相关硬化性胆管炎; IgG4相关硬化性疾病

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0 引言
免疫球蛋白G4相关硬化性胆管炎(Immunoglobulin G4-related sclerosing cholangitis, IgG4-SC)是一种新近认识的与IgG4密切相关、对类固醇激素敏感的慢性胆管炎症性疾病, 以IgG4阳性的浆

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细胞组织浸润、纤维化及闭塞性静脉炎为主要特征[1-3]. IgG4-SC是IgG4相关硬化性疾病(IgG4-related sclerosing disease, IgG4-RSD)中的特殊类型, 后者常致弥漫性或广泛的组织纤维化、闭塞性静脉炎及IgG4阳性浆细胞浸润, 可能受累的器官或组织包括胰腺、胆管、胆囊、泪腺、唾液腺、后腹膜、肺、肝脏、胃肠道、肾脏、中枢神经系统、甲状腺、乳腺、前列腺、输尿管、子宫颈和淋巴结等[4-7]. IgG4-RSD还可累及小肠[8]、眼外肌[9]、肌锥内脂肪[9]及三叉神经[9,10]. 有研究发现, 164例眼部淋巴瘤患者中, 6例被确诊为IgG4-RSD, 其眼附属器可见大量IgG4阳性浆细胞浸润[11]. 此外, 以硬化性肠系膜炎[12]、心血管系统多灶性纤维化[13]以及泪囊炎[14]为特征的IgG4-RSD也见报道. 随着研究的不断深入, 其累及的器官或组织可能更为广泛. IgG4-SC常伴有自身免疫性胰腺炎(autoimmune pancreatitis, AIP), 其临床表现及影像学特征与原发性硬化性胆管炎(primary sclerosing cholangitis, PSC)十分相似[1,2,15,16], 甚至有学者认为IgG4-SC为PSC的变异型[16]. 但二者的关系仍存在争议, 本文就该领域的最新进展概述如下.

1 IgG4的特征及功能

免疫球蛋白G(immunoglobulin G, IgG)有4个亚型: IgG1、IgG2、IgG3和IgG4[4]. IgG4约占1%-7%, 其平均浓度仅为0.35-0.51 mg/mL[4]. 与其他IgG亚型不同, 健康人血清中IgG4的含量变化非常显著[17], 一般波动于10 μg/mL-1.4 mg/mL不等[4]. IgG4的生成部分依赖于介导过敏反应及诱导IgE生成的Th2细胞的辅助激活, 因此诱导IgE生成的过敏原也可诱导产生IgG4[17]. IgG4在大疱性皮肤病、特异性湿疹、支气管哮喘以及缓解寄生虫感染时IgE介导的炎症反应中起重要作用, 但IgG4抗体在IgG4-RSD中的潜在致病机制仍不清楚[4,17]. IgG4抗体极其活跃, 涉及半分子交换的连续过程, 即“Fab-臂交换”, 这种不对称的抗体交换通常导致两个不同的抗原位点, 但多数为单价抗体[17,18]. 因IgG4的产生需要Th2细胞的辅助, 后者主要分泌interleukin(IL)-4、IL-5、IL-6、IL-10和IL-13, 在诱发过敏反应中起决定性作用, 故IgG4的免疫应答主要局限于非微生物抗原(non-microbial antigens)[18]. IgG4免疫调节的另一个典型特征倾向于只出现在持续的免疫反应后, 在IgE介导的过敏反应中, IgG4抗体的出现通常与症状的缓解密切相关, 这或许是由于在肥大细胞和/或抗原呈递细胞(antigen-presenting cell)水平产生的抗原阻滞作用[18]. IgG4一般无生物学活性, 其与IgG4-RSD的关系可能反映了触发IgG4阳性浆细胞过度浸润的抗炎细胞因子的大量产生[18]. IgG4不太可能引发过敏症状, 特异性IgG4抗原的出现表明抗炎、耐受诱导机制已被激活[18]. 由于IgG4亚型的存在, 其上调抗炎因子及自身的抗炎特性完全有助于免疫系统抑制不适当的炎症反应[18].

2 IgG4-SC的发病机制

IgG4-SC的发病机制尚不清楚, 可能与Th2型免疫反应或调节性T细胞(regulatory T-cells, Tregs)被激活有关[19]. 近年来研究发现, 肠道微生物致Th2型免疫反应激活可能是IgG4-SC的免疫病理学基础[19]. 应用实时定量PCR检测发现, IgG4-SC患者组织中IL-4/干扰素(interferon-gamma, IFN-γ)、IL-5/IFN-γ、IL-13/IFN-γ的比率显著高于对照组, 采用原位杂交技术观察发现, 淋巴细胞内的IL-4呈显著表达[19]. T细胞被激活后, IgG4-SC的外周血单核细胞主要产生IL-4、IL-5、IL-10、IL-13等Th2型细胞因子[19]. IgG4-SC患者血及组织中Tregs明显增加, Foxp3(forkhead box P3, 一种特殊的Tregs转录因子)的mRNA表达也显著高于传统的自身免疫性疾病患者, 2种调节性细胞因子IL-10和TGF-β(转化生长因子-β)也显著表达[19]. 应用免疫组织化学研究发现, IgG4-SC患者受累组织中的$CD4^+CD25^+Foxp3^+$ Tregs显著增加, $Foxp3^+$细胞数量与$IgG4^+$浆细胞数量显著相关[19]. 此外, AIP患者血清$CD4^+CD25^{high}$ Tregs显著高于慢性胰腺炎患者, 并与血清IgG4水平显著相关, 而天然Tregs则显著减少, 由此推论Tregs减少可能涉及IgG4-RSD的发生, 而$CD4^+CD25^{high}$ Tregs增加可能涉及IgG4-RSD的进展[19].

3 IgG4-SC的临床特征

IgG4-SC是对类固醇激素敏感、与AIP密切相关的胆管炎性疾病, 其临床表现及影像学特征与PSC十分相似[15]. IgG4-SC几乎与AIP并存, 其发病年龄大于典型的PSC患者[3,20], 其主要表现为阻塞性黄疸、消瘦、轻度腹部不适、发热、肝功转氨酶异常及血清IgG4水平显著升高[1,19], 阻塞性黄疸为IgG4-SC最常见表现[3,20], 这可能与AIP导致的胰头肿大或严重的胆管狭窄有关[19], 但如何与PSC、胰腺癌(pancreatic cancer, PCa)

■研发前沿
AIP的临床及影像学特征有时酷似胰腺癌(PCa), 因此迫切需要精确的诊断方法予以鉴别, 检测EUS-FNA标本内KRAS癌基因的突变、抑癌基因的丢失及端粒酶活性等或许有助于AIP与PCa的鉴别诊断. 因此, 研究EUS-FNA标本中KRAS基因突变及抑癌基因杂合子的丢失情况应是目前努力的方向.

■相关报道
Nakazawa等阐述了IgG4-SC的影像学分型及其相关诊断程序的最新国际共识, 对IgG4-SC诊断的规范和完善有指导意义.

所致黄疸鉴别仍面临挑战[21]. 此外, IgG4-SC还可并发涎腺炎[22]、肺炎性假瘤[23]、腹膜后纤维化[24]、肝肾损害[25]、织脉周炎(periaortitis)[26]、胰腺多发假性囊肿[27]、糖尿病[19]及淋巴结肿大[28]等. IgG4-SC的发病率迄今尚不清楚, 部分IgG4-SC的症状与PSC重叠, 后者血清中IgG4水平也显著升高[29-31], 而某些IgG4-SC也可不伴发AIP[3,4,20]. 血清IgG4增高无疑是IgG4-SC最具特异性的指标, 其他敏感而非特异的指标还包括γ-球蛋白增高(见于50%患者)、IgG增高(60%-70%)、抗核抗体(40%-50%)、类风湿因子(20%)、嗜酸性粒细胞增多(15%-25%)[19]. 此外, 抗SS-A、抗SS-B、抗线粒体抗体及抗中性粒细胞胞浆抗体也可异常(<5%)[19]. 血清IgG4增加还不能作为IgG4-SC诊断的金标准, 而胆汁中IgG4含量升高似乎可作为IgG4-SC一种新的诊断指标, 以此可与PSC相区别[32]. 大多数IgG4-SC病例的肝内和肝外胆道系统均可严重受累[4], 虽然其影像学特征酷似PSC, 但差异之处在于IgG4-SC对类固醇激素疗效显著, 而PSC除肝移植外迄今尚无有效的治疗手段[20,33-35]. IgG4-SC易误诊为PSC而延误治疗, 部分IgG4-SC还可误诊为胆管癌(cholangiocarcinoma, CC)而接受不必要的手术治疗. 因此, 制定有效的IgG4-SC诊断方案非常必要.

4 IgG4-SC的影像学特征

内镜逆行胰胆管造影(endoscopic retrograde cholangiopancreatography, ERCP)不仅显示IgG4-SC患者胆管树的特征性狭窄, 而且也显示其胰管狭窄[1]. 胆总管远端最常受累(约占90%), 胆管树的任意一处均可出现典型的狭窄, 约10%的IgG4-SC患者肝内胆管狭窄与PSC十分相似[1]. 胆管造影显示, IgG4-SC患者表现为肝内外胆管的弥漫性或局限性狭窄, 与PSC及部分CC患者的胆管影像特征相似[3]. Ghazale等[3]研究显示, 53例行胆道造影检查的IgG4-SC患者中, 51%显示胆总管胰腺内段狭窄, 49%涉及近段肝外胆管及肝内胆管狭窄, 其中, 9%为近段肝外胆管狭窄, 8%为肝内胆管狭窄, 32%显示多部位狭窄. Kalaitzakis等[36]对20例IgG4-SC、10例PSC及10例CC患者的内镜逆行胆管造影(endoscopic retrograde cholangiography, ERC)分析发现, 尽管ERC诊断IgG4-SC的特异性很好, 但敏感性很差, 仅靠ERC检查, 许多IgG4-SC患者可能被误诊为PSC或CC. 换言之, 依据ERC检查结果并不能准确将IgG4-SC与PSC或CC鉴别, 其他的一些辅助诊断策略对这些疾病的鉴别或许非常重要.

5 IgG4-SC的组织病理学特征

超声内镜(endoscopic ultrasonography, EUS)引导下的胰腺活检可能对AIP有诊断价值[1]. 尽管胆管活检的确切诊断价值尚存争议, 但活检组织中强烈的IgG4阳性浸润在IgG4-SC、AIP十分常见, 而PCa则无[1]. 肝活检对IgG4-SC或AIP的诊断并非绝对必要, 但IgG4阳性细胞＞10个/HP可能有助于IgG4-SC与PSC鉴别[1]. IgG4-SC的组织学特征主要表现为肝脏门管区的淋巴浆细胞浸润、纤维化和闭塞性静脉炎, 胆管壁也可见密集的淋巴浆细胞浸润及纤维化, 常以回旋状或席纹状排列[1,37,38]. 炎症细胞以淋巴细胞、浆细胞为主, 也可见较多嗜酸性粒细胞, 偶可占优, 免疫组织化学染色显示富含IgG4的淋巴浆细胞浸润, 呈弥漫性或局灶性分布[38]. IgG4的免疫组织化学染色对IgG4-SC的病理学诊断意义重大[37-39]. Deshpande等[15]采用形态学和免疫组织化学方法, 对10例IgG4-SC和17例PSC的肝活检或术后组织标本对比研究发现, 5例IgG4-SC(50%)的门管区组织中可见到成纤维细胞、浆细胞、淋巴细胞和嗜酸性粒细胞组成的特异性纤维炎症结节. 6例IgG4-SC可见到IgG4阳性的浆细胞浸润(>10个细胞/HP, 平均60个/HP, 范围: 0-140个/HP), 而全部PSC则显著低于此数值(平均0.08个/HP, 范围: 0-1个/HP), 以此可与PSC鉴别.

6 IgG4-SC分型及诊断程序的最新国际共识

Nakazawa等[20]对1991-2010年3月间发表的IgG4-SC相关英文文献进行了回顾性分析, 考虑所涉及的IgG4-SC资料有限, 还纳入了其所在医院逾19年的IgG4-SC诊治经验. 结果显示, IgG4-SC多见于男性, 发病年龄明显晚于PSC, 其主要临床表现为阻塞性黄疸和血清IgG4水平显著升高, 除肝脏受累外, 常合并AIP, 而IgG4-SC合并炎症性肠病(inflammatory bowel disease, IBD)少见, 仅为0%-6%. 根据胆管影像所示的狭窄部位不同, 将IgG4-SC分4型. 1型: 胆总管下段局限性狭窄; 2型: 肝内外胆管弥漫性狭窄; 3型: 肝门区胆管及胆总管下段狭窄; 4型: 肝门区胆管局限性狭窄. 2型需与PSC鉴别, 而1型、3型和4型需与CC鉴别. IgG4-SC的CT扫描结果显示受累胆管的管壁增厚, 边界清晰, 增强CT扫描显示动脉晚期强化, 延迟期均匀强化, 但无血管受累. 胆管

内超声(intraductal ultrasonography, IDUS)显示的非狭窄区胆管管壁厚度>0.8 mm为IgG4-SC的最典型特征, 以此可与CC鉴别. IgG4-SC的组织学特征与其他IgG4-RSD相似, 为IgG4阳性的淋巴细胞浆细胞浸润、组织纤维化及闭塞性静脉炎. 根据以上临床特征, 他们提出了IgG4-SC的如下诊断程序. 对于胆管局限性或多发性狭窄的阻塞性黄疸患者, 除与PCa、CC及PSC鉴别外, 临床医生还应注意与IgG4-SC鉴别. 当确定胰腺有胰管狭窄时, 即可排除PCa. 当出现明显的多发性肝内胆管狭窄时, 应根据胆管及肝活检组织中的IgG4免疫组织化学染色结果与PSC鉴别. 合并AIP无疑是诊断IgG4-SC的最有力依据, 而合并IBD则高度提示PSC. 当肝门区被确定有狭窄时, 应通过超声(ultrasound, US)、EUS、IDUS及胆管组织活检与CC鉴别. 根据IgG4-SC的胆管影像特征所制定的诊断程序提示, 有1型表现者, 应关注胰腺, 及时行超声内镜引导下-细针穿刺(endoscopic ultrasonography-guided fine needle aspiration, EUS-FNA)以排除PCa; 对于2型表现者, 主要应与PSC鉴别, 结肠镜检查、肝活检及IgG4的免疫组织化学染色有助于确诊; 而对3型、4型表现者, 应重点与CC鉴别, 可行EUS、IDUS检查, 必要时行胆管活检以协助诊断. 倘若经上述检查仍不能确诊, 可采用类固醇激素行短期试验性治疗.

7 IgG4-SC的最新诊断标准

最近, Nakazawa等[40]又制定了最新的IgG4-SC诊断标准. 他们依据胆管影像学检查结果, 将62例IgG4-SC患者分成3组, 以便与PCa、PSC及CC鉴别. A组32例, 与PCa特征相似(1型); B组15例, 与PSC相似(2型); C组15例, 与CC相似(3型、4型). 35例PCa、40例PSC及32例CC作为对照组. 他们回顾性比较了A组与PCa, B组与PSC, C组与CC之间的临床表现、影像学、血清学、组织病理学特征以及其他器官受累情况. 结果显示, 并发AIP(P<0.001)和其他器官受累(特异性100%)是全部3组IgG4-SC患者常见的有效诊断参数; 血清IgG4升高是A组和B组IgG4-SC患者的有效诊断参数(P<0.001); 胆管造影(P<0.001)、肝活检(特异性100%)及除外IBD(特异性100%)是B组的有效参数. 胆管内超声结果(P<0.001)及经胆道活检除外恶性肿瘤(特异性100%)是C组的有效参数. 依据包含P<0.001或特异性100%的这些参数所制定的IgG4-SC诊断标准其敏感性为100%, 特异性为96.3%. 因此, 基于胆管影像学分型的IgG4-SC诊断标准有助于其与PCa、PSC和CC的鉴别. 然而, Ohara等[41]认为, 由于IgG4-SC与PSC、PCa和CC的影像特征相识, 仅凭胆管影像学特征难以与之鉴别. 因此, Ohara等[41]制定的IgG4-SC最新诊断标准应同时具备下述条件: (1)典型的胆管影像结果; (2)血清IgG4浓度升高; (3)除胆管本身病变外, 还与其他IgG4-RSD并存; (4)典型的组织病理学特征. 此外, 类固醇疗效可作为确诊IgG4-SC的额外选择标准.

8 IgG4-SC与AIP的关系

尽管有IgG4-SC未合并AIP的个案报道[42], 但大量的研究显示, IgG4-SC几乎与AIP并存[26,43-46], 而大约50%-90%的AIP也常并发IgG4-SC[4], 可见IgG4-SC与AIP关系密切. IgG4-SC患者血清IgG4显著升高, 而70%的AIP患者同样IgG4含量也明显增加, 二者是重叠抑或为独立的疾病尚存争议[47]. 未合并AIP的IgG4-SC, 其诊断颇具挑战性, 甚至易误诊为CC而行手术治疗, IgG4阳性浆细胞的检测尤为重要, 可采取3种不同的活检方法检测[19]: (1)乏特氏壶腹活检; (2)肝穿刺活检; (3)胆管活检. AIP除表现为胰腺肿大及合并IgG4-SC外, 也常有胰腺外器官受累的表现[48], 其发病机制除与IgG4有关外, 还涉及多种自身抗体[49,50]. 此外, AIP组织中胰蛋白酶原及其他胰酶含量显著下降, 胰蛋白酶阳性的腺泡细胞缺失, 血清中抗胰蛋白酶原PRSS1、PRSS2的自身抗体及抗胰蛋白酶抑制因子PSTI的自身抗体显著升高, 提示其自身免疫过程可能涉及胰腺腺泡细胞及其分泌的各种酶[49]. AIP胰腺呈弥漫性或局限性肿大[51-53], 发病率约占慢性胰腺炎的5%-6%[54]及胰腺良性病变的1/3[55], 多见于老年人[56], 以IgG4阳性淋巴浆细胞浸润、纤维化、闭塞性静脉炎及对类固醇激素的有效应答为特征[51,52,57,58], 动态CT扫描示胰腺实质延迟增强, 灌注CT显示胰腺血流灌注减少[59]. 新的国际共识[5]将AIP分为淋巴浆细胞硬化性胰腺炎(lymphoplasmacytic sclerosing pancreatitis, LPSP)和特发性导管中心性胰腺炎(idiopathic duct-centric chronic pancreatitis, IDCP)2种类型, 前者不伴粒细胞上皮损伤(granulocyte epithelial lesions, GELs), 而后者伴有GELs, 并可致中小胰管或腺泡的破坏和闭塞. Kamisawa等[60]研究发现, AIP存在地域差异, LPSP和IDCP不仅病理特征不同, 临床表现也各不相同.

■创新盘点

本文详尽阐述了IgG4特性、IgG4-SC分型、影像学特征、诊断程序和诊断标准的最新国际共识、以及IgG4-SC与AIP、PSC及CC的关系, 为该领域的进一步研究提供了大量有价值的参考信息.

■应用要点
本文详尽阐述了IgG4-SC近5年的研究进展, 对该领域的基础与临床研究有一定指导意义.

9 IgG4-SC与PSC的关系

血清IgG4含量升高已作为IgG4-SC敏感的血清学诊断指标. PSC是硬化性胆管炎(sclerosing cholangitis, SC)中的一种特殊类型, 是以大中型胆管破坏、僵硬、胆管同心性纤维化为特征的一种慢性炎症性肝病[61], 其典型表现为胆汁淤积、大胆管病变及并发IBD, 肝移植是终末期PSC唯一有效的治疗措施[30]. IgG4-SC与PSC不仅对类固醇激素反应不同, 其组织病理学特征也迥异[19]. 但二者因临床及影像特征相似, 美国肝病研究学会(AASLD)建议对全部疑诊PSC的患者行血清IgG4检测, 以排除IgG4-SC. 研究显示, 9%的PSC患者血清IgG4升高, 且似乎更易发展至肝衰竭[47]. Navaneethan等[29]发现, 50例PSC患者中10例血清IgG4升高, 且其术后生存率显著低于IgG4正常的PSC患者. 亦有研究证实, 12%的PSC患者血清IgG4升高[62]. Kato等[63]发现, 血清IgG4升高的PSC患者若并发多器官淀粉样变性或许有助于其与IgG4-SC鉴别. IgG4-SC与血清IgG4升高型的PSC究竟是重叠抑或是独立疾病仍有待于进一步研究. 为评价SC患者常规检测IgG4的临床意义, Alswat等[30]对168例SC患者的回顾性研究表明, SC是一类病因和临床表现各异的肝脏疾病, 对全部SC患者行IgG4检测有重要意义, 这或许有助于对临床特征差异显著的疾病群体鉴别.

10 IgG4-SC与CC的关系

IgG4-SC有时与CC十分相似, 因临床及影像特征不典型, 尤其是未合并AIP者更易误诊为恶性胆道狭窄而接受不必要的手术治疗. 最近, 已见IgG4-SC误诊为CC的散在报道[64,65]. 此外, Harada等[66]研究发现, 43%的肝外CC可见丰富的IgG4阳性浆细胞浸润, 其分子机制在于CC细胞或许充当非专职抗原呈递细胞(nonprofessional antigen-presenting cells, APCs)和Foxp3阳性调节细胞(Foxp3-positive regulatory cells)的角色, 通过调节IL-10的生成间接或直接诱导IgG4阳性细胞的组织浸润. 这无疑使IgG4-SC和CC的鉴别更加困难. Nowatari等[67]报道2例罕见的位于肝门部的IgG4-SC病例, 酷似于肝门部的CC. 他们认为, 在确定诊断时, 应考虑是否累及其他器官, 如胰腺、唾液腺、腹膜后、淋巴结、肾脏以及慢性炎症性改变等[67]. 根据多器官受累及血清IgG4的检测可以准确诊断IgG4-SC, 从而避免不必要的外科大手术, 而代之以有效的类固醇激素治疗[67]. Chung等[64]报道了1例术前诊断为CC而行肝外胆管切除的肝管空肠吻合术病例, 后经组织病理学检查确认为IgG4-SC. 此病例的误诊凸显了术前诊断IgG4-SC的难度. 糖蛋白抗原19-9(carbohydrate antigen 19-9, CA19-9)是检测PCa的主要标志物, 但尚不能以此鉴别CC和良性胆道狭窄, 如IgG4-SC和PSC等. Sandanayake等[68]研究发现, CC患者血清中富亮氨酸α-2-糖蛋白1(leucine-rich α-2-glycoprotein 1, LRG1)、CA19-9及IL-6的含量显著高于IgG4-SC和PSC患者. 提示联合检测LRG1、CA19-9和IL-6有助于CC的诊断, 尤其适用于高风险PSC患者.

11 IgG4-SC与PBC的关系

IgG4-SC以血清IgG4显著升高为特征, 与原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)均可致肝功异常[69]. PBC是一种慢性胆汁淤积性自身免疫性肝病, 以血清特异性抗线粒体抗体(antimitochondrial antibody, AMA)增加、慢性非化脓性破坏性小胆管炎为特征, 应用熊去氧胆酸(ursodeoxycholic acid, UDCA)可缓解症状, 但对免疫抑制剂及类固醇激素不敏感[70]. IgG4-SC常合并AIP, 对类固醇激素敏感, 而PBC可伴发干燥综合征(sjögren syndrome, SS)、硬皮病(scleroderma)等自身免疫性疾病, 但IgG4-SC与PBC的关系尚不清楚[69]. 最近, Naitoh等[69]报道了1例IgG4-SC与PBC重叠, 经强的松龙(prednisolone)和UDCA联合治疗成功的病例. 患者除血清转氨酶、AMA显著增高外, 血清IgG4为968 mg/dL(正常范围: 4.8-105.0 mg/dL), 内镜逆行胰管造影(endoscopic retrograde pancreatography, ERP)显示, 胰头部主胰管呈局灶性不规则狭窄, 体尾部胰管呈节段性狭窄. ERC示肝内胆管弥漫性狭窄. IDUS显示胆管壁连续性增厚. 肝活检病理显示, 门管区及胆管壁可见中等量的淋巴浆细胞浸润, 并可见大量的IgG4阳性浆细胞浸润. 据此, 该病例诊断为IgG4-SC、AIP和PBC, 并经类固醇激素和UDCA联合治疗取得较好的疗效.

12 IgG4-SC的治疗

自身免疫机制可能在IgG4-SC的发生发展中起重要作用, 类固醇激素治疗有效也被作为IgG4-SC的辅助诊断标准, 尤其对临床和影像特征与PSC酷似而难以鉴别的患者, 激素治疗是否有效是与PSC区别的重要方法. 采用经口胆道镜观察IgG4-SC患者激素治疗前后的胆管黏膜变

化或许有助于评估疗效[46]. 但有关激素治疗方案的最佳选择还有待于进一步研究, 因已发表的相关研究资料缺乏, 目前尚难确定类固醇激素治疗IgG4-SC的推荐剂量和持续时间[19]. 采取传统的激素口服治疗抑或是冲击治疗仍存争议, 治疗后复发率较高仍是目前面临的主要问题. Ghazale等[3]研究发现, 尽管IgG4-SC对激素治疗敏感性很高, 但初次治疗后的复发率高达54%. 激素治疗和手术治疗的复发率相比并无显著差异, 而近段胆管狭窄较远段胆管狭窄的复发率更高. 激素治疗者IgG4持续升高或治疗后再次升高或可预示复发[71].

13 结论

尽管IgG4-SC被发现仅10余年, 但对其临床、影像及组织病理学的研究已取得飞速进展, IgG4-SC诊断标准的最新国际共识无疑会使诊断更加规范和完善, 而IgG4-RSD家族新成员的不断加入, 也使研究范围更加广泛. 然而, 作为IgG4-SC始动因素的IgG4其功能和特性却知之甚少, IgG4-SC的病因和发病机制迄今仍不清楚, 其与PSC和AIP的关系尚存争议, 这些问题均有待于更进一步的探讨, 其研究空间十分广泛, 前景值得期待.

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■名词解释
硬化性胆管炎: 一组慢性进行性纤维炎症性胆管疾病, 其发生与炎症、缺血、感染等多种因素有关. 按病因分为原发性和继发性2类.

■同行评价
本文对IgG4相关硬化性胆管炎的研究进展进行了述评, 为该领域的进一步研究提供了大量有价值的参考信息.

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