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细胆管癌的临床病理特征

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Clinical and pathological characteristics of cholangiolocellular carcinoma

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Abstract

Cholangiolocellular carcinoma (CLC), due to its special cell origin, has dual clinical and radiological features of hepatocellular carcinoma and cholangiocellular carcinoma, and has a relatively good prognosis due to the characteristics of inert growth. Its growth characteristics and clinical characteristics are obviously different from those of traditional intrahepatic cholangiocarcinoma (ICC). Therefore, CLC is a special type of primary liver malignancy. With regard to cell origin, clinical pathology, growth characteristics, and prognosis, CLC is a distinct disease from traditional hepatic cholangiocarcinoma; however, it is often confused with ICC in the relevant research worldwide. In this paper, we review the clinical and pathological characteristics of CLC to raise the attention to this problem and strengthen the relevant research.

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Key Words: Cholangiolocellular carcinoma; Biological feature; Prognosis

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摘要

细胆管癌(cholangiolocellular carcinoma, CLC)由于其特殊的细胞起源, 具有肝细胞癌和胆管细胞癌的双重临床病理和影像学特点, 由于惰性生长的特点, 预后相对较好, 其生长特点和临床特征明显有别于传统的肝内胆管癌(intrahepatic cholangiocarcinoma,

ICC), 是一种特殊类型的原发性肝脏恶性肿瘤。在细胞起源、临床病理特征、生长特点和预后等方面与传统意义的ICC是两种截然不同的疾病, 但国内外有关ICC的研究中往往将两者混为一谈, 没有明确的区分。本文就CLC临床病理特征进行综述, 以期引发大家对这一问题的重视, 并加强相关的研究。

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关键词: 细胆管癌; 生物学特性; 预后

核心提要: 细胆管癌(cholangiolocellular carcinoma, CLC)是一种罕见的肝脏恶性肿瘤, CLC起源于肝祖细胞, 与典型的肝内胆管癌相比, 影像学上可以显示出肝细胞癌和胆管癌的双重特征; 临床上呈明显的惰性生长, 预后相对要好很多, 临床上应加强鉴别和区分对待。

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0 引言

首先让我们来看一下细胆管癌的英文翻译, “Cholangiolocellular carcinoma”, 与胆管细胞癌的英文 “cholangiocellular carcinoma” 仅有细微差异, 但两种疾病从起源、临床症状、治疗和预后等各个方面均存明显差异, 甚至可以说细胆管癌(cholangiolocellular carcinoma, CLC)和胆管细胞癌(cholangiocellular carcinoma, CCC)是两种截然不同的疾病, 不应混为一谈。我们曾遇到一些患者, 因肝占位长期随访(1-3年), 后行手术, 病理示肝内胆管癌(intrahepatic cholangiocarcinoma, ICC), 但其生长缓慢、恶性程度较低的病程特点与传统ICC快速进展的特征明显不符, 术后进一步行病理及免疫组化检测, 后证实为CLC。

1 CLC的细胞起源

CLC是一种罕见的肝脏恶性肿瘤, 在最新的世界卫生组织(World Health Organization, WHO)分类中被归类为具有干细胞特征的肝细胞-胆管细胞混合型肝癌^[1]。最近的研究表明: CLC来源于Hering管内的肝祖细胞(hepatic progenitor cell, HPC), HPC具有干细胞特征, 可分化为肝细胞和胆管细胞^[2]。然而, 考虑到CLC形态学和免疫组织化学的研究结果, 一些研究人员提出CLC可能来源于小叶间胆管, 而不是HPC所存在的Hering管或胆小管^[3,4]。前期的研究发现CLC的癌管大小远大于胆小管, 与小叶间胆管的大小相似, CLC胆管、胆小管和小叶间胆管的

平均直径分别为31.8、13.8和26.5 μm ^[3]。此外, 免疫组织化学染色发现HPC标志物阳性的情况不仅见于胆小管, 还见于小叶间胆管。CLC来自Hering管或胆小管, 其特征是在大量纤维基质内出现类似于胆小管和导管反应样的小腺体^[3,4]。因此, CLC的起源仍然存在争议, 需要更详细的分子水平研究来阐明CLC的起源问题。而通常型的ICC, 或者肝内大胆管癌主要起源于较粗的肝内胆管(隔胆管, 区域胆管, 段胆管等)。

2 CLC的病因

尽管CLC的详细发病机制尚不清楚, 但研究发现患者常存在慢性病毒性肝炎、非酒精性脂肪肝病和酗酒导致的慢性肝损伤^[1,5]。此外, 前期报道显示HPC可以被慢性肝损伤所激活并造成导管内反应^[6,7]。这些发现提示慢性肝损伤激活HPC是CLC的重要病因之一。很多情况下, CLC患者伴有丙型肝炎病毒或乙型肝炎感染的基础, 血管造影显示血管丰富^[8]。因此, 在临床上CLC也常被误诊为肝细胞癌(hepatocellular carcinoma, HCC)^[9]。肝内大胆管癌则主要与肝内胆管结石、胆道寄生虫病等有关。

3 CLC的临床分类

Steiner等^[10]首次报道, CLC占有原发性肝脏恶性肿瘤的1%, 而日本报道的发生率为0.57%^[11]。最近随着对HPC的深入研究, 发现HPC存在于Hering管内, 而CLC起源于这些细胞^[12]。因此, 在2010年最新的WHO消化系统肿瘤分类中, 将其归类为具有干细胞特征的混合型肝细胞-CCC^[13], 而在第5版的日本原发性肝脏恶性肿瘤的临床和病理学分类规范中, 提出CLC是独立于ICC的一种疾病^[14]。

4 CLC的影像学特点

CLC的影像学表现多样^[15-17]。在影像学上可以显示出HCC和CCC的双重特征, 例如具有早期强化、延迟消退的特点, 也可以表现为早期边缘增强、延迟向心填充的特点, 与通常类型的肝内胆管癌(intrahepatic cholangiocarcinoma, ICC)相比, 肿瘤近端胆管狭窄和外周胆管扩展的影像学表现非常少见。这些表现取决于纤维基质细胞的数量和分布情况^[15]。此外, CLC被认为由各种组织学特征的区域所组成, 例如各种比例的CLC、HCC和CCC成分组成的不同区域^[1,18]。在MRI的弥散加权图像上可表现为高信号。

有研究报道了两种不同表现的CT增强特点, 分别为早期整体强化且延迟消退和持续边缘增强且向心性延迟充盈^[5]。在CLC患者中很少观察到肿瘤侵入肝内血管的情况^[19], 而在ICC、转移性肝癌和HCC中经常伴有血管侵犯的情况^[20,21]。PET-CT在ICC诊断中的敏感性要

高于肝门部胆管癌和肝外胆管癌^[22,23]. PET-CT在CLC鉴别诊断中的作用仍不明确^[17,24,25].

5 CLC的组织病理学特点

在显微镜下, CLC通常存在3种形态模式: CLC区域、HCC区域和ICC区域^[12,25]. Kozaka等^[26]将“纯CLC”定义为仅由CLC组成而没有任何HCC/CCC组分的肿瘤. 更多的情况下, CLC定义为至少80%^[25]或90%^[12]的肿瘤区域由经典CLC组成.

CLC表现为胆管腔侧EMA免疫组化染色阳性, 且肿瘤细胞内Hep-par 1阴性, CK19和NCAM阳性, 借此可以明确CLC的诊断. 在组织学上, CLC细胞的特点如下: 纤维组织丰富, 内有鹿角样的细腺管结构^[27]. 通过基因谱分析: 与其他HPC衍生的肝脏肿瘤相比, CLC是一类独特的分子实体肿瘤, 表现为TGF- β 信号通路和炎症-免疫应答信号通路的显著性上调, 例如白细胞介素-6、TNF- α 和趋化因子及其受体, 这些都是血管生成和炎症细胞浸润到肿瘤中的重要因子^[28]. 这些发现表明CLC可能与血管生成和炎症密切相关, 但仍需要进一步的研究来阐明这些基因上调的重要性和具体分子机理. 而普通型的ICC, 其组织学表现为腺管直径明显较粗, EMA染色在胞浆阳性.

6 CLC的临床表现

CLC伴有门静脉侵犯的几率较低, 肿瘤组织内残留门静脉管道的数量明显高于ICC组, 通过组织学检查发现CLC主要表现为替代性生长模式, 肿瘤细胞围绕但不破坏肿瘤内残留门静脉血管^[13]. 此外, CLC组肝内转移的发生率明显低于ICC组^[29]. CLC与其他肝脏恶性肿瘤相比, 肿瘤直径较小(平均值3.5 cm)^[16], 计算所得的CLC肿瘤倍增时间(tumor doubling time, TDT)为285 d, 而HCC和CCC的中位TDT分别为85.7 d和70 d^[30]. 这些数据表明缓慢增长是CLC的特征之一.

与CCC相比, CLC行根治性切除的预后较好^[16,31], CLC组5年总生存率和无瘤生存率明显高于ICC组^[16]. 由于肝移植效果不佳, CCC患者并不适合行肝移植治疗^[28], 但CLC患者却可能从肝移植中获益. 因此, 当肝脏肿瘤显示出与CCC相似的影像学表现、且缓慢生长时, 我们必须考虑CLC的可能性, 活检可能有助于制定下一步的治疗策略和治疗建议.

7 结论

CLC的发病原因, 细胞起源, 免疫组化和病理表现都和通常型的ICC不同, 其影像学表现具有一定的特点, 但由于其病理基础的多样性, 这些影像学表现往往缺乏特异性. CLC肿瘤生长缓慢, 预后较好, 治疗原则上应有别

于通常型的ICC. 在临床工作和研究中应区分CLC和通常型的ICC, 加强对CLC的认知和研究.

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