类癌综合征和类癌性心脏病的诊疗新进展

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【摘要】类癌较为罕见,在临床中容易被误诊,其衍生的类癌综合征可出现血管舒缩、胃肠道动力增高、支气管痉挛和类癌性心脏病的改变,后者主要表现为右心瓣膜(以三尖瓣多见)开闭功能受限。多模态心血管影像学在类癌性心脏病的诊断和预后评价中扮演了重要角色。放射性核素肽受体介导治疗靶向给药,通过降低血中激素水平可有效治疗类癌综合征,同时,经导管右心瓣膜置换术也在少数类癌性心脏病患者中进行了尝试。现就类癌综合征和类癌性心脏病的诊疗新进展进行综述,以期增强临床医生对该病的认识,提供更优化的治疗途径。

【关键词】类癌;类癌综合征;类癌性心脏病
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Diagnosis and Treatment of Carcinoid Syndrome and Carcinoid Heart Disease

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【**Abstract**】Carcinoid is rare and easy to be misdiagnosed in clinical practice. Its derived carcinoid syndrome can appear changes in vasomotor contraction, increased gastrointestinal motility, bronchospasm and carcinoid heart disease. The latter is mainly characterized by limited opening and closing function of right heart valve (most commonly tricuspid valve). Multimodal cardiovascular imaging plays an important role in the diagnosis and prognosis of carcinoid heart disease. Radionuclide peptide receptor-mediated targeted therapy can effectively treat carcinoid syndrome by reducing the level of hormone in blood. At the same time, transcatheter right heart valve replacement has also been tried in a few patients with carcinoid heart disease. This paper reviews the new progress in the diagnosis and treatment of carcinoid syndrome and carcinoid heart disease, in order to enhance clinicians' understanding of the disease and provide more optimized treatment approaches.

【**Key words**】Carcinoid; Carcinoid syndrome; Carcinoid heart disease

类癌是起源于消化道和其他器官的一类肿瘤的总称,恶性程度较低,病因尚不明确,因癌细胞内含有亲银性分泌颗粒,故又称亲银细胞癌或嗜银细胞癌。由于癌细胞可分泌血管活性物质,可引起血管舒缩、胃肠道活动增强、低血压和支气管痉挛等症状,被称为类癌综合征(carcinoid syndrome, CS)。随着肿瘤医学的发展,类癌患者的生存率和生活质量明显提高,但类癌性心脏病(carcinoid heart disease, CHD)引起的致残率和致死率却易被忽视[1],现就 CS 和 CHD 的诊治进展进行综述。

1 类癌和 CS

1.1 类癌的临床特征

类癌临床少见,年发病率约为 5.1/10 万[2],原发灶呈局限性和浸润性缓慢生长,约 67.5% 首发于消化道,约 25.3% 首发于支气管,罕见于卵巢、睾丸和甲状腺等器官。消化道类癌的预后较好,转移情况取决于肿瘤的大小,<1 cm 的肿瘤发生转移的概率为 2%,>2 cm 的肿瘤转移概率显著增加。据 Modlin 等[3]在 21 世纪初统计,类癌伴小肠远处转移患者的 5 年生存率为 21%~50%。随后进一步研究发现,类癌细胞大都存在生长抑素受体亚型的表达,可介导生长抑素类似物而抑制肿瘤的生长,诱导肿瘤细胞的凋亡[4]。如今,随着类癌患者生存率的不断升高,其症状和合并症越来越受到重视。

1.2 CS 的定义和发病机制

Thorson 等[5]于 1954 年首次定义了 CS:肠道中段实体肿瘤分泌大量生物活性胺(包括 5-羟色胺、儿茶酚胺和组胺)、多肽和其他分子,其中 5-羟色胺是最主

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要的成分,其经肿瘤细胞(主要是肠嗜铬细胞)产生分泌后,进入肝脏被代谢为 5-羟吲哚乙酸(5-hydroxy indole acetic acid,5-HIAA)则不再具备生物活性。但当 5-羟色胺进入全身血液循环,会出现 CS 的典型症状,即腹泻、潮红和 CHD。行尿液 5-HIAA 检查,可反映患者体内 5-羟色胺的水平,因此被广泛用作类癌患者随访的标志物。肠道前段肿瘤分泌的活性物质较少,而肠道后段肿瘤基本不分泌活性物质,因此 CS 很少见于肠道前段和后段的类癌患者,而更多见于肠道中段的类癌患者,尤其是合并有肝脏转移灶和卵巢转移灶的类癌患者[6]。

CS 中,轻度腹泻和阵发的皮肤黏膜潮红见于 80% 的患者[7],长期的 5-羟色胺超负荷可导致患者全身脏器广泛性纤维化,50% 以上的类癌患者存在心脏受累,其中 97% 仅表现为三尖瓣损害,偶伴肺动脉瓣受损;此外,临床少见肠系膜纤维化,导致肠梗阻和腹痛,偶有患者腹膜后纤维化,可继发肾积水[8-9]。值得注意的是,类癌危象虽罕见,但若不及时处理常危及生命,它是因肿瘤短期内大量分泌血管活性因子,使患者出现血压剧烈波动(低血压或高血压)、持续性皮肤潮红、哮喘发作、窒息、意识模糊及昏迷等征象[10]。5-羟色胺是 CS 的主要原因,轻症患者可先对症处理,根治需手术摘除肿瘤。

2 CHD 的表现和诊断

CHD 的特征是心内膜和瓣膜出现纤维化,也被称作“类癌斑块”,多发生于右心瓣膜,主要表现为三尖瓣增厚和开闭功能受限,肺动脉瓣狭窄和/或关闭不全可伴随或单独发生,但都比较少见,患者常因右心衰竭的症状就诊。其潜在机制被认为是 5-羟色胺刺激胶原合成增加,进而出现“类癌斑块改变”。研究显示,CHD 患者尿中 5-HIAA 的含量明显高于不合并 CHD 的类癌患者,印证了上述机制在 CHD 中的作用[11]。CHD 罕见累及左心瓣膜,这是由于肺泡内膜如同肝脏一样,可将 5-羟色胺代谢为 5-HIAA 排泄出体外[12]。罕见类癌肿瘤的心内转移灶呈实性占位,不伴瓣膜形态的改变,要注意和心脏副神经节瘤相鉴别。CHD 患者的预后较差,因此推荐类癌患者(尤其尿中 5-HIAA >100 mg/24 h 的患者)应进行长期的超声心动图随访,以期能早发现和早治疗,改善预后[13]。

2.1 多模态影像学检查在 CHD 中的价值

多模态影像学检查在 CHD 的诊断中具有重要价值,其中超声心动图在 CHD 中的诊断、随访和围手术期评估中不可或缺。CHD 主要表现为右心房增大,三尖瓣叶及瓣下腱索增厚和挛缩(类似风湿性改变,但罕有左心瓣膜受累可做鉴别),慢性形态改变可导致瓣叶活动显著降低,特异性地表现为恒定的“半开放”位置,瓣口形态在整个心动周期均无明显变化,狭窄和反流同时出现[14]。如累及肺动脉瓣,可显示肺动脉增宽,肺动脉瓣叶可显示类似三尖瓣叶改变声像图,多数合并肺动脉瓣反流,伴或不伴肺动脉瓣狭窄[15]。三维超声心动图和经食管超声心动图检查(trans-esophageal echocardiography,TEE)能更好和更直观地显示三尖瓣瓣叶、瓣环和瓣下腱索等。TEE 因食管探头的位置更加贴近心脏,二维图像和血流显像的分辨率更优,尤其是三维 TEE 技术对 CHD 导致的三尖瓣病变具有更大的诊断价值[16]。

CHD 除累及右心瓣膜外,还可表现为心脏的转移性类癌肿瘤(metastatic carcinoid tumor involving the heart,MCH),虽然心内转移灶十分罕见,但梅奥中心曾报道 11 例 MCH 患者,是迄今最大样本量的研究报告,大部分病例均在术中病理检查时才得以确诊。回顾术前超声心动图表现为心包内侧类圆形、包膜完整和分界清晰的等回声团块。这 11 例患者中,MCH 累及右心室占 40%,左心室占 53%,室间隔占 7%[17]。心内转移灶十分罕见,>1.0 cm 的占位在超声上较易辨识出来。

对于超声图像质量不佳的患者,心脏磁共振不仅可任意角度成像,具有较高的空间分辨率,而且可定量反流程度,评价右心容积和功能,这对于后期随访,选择恰当的干预时机具有十分重要的价值[18]。当 CHD 的病变主要累及肺动脉瓣时,超声不易观察到,此时心脏磁共振的诊断价值就更加凸显。早期 CHD 病变较轻微时,超声的敏感度也较低,延迟钆增强心脏磁共振可显著提高诊断的敏感性,给予预警,其敏感性可参照类似的瓣膜疾病。心脏增强计算机断层扫描可在术前帮助鉴别冠状动脉是否存在病变,有利于手术策略的制定[14]。正电子发射断层显像(positron emission tomography,PET)利用 CHD 患者体内生长抑素受体增多的特点,将生长抑素与特殊的放射性物质(如^{68}镓)耦合进入体内,被肿瘤细胞摄取后有利于 PET 的定性诊断,诊断的敏感性为 97%,特异性为 92%,但由于 PET 价格昂贵,限制了其临床应用[19]。

2.2 CS 引起的其他心血管不良反应

5-羟色胺的过量产生是 CS 和 CHD 的主要原因,其他生物活性胺也同样可引起心血管不良反应。约 40% 的 CS 患者可产生过量的儿茶酚胺[20],从而引起心率变异性增高(自主神经功能失调的表现),多发于 CHD 的早期阶段,伴随着尿中儿茶酚胺及其代谢物含量的升高[21]。体内过量的儿茶酚胺也可导致低血压,

但仅见于散发病例。此外,肠道周围的生物活性胺浓度显著高于全身,因此可出现肠道弹性血管硬化症,表现为入肠和出肠的小血管弹性纤维增多,易导致肠道坏死,发生率约占类癌患者的 33%[22]。

3　类癌和 CHD 的治疗

类癌虽为良性肿瘤,生长缓慢,但会严重影响患者的生活质量[23],治疗决策取决于肿瘤原发灶的大小和位置,治疗方式包括手术切除和消融治疗。

为了控制 CS 的全身症状,可使用放射性核素肽受体介导治疗,随着对发病机制研究的不断深入,大量新兴药物已用于临床治疗 CS,且药效良好,比如第一代生长抑素受体类似物奥曲肽,临床应用已有 20 多年的历史,药效明确,耐受性好。但药物的作用时间短,长期使用肿瘤细胞会产生抗药反应[24]。近来研究发现雷帕霉素、舒尼替尼、细胞毒性化疗、α 干扰素以及新一代的生长抑素受体类似物等的药效均更加确切[25],但由于类癌是罕见病例,缺乏相关的大样本量研究和相关药物的具体有效率数据。

CHD 患者如出现右心衰竭的症状,可用利尿剂减轻症状。现无证据表明生长抑素受体类似物可阻止或延缓 CHD 的进展。瓣膜置换可能是临床治疗三尖瓣受累患者的有效方式,但围手术期的死亡率较高[26-27],其死亡率与右心瓣膜疾病类似,随着经导管瓣膜置换的兴起和发展,微创瓣膜置换也尝试着应用于 CHD 患者。2015 年,*JACC* 杂志上发表了 1 例经导管置换肺动脉瓣的 CHD 患者[28]。该例女性患者 77 岁,因 CHD 导致三尖瓣及肺动脉瓣显著反流,同时合并冠心病。因患者一般状况较差,难以同时接受体外循环下两个瓣膜置换 + 冠状动脉旁路移植术,经多学科联合讨论后将治疗方式改为体外循环下三尖瓣生物瓣置换 + 冠状动脉旁路移植术,术后因持续的右心衰竭再次接受经导管肺动脉瓣置换术,手术成功。这为 CHD 患者的治疗提供了新的思路和选择,并已证实效果确切且良好,但术后瓣膜的耐久性及是否会再次受到 CS 的影响还未可知,有待于进一步的研究。类癌心脏转移的患者一旦确诊,只能选择体外循环下占位切除术,术后未见复发报道[29]。

CHD 患者预后较差,一项研究在 1981—2000 年随访了 200 例 CHD 患者(迄今为止样本量最大的研究),其中 149 例患者的中位死亡时间为 2.6 年,其死亡主要原因是右心瓣膜损害导致的右心衰竭,结果同时显示右心瓣膜置换术可显著提高 CHD 患者的生存率和生存时间[30]。因此,虽然该病的发病率较低,但增强临床医生对该病的认识,有助于提高患者的生活质量和生存率。

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