

甲状旁腺癌临床诊断与管理

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摘要

甲状旁腺癌是罕见的恶性肿瘤, 它的临床表现是甲状旁腺素升高、高钙血症以及全身各个系统的相关症状, 它的罕见性, 加上其多样化的临床表现, 使其诊断特别具有挑战性。近年来随着医疗水平的不断提高, 甲状旁腺癌的发现也相对增多, 在临床上诊断甲状旁腺癌时应从临床表现、实验室检查、影像学检查、和病理学检查多个方面考虑, 早期诊断、早期治疗可以有效改善患者预后。治疗以外科手术治疗为主, 手术的彻底性可以有效降低肿瘤的复发。本文旨在对甲状旁腺癌进行一个综述, 提高临床医生对甲状旁腺癌的认识, 避免漏诊、误诊带来的不良后果。

关键词

甲状旁腺癌, 诊断, 治疗, 外科手术

Clinical Diagnosis and Management of Parathyroid Carcinoma

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Abstract

Parathyroid carcinoma is a rare malignant tumor whose clinical manifestations include elevated parathyroid hormone levels, hypercalcemia, and systemic symptoms affecting various organs. Its rarity, coupled with its diverse clinical presentation, renders diagnosis particularly challenging. In recent

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years, with continuous advances in medical standards, the detection rate of parathyroid carcinoma has relatively increased. Clinically, diagnosis should consider multiple aspects including clinical presentation, laboratory tests, imaging studies, and pathological examination. Early diagnosis and treatment can significantly improve patient prognosis. Surgical intervention remains the primary treatment modality, with thoroughness of resection effectively reducing tumor recurrence. This article aims to provide a comprehensive review of parathyroid carcinoma, enhancing clinicians' awareness of this condition and thereby preventing the adverse consequences of misdiagnosis or missed diagnosis.

Keywords

Parathyroid Carcinoma, Diagnosis, Treatment, Surgery

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1. 引言

甲状旁腺癌是一种罕见的内分泌恶性肿瘤, 占所有癌症的不到 0.005%。大多数原发性甲状旁腺功能亢进症病例是由甲状旁腺腺瘤引起的, 其中甲状旁腺癌是原发性甲状旁腺功能亢进的罕见病因(少于 1%)。诊断甲状旁腺癌具有挑战性, 通常是在术后病理中得到诊断[1]。甲状旁腺癌的最佳治疗方法是手术切除, 标准手术范围包括肿瘤、同侧甲状腺腺叶和峡部以及邻近受累结构的切除, 但是术后仍有较大复发或远处转移风险。甲状旁腺癌患者大多死于严重的高钙血症及相关并发症, 而非肿瘤负荷本身[2]。临床上对甲状旁腺癌的早期诊断对患者的预后有着重要意义, 而甲状旁腺癌的罕见性, 加上其多样化的临床表现, 使其对其的早期识别较为困难, 因此加强我们对甲状旁腺癌的全面了解。本文对甲状旁腺癌的流行病学、病因、临床表现、诊断与治疗等多个方面进行综述。

2. 流行病学及病因

甲状旁腺癌是一种罕见的恶性肿瘤, 据估计每年每百万人中有 0.4~0.6 例患有甲状旁腺癌[3], 与甲状旁腺腺瘤不同的是, 甲状旁腺腺瘤在女性中的发病率是男性的三倍, 但甲状旁腺癌的男女发病比例相近, 患者平均发病年龄在 45 至 59 岁之间, 比甲状旁腺腺瘤患者年轻十年[4]。甲状旁腺癌的发病率低但随着临床对甲状旁腺癌的认知加深和诊断手段的提升, 呈现上升趋势, 我国的甲状旁腺癌报道也逐渐增多[5]。

甲状旁腺癌的病因目前尚不明确, 报道的病例大多数是散发的。它的病因可能与甲状旁腺功能亢进-颌骨肿瘤综合征、多发性内分泌肿瘤 I 型有关[6][7]。在散发性甲状旁腺癌中, 约 70% 的病例存在 CDC73 突变; 甲状旁腺功能亢进-颌骨肿瘤综合征的患者易发生多发性甲状旁腺肿瘤, 其中约 15% 最终进展为癌[8][9]。可对以下患者进行种系突变检测: (1) 年龄 < 40 岁发病; (2) 有甲状旁腺癌或多发性甲状旁腺肿瘤个人史或家族史; (3) 合并颌骨骨化性纤维瘤或肾脏病变; (4) 病理提示 CDC73 蛋白表达缺失。若检测到种系突变, 应推荐其一级亲属进行遗传咨询与突变检测, 并建议突变携带者定期监测血钙、PTH 及颌骨影像学, 以便早期发现病变。有研究结果显示约 18% 的甲状旁腺癌中存在 PRUNE2 突变, 突变破坏了 PRUNE2 的抑癌功能, 导致细胞转化失控, 从而提高了甲状旁腺癌的易感性[10]。有头颈部放射史, 慢性肾衰导致的继发性甲状旁腺功能亢进的病人更易患甲状旁腺癌[11]。

3. 临床表现

甲状旁腺癌主要的临床表现为甲状旁腺素(Parathyroid hormone, PTH)升高和高钙血症。甲状旁腺癌的

临床表现可累及多个系统, 当它涉及消化系统时, 通常会引起恶心、呕吐等症状, 少数患者还会引起胰腺炎的表现[12][13]; 泌尿系统受累通常表现为肾绞痛、肾结石和肾功能不全; 骨骼受累通常会导致骨痛和病理性骨折, 并可能导致棕色瘤[14]; 棕色瘤在影像学上表现出明显的溶骨性改变, 它是由甲状旁腺激素升高引起的肿瘤样病变, 也称为纤维性囊性骨炎。它通常需要与恶性骨肿瘤和骨转移区分开来。这种表现通常不需要特殊治疗, 因为它通常在手术切除甲状旁腺癌后随着 PTH 恢复正常后自然恢复[15]-[17]。颈部肿块是甲状旁腺癌的常见表现, 少数甲状旁腺癌是无功能的, 其特征是 PTH 水平正常, 缺乏高钙血症等症状, 因此难以被发现, 通常是患者触及颈部无痛性肿块而发现的[14][18][19]。

4. 诊断

甲状腺旁腺癌的诊断除了临床表现以外, 还依赖于实验室检查及影像学检查辅助诊断, 以及最重要的病理学诊断。

4.1. 实验室检查

甲状旁腺癌的主要特征就是高钙血症和高 PTH 水平, 当 PTH 超过正常上限 10 倍时高度怀疑甲状旁腺癌[20]。血清碱性磷酸酶明显升高时需高度警惕甲状旁腺癌, 有研究表明当血清碱性磷酸酶 $> 285 \text{ IU/L}$, 诊断甲状旁腺癌的敏感度和特异性分别为 83.3% 和 97.0% [21]。

4.2. 影像学检查

颈部超声是临床上诊断甲状腺疾病首选的检查, 肿瘤大小 $> 3 \text{ cm}$ 、低回声、边界不规则、纵横比 > 1 、侵入周围组织等超声表现都提示甲状旁腺癌可能, 另外在临床考虑恶性可能时, 还可以同步检查颈部淋巴结, 评估是否有转移[22]。99mTc-MIBI 甲状旁腺显像主要用于甲状旁腺的定位, 有研究结果显示当 99mTc-MIBI 甲状旁腺显像、4D-CT、与超声联合应用时敏感度明显提高达 100% [23]。甲状旁腺肿瘤在 CT 上有边界不规则、纵横比 > 1 、有钙化灶、肿瘤侵犯周围组织、增强扫描呈轻度强化等表现时提示有恶性可能[24], 良性腺瘤则多小于 2 cm , 边界清晰。甲状旁腺良性病变在 MRI 表现为: 体积较小、信号均匀、边界清晰; 而甲状旁腺腺癌则表现为体积较大、信号不均、边界模糊[25]。甲状旁腺癌及其转移灶在 PET/CT 上常表现为高代谢, PET/CT 可以初期评估甲状旁腺癌范围、在手术切除后评估术后癌组织残留情况、识别复发的肿瘤[26]。由于 PET/CT 的价格昂贵, 在临床上难以作为甲状旁腺癌鉴别的常规检查, 但它可以作为其他影像学检查的补充检查。临床上怀疑甲状旁腺癌时行细针穿刺活检易受甲状腺组织影响, 还有肿瘤种植转移的风险, 细针穿刺活检在甲状旁腺癌的应用价值还需进一步研究[27]。

4.3. 病理学检查

诊断甲状旁腺癌的方式是肿瘤发生远处转移, 但这一般发生在疾病晚期[28]。那么在通过术后组织病理学分析诊断甲状旁腺癌具有重要作用。甲状旁腺癌肉眼观一般大于 3 cm 、形状不规则、分叶状, 可能与周围组织粘连、浸润等, 其病理学特征一般有粗纤维带、有丝分裂象、小梁生长模式以及包膜或血管的侵袭[29]。随着免疫组化技术不断进步, 它成为诊断甲状旁腺癌不可或缺的工具。Parafibromin 是 HRPT2 基因的一种蛋白产物, 当 parafibromin 的核免疫反应性丧失时, 在诊断甲状旁腺癌方面表现出高敏感性和特异性 96% 的甲状旁腺癌患者 parafibromin 免疫反应性丧失; 绝大部分的甲状旁腺良性病变呈 parafibromin 核免疫反应阳性; 在 9 例甲状旁腺功能亢进-颌骨肿瘤综合征患者的甲状旁腺腺瘤中 8 例也显示免疫核反应缺失, 这提示 parafibromin 核免疫反应缺失与甲状旁腺肿瘤发生有一定的联系[30]。甲状旁腺癌侵入甲状腺后, 通常变得难以与甲状腺病变区分开来。GATA-3 作为甲状旁腺组织的可靠且特异性的标志物, 不会对甲状腺组织进行染色。在一个研究中所有甲状旁腺病变均表现出阳性 GATA3 染色,

而甲状腺肿瘤、肾细胞癌、胸腺上皮肿瘤和类癌细胞呈阴性[31]。此外, 嗜铬粒蛋白 A 在甲状旁腺病变中表现出高敏感性, 可与 GATA3 联合用于诊断甲状旁腺疾病[32]。Ki67 是一种在细胞增殖的各个阶段表达的蛋白质, 通常在恶性肿瘤中高表达, 甲状旁腺肿瘤中的 Ki67 指数大于 5% 提示恶性肿瘤[33]。术中冰冻对甲状旁腺癌的诊断价值有限, 有研究结果显示准确率为 16.7% [34], 另一项研究的术中冰冻准确率仅有 15.04% [5]。

5. 治疗

5.1. 外科手术

甲状旁腺癌首选的治疗方式就是手术切除, 切除范围包括完整的肿瘤组织、同侧甲状旁腺叶切除术联合峡部切除术以及邻近受累结构的切除。术中可以对甲状旁腺素进行动态监测, 评估是否完全切除病灶, 避免癌组织残留。关于是否行预防性颈淋巴结清扫术, 目前尚未达成共识, 有学者认为没有足够的证据可以支持预防性清扫淋巴结有助于改善患者的存活率, 肿瘤 $\geq 3\text{ cm}$ 的患者淋巴结转移率显著高于 $< 3\text{ cm}$ 者, 肿瘤 $\geq 3\text{ cm}$ 是淋巴结转移的独立危险因素, 在这一情况下可考虑中央区淋巴结清扫; 对于肿瘤较小、无侵犯周围组织的患者, 淋巴结清扫的必要性较低。淋巴结转移情况未影响患者的生存率, 还需考虑到淋巴结清扫术带来的喉返神经损伤、甲状旁腺功能减退等手术风险, 应基于肿瘤大小与局部侵犯程度等情况决定是否行中央区淋巴结清扫术, 而不是常规手术[35][36]; 也有学者支持预防性清扫同侧中央区淋巴结, 他们认为以根治性切除为目的, 同侧中央区淋巴结清扫应纳入手术标准[37][38]。甲状旁腺癌在术前与其他甲状旁腺肿瘤的鉴别诊断相对困难, 许多患者在第一次手术仅行单纯的甲状旁腺肿物切除术。对于这部分第一次手术仅行肿物切除的甲状旁腺癌患者, 及时的二次手术可以改善患者的预后[39][40]。

术后并发症有术后出血、甲状旁腺功能减退症、喉返神经麻痹等。患者在术前长期处于高钙血症, 在手术切除之后可能会有严重的低钙血症表现, 因此在术后需定期复查患者血钙、PTH 水平, 适当补充钙剂及维生素 D 预防低钙血症表现。建议术后第 1 个月每 2 周检测血钙与 PTH, 第 2、3 个月每月一次, 之后每 3 个月或半年复查一次, 持续 2 年; 后续视复查情况可延长至每年一次, 若出现临床症状则及时就诊。主要监测 PTH、电解质及肾功能, 必要时行颈部超声或全身影像学检查。

甲状旁腺癌复发一般表现为 PTH 明显升高、高钙血症或颈部局部肿物[41]。对于复发的患者仍可以积极手术切除复发病灶, 可有效控制高钙血症并延长生存期。若患者无法耐受手术或病灶无法切除, 可考虑局部消融治疗(如射频消融、微波消融), 其创伤小、恢复快, 适用于部分不宜再手术的局部复发或转移灶, 但长期控制效果仍需更多研究支持。除此以外还需控制患者的高钙血症, 大多数患者是死于高钙血症及相关并发症。高钙血症会引起一系列临床症状, 如恶心、呕吐、便秘、多尿、脱水、嗜睡、昏迷、肾功能损害及骨质疏松等; 双膦酸盐、西那卡塞、降钙素等药物用于甲状旁腺癌患者高钙血症的控制; 地舒单抗是双膦酸盐或西那卡塞无法控制患者血钙后的一个药物选择, 它适用于难治性高钙血症; 当患者出现高钙血症危象时, 可以用生理盐水扩容、利尿剂、透析等方法紧急降钙治疗[42]-[44]。

5.2. 辅助治疗

甲状旁腺癌的术后放疗在临床上还未广泛应用, 目前有关甲状旁腺癌术后放疗的研究较少、缺乏大量样本量, 它的价值还需有更多的证据支持[45]。术后化疗对甲状旁腺癌的作用也同样缺乏足够的证据支持, 由于甲状旁腺癌的罕见性, 术后化疗仅用于少量的病例, 甲状旁腺癌的化疗也没有一个标准化的方案[4]。索拉非尼是一种靶向治疗药物, 有研究报道它用于一名肺转移的甲状旁腺癌患者的治疗后, 患者的血钙、PTH 水平恢复正常, 肺部转移瘤缩小[46]。这说明靶向治疗在甲状旁腺癌具有一定的应用价值,

但仍需更多的研究进一步证明。

6. 分期与预后

由于甲状旁腺癌的罕见性, 缺乏统一的分期标准。有些学者依据其他恶性肿瘤的 TNM 分期进行了甲状旁腺癌的分期。Shaha 等提出的甲状旁腺癌 TNM 分期是 T1: 肿瘤 < 3 cm; T2: 肿瘤 ≥ 3 cm; T3: 无论肿瘤大小, 侵犯周围软组织; T4: 侵犯气管、食管或复发[47]。Talat 与 Schulte 等[48] [49]提示的分期认为肿瘤侵犯包膜为 T1, 侵犯除气管、食管、喉以外的软组织为 T2, 侵犯血管为 T3, 侵犯喉、气管、下咽部、食管、喉返神经以及颈动脉等重要器官为 T4。甲状旁腺癌是进展相对缓慢的恶性肿瘤, 其预后差异较大, 没有明显的特征与预后相关, 现在尚未建立评估预后的标准方案[2] [50]。甲状旁腺癌的 5 年生存率约为 85%, 10 年生存率在 35%至 79%之间。有研究表示可能与预后相关的因素有年龄、性别、肿瘤大小, 淋巴结转移阳性对预后的影响还有待进一步商榷[36]。第一次手术切除的彻底性对预后有着重要作用, 甲状旁腺癌根治性切除术后局部复发率为 8%, 长期生存率达 89%; 而不完全切除则分别为 51%和 53% [50]。

7. 总结

甲状旁腺癌是一种罕见的恶性肿瘤, 早期的甲状旁腺癌患者缺乏特殊的临床表现, 加上其罕见性, 使得易发生漏诊及误诊, 特别是在与如今高发的甲状腺肿瘤进行鉴别时, 建议常规行颈部 CT、甲状腺功能、PTH 及电解质水平检查。甲状旁腺癌最重要的治疗就是外科手术, 应保证第一次手术切除的彻底性, 避免局部残留。对甲状旁腺癌患者要长期随访 PTH 及血钙水平, 早期发现肿瘤复发或转移进行第二次手术可以改善患者预后。大部分甲状旁腺癌后期死于严重的高钙血症, 定期监测血钙, 予药物进行控制可以有效延长患者生存期和提高生活质量。

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