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IPMN伴瘘管形成的研究进展

胡慧艺，何　松*

重庆医科大学附属第二医院消化内科，重庆

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摘　要

在胰腺导管内乳头状黏液性肿瘤(Intraductal papillary mucinous neoplasm, IPMN)患者中，合并瘘管形成是一种罕见但重要的并发症。研究表明，IPMN可通过机械穿透或自身消化等机制形成瘘管，导致其向邻近器官扩展。瘘管形成最常见的受累器官包括胃、十二指肠和胆道，其中胃和十二指肠的瘘道发生率较高。此外，合并瘘管形成可能提示IPMN恶性转变风险高，预后不良。对于伴有瘘管形成的IPMN患者，手术干预是一种重要的治疗策略。一些研究指出，对于主胰管型IPMN，尤其是伴有浸润癌的情况，应积极手术治疗，如全胰腺切除术，以实现完全切除。总的来说，IPMN伴瘘管形成的病例具有一定的临床挑战性，需要综合考虑患者的年龄、肿瘤特征以及手术风险等因素，以制定最佳的治疗方案。本文拟从发病机制、诊断及治疗方面对IPMN合并瘘管形成展开叙述，以期提高临床医生对其的认识，更好地指导临床实践，并为患者的诊断和治疗提供更有效的支持。

关键词

胰腺导管内乳头状黏液性肿瘤，瘘管形成，内镜超声，诊断，治疗

Review on IPMN with Fistula Formation

Huiyi Hu, Song He*

Gastroenterology and Hepatology Department, The Second Affiliated Hospital of Chongqing Medical University, Chongqing

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Abstract

In patients with intraductal papillary mucinous neoplasm (IPMN), the formation of fistulas is a rare but significant complication. Studies have shown that IPMNs can form fistulas through mechanisms such as mechanical penetration or autolysis, leading to extension into adjacent organs.

*通讯作者。

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The most commonly affected organs by fistula formation include the stomach, duodenum, and biliary tract, with the incidence being higher in the stomach and duodenum. Additionally, the presence of a fistula may indicate a high risk of malignant transformation of IPMN and a poor prognosis. For patients with IPMN complicated by fistulas, surgical intervention is an important treatment strategy. Some research suggests that for main pancreatic duct type IPMN, especially when associated with invasive cancer, active surgical treatment such as total pancreatectomy should be considered to achieve complete resection. Overall, cases of IPMN with fistula formation present certain clinical challenges and require comprehensive consideration of patient age, tumor characteristics, and surgical risks to formulate the best treatment plan. This article aims to discuss the pathogenesis, diagnosis, and treatment of IPMN with fistula formation, in hopes of increasing clinicians' understanding of the condition, better guiding clinical practice, and providing more effective support for patient diagnosis and treatment.

Keywords

Intraductal Papillary Mucinous Neoplasm, Fistula Formation, Endoscopic Ultrasound, Diagnosis, Treatment

1. 背景

胰管内乳头状黏液性肿瘤(Intraductal papillary mucinous neoplasm, IPMN)是一种起源于胰腺导管上皮细胞的病变，以胰管内部形成分泌大量黏液的带有乳头状突起的肿瘤组织为特点。IPMN 的良恶性程度跨度较大，可从非侵袭性的腺瘤发展到具有不同侵袭性的侵袭性肿瘤，包括 PDAC 及浸润性胶样癌。根据影像学检查和/或组织学，IPMN 在形态学上分为 3 种类型：主导管(main-duct, MD)、分支导管(branch-duct, BD)和混合型(mixed type) [1]。在 IPMN 的发展过程中，瘘管形成是一种罕见但重要的并发症。瘘管形成指 IPMN 与邻近器官之间的异常通道形成。其中，主胰管型最容易合并瘘管形成，且 MD-IPMN 比 BD-IPMN 更易发生浸润性癌[2]。Tanaka M 等人发现，IPMN 最常侵袭胃、十二指肠和胆道系统的瘘管[3]。IPMN 伴瘘管形成的患者其临床表现常常不典型，包括腹痛、消化不良、体重减轻等症状[4]。对于这类患者，临床医生需要密切关注病情的发展，及时进行影像学检查以明确病变的范围和严重程度。在治疗方面，手术切除是目前主要的治疗手段，尤其是对于恶性转化可能性高的病例[3] [5]-[11]。总的来说，瘘管形成往往提示 IPMN 向恶性转化的风险较高，增加了 IPMN 手术治疗的复杂性，且瘘管的存在可能与较差的预后相关联[3]。随着内窥镜和影像技术的改进，近年来，IPMN 穿透各种器官的报道越来越多。然而，IPMN 伴瘘管形成的诊治缺乏系统概述。因此本文拟从发病机制、诊断及治疗方面对 IPMN 合并瘘管形成展开叙述，以期提高临床医生对其的认识，更好地指导临床实践，并为患者的诊断和治疗提供更有效的支持。

2. 发病机制

IPMN 引起瘘管形成的机制仍存在争议。迄今为止，IPMN 瘘管的器官包括胃、十二指肠、胆管、小肠、结肠、门静脉、脾脏和胸壁[12]。从理论上讲，IPMN 可以在所有邻近器官中形成瘘管[3] [4] [5] [13] [14]。据日本的报告，IPMN 最常侵犯的器官依次为十二指肠(64%)、胆总管(56%)和胃(17%) [4] [14]。

十二指肠是最常见的侵犯部位，因为主要病变最常位于胰头部(68%) [15]。胃、十二指肠和胆管与胰腺的接触面积相对较大，因此这些部位形成瘘管风险较高。此外，与空腔脏器相比，实质器官(比如脾脏)极少与胰腺形成瘘道，这可能与实质器官对胰管内压升高的抵抗力更高相关[1] [2] [16] [17]。

关于瘘管形成的发病机制，目前有以下几种理论：① 肿瘤细胞直接侵袭；② 机械性穿透；③ 胰酶自身消化所致[6] [18] [19]。其中，近三分之一的患者可发现 IPMN 直接侵袭周围组织器官。并且，在合并多器官瘘的 IPMN 患者中，瘘管周围的肿瘤侵犯更为常见，这可能提示了合并多器官瘘的 IPMN 恶性程度更高，侵袭力更强。第二，机械性穿透可能是由于 IPMN 产生大量粘液，发生一系列炎症反应，导致胰腺导管内压力增加，最终穿透邻近脏器。最后，Yamada 等人[6]发现在 IPMN 合并瘘管形成的病例中，在病理学上可观察到胰管壁和实质被溶解，因此胰酶的自身消化也被认为是可能的机制之一。此外，他们还提出后两种机制可综合发挥作用：首先，胰腺导管内压力增加，侵蚀胰管上皮；接着，胰酶分泌，自身消化，导致胰管及实质溶解，胰管穿孔进入胰腺周围脂肪组织；并且，胰腺周围组织炎症反应导致新形成的瘘道与周围邻近器官粘连；最后，邻近器官自身消化，最终形成瘘管。

3. 诊断

IPMN 伴瘘管形成的诊断在临床实践中具有一定的挑战性，主要体现在明确瘘管侵犯部位及恶性程度上。在临床表现上，患者可能会出现胰管梗阻引起的腹痛。同时，由于瘘管形成，消化道内容物可能会进入胰管，导致发热等症状。此外，由于肿瘤的压迫和影响，患者可能会出现体重减轻等全身性症状。体格检查时可能患者可能表现出腹部压痛、腹部肿块等症状。这些体征可能与胰腺管道的阻塞和瘘管形成有关。在临床实践中，对于怀疑患有 IPMN 并伴有瘘管形成的患者，应该进行全面的影像学检查和病理学评估，必要时完善 EUS-FNA 检查，以明确诊断并制定相应的治疗方案[20]。

3.1. 影像学诊断

影像学诊断对于诊断 IPMN 合并瘘管形成至关重要。CT 和 MRI 是常用的影像学检查手段，能够清晰显示胰腺内的肿瘤和瘘管与邻近器官的解剖关系。在无症状患者中胰腺囊肿伴浸润性癌并不常见，特别是囊肿 < 5 mm 时，因此此时可能不需要进一步检查，但仍建议进行规律随访[16] [20] [21] [22]。然而，对于>5 mm 的囊肿，推荐进行胰腺增强 CT 或 MRI 联合磁共振胰胆管造影(MRCP)，以更好地鉴定病变[23]。与 CT 相比，MRI 更容易发现病变(MRI vs. CT: 19.9% vs. 1.2%) [22] [24]。目前放射科医师一致建议使用 MRCP 作为首选检查，因为其分辨率高，有助于识别隔膜、结节和胰管交通等结构，且具有辐射暴露的优点[7] [8] [9] [25]。然而，影像学检查在区分良恶性病变的准确性有限。在临床实践中，需综合利用多种影像学技术，提高 IPMN 伴瘘管形成的诊断准确度，为患者制定更合理的治疗方案提供重要依据。

3.2. 内镜及实验室检查

根据瘘管侵犯器官不同，内镜的诊断作用不一。在胃、十二指肠、结肠瘘管形成中，内镜检查可从大体上观察瘘道口的位置、形态、黏液分泌情况，并可进行活检，通过病理学检查明确瘘管周围组织的性质和恶性程度[13] [26] [27]。在胆管、小瘘管形成中通常不选择内镜检查。在无法直观检查瘘管时，EUS-FNA 的使用则有助于评估病灶恶性程度[28]。CEA 升高是区分粘液性囊肿与非粘液性囊肿的标志物，但不是恶性囊肿和良性囊肿[20] [29] [30]。≥192~200 ng/ml 的临界值诊断粘液囊肿的准确率为~80% [29]。囊液淀粉酶在 IPMN 中升高不均匀[29]。浆液性囊肿的 CEA 和淀粉酶水平通常较低。细胞学检查具有诊断意义，但敏感性受到细胞稀少的限制。囊肿液体的分子分析用于诊断仍在不断发展中。研究表明，KRAS

突变的检测更准确地支持了粘液性囊肿的诊断，但并不一定支持恶性囊肿的诊断[31] [32] [33]。最近的研究指出，GNAS 突变可能有助于区分具有临床意义的粘液性囊肿和可以保守管理的惰性囊肿[30] [34]。进行囊液分析要求检验人员具备一定的专业技能，因此在临床实践中，应当重视相关技术人员的培养与培训，提高检查结果的参考价值。

3.3. 病理学检查

通过活检或手术标本的病理学检查，可以对瘘管形成情况进行评估，包括瘘管的大小、形态和与周围组织的关系[7] [8] [9] [25]。如瘘管周围活检提示肿瘤浸润可能，则提示手术范围可能需要扩大。除此以外，病理学家会检查肿瘤组织的细胞特征，包括肿瘤细胞的形态、核分裂活性、核仁大小和数量，以及是否有异型性，还会观察有无黏液分泌和乳头状结构等等。

4. 治疗

IPMN 伴瘘管形成的治疗方案需要综合考虑患者的临床情况和病变特点。由于其罕见性和广泛的不典型增生，IPMN 伴瘘管的治疗策略尚未确定。手术治疗是目前治疗 IPMN 伴瘘管形成的主要方式之一[1] [2] [3] [10] [11] [14] [16] [17]。在 MD-IPMN 的情况下，考虑到肿瘤细胞恶性转化和导管内播散的风险较高，采用扩大胰腺切除术(如胰十二指肠切除术)，可能实现手术切缘阴性[5] [35]。此外，即使瘘管周围没有肿瘤细胞，肿瘤仍可能通过瘘管传播到受影响的器官[36]。一些病例报告，IPMN 患者在接受治疗后出现了远处转移，其中一些转移病灶与原发肿瘤的位置和形态相似，这也暗示了肿瘤可能通过某种途径传播到其他器官[36]。因此，对于伴有瘘管形成的 MD-IPMN 患者，应推荐积极的手术策略，例如扩大胰腺切除术和同时切除浸润器官。然而，对于 BD-IPMN 病例，鉴于恶性潜力较低，建议采取更保守的治疗[5]。此外，考虑到瘘管由于非恶性机制所形成的可能性，BD-IPMN 形成的瘘管并不总是需要手术[19]。因此，如果术前检查能够证明瘘管周围没有恶性细胞，则不需要切除瘘管。但是，考虑到伴随胰腺导管腺癌的风险，对于伴有瘘管形成的 BD-IPMN，可能需要进行主动监测而不进行手术[17]。此外，对于年长患者，特别需要谨慎评估手术风险和潜在的并发症，以制定个性化的治疗方案。

根据患者的具体情况，内镜治疗在一些情况下也可以作为治疗选择，例如通过内镜途径进行瘘管的引流或支架植入，以减轻症状和改善患者的生活质量[26] [27]。药物治疗在一定程度上可以帮助控制症状和病情的进展，但并非治愈的主要手段，通常作为辅助治疗手段使用[37]。

综合来看，针对 IPMN 伴瘘管形成的治疗应该是个性化的，需要根据患者的具体情况和病变特点来选择合适的治疗方案。手术治疗、内镜治疗和药物治疗在不同情况下可能会结合应用，以达到最佳的治疗效果。在治疗过程中，重点应该放在减轻症状、预防并发症和提高患者的生活质量上，同时密切监测病情的变化，及时调整治疗方案，以取得良好的治疗效果。

5. 总结与展望

研究表明，IPMN 伴瘘管形成在临床上并不常见，但近年来的报道逐渐增多。然而，IPMN 伴瘘管形成的诊治缺乏系统概述。未来的研究可以重点关注 IPMN 伴瘘管形成的治疗策略。此外，还可以探讨 IPMN 伴瘘管形成与肿瘤恶变的关系，以及如何提高对该疾病的早期诊断率和治疗效果。通过进一步的研究，有望为临床医生提供更多有效的干预手段，提高患者的生存率和生活质量。

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