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MSI-H的晚期残胃癌患者接受免疫治疗一例报道及文献复习

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摘 要

胃癌(gastric cancer, GC)是世界范围内第五大常见恶性肿瘤，也是癌症相关死亡的第四大原因。目前，晚期胃癌的治疗方法主要是化疗和靶向治疗，免疫治疗也已成为胃癌的新治疗选择。2017年帕博利珠单抗被美国FDA批准用于PD-L1表达的局部晚期或转移性胃或胃食管结合部癌(gastric cancer/gastroesophageal junction carcinoma, GC/GEJC)。此外，胃癌中高度微卫星不稳定(microsatellite instability-high, MSI-H)的患者更可能出现PD-L1过度表达，对于免疫治疗显示出更好的疗效。残胃癌(gastric stump cancer, GSC)是指胃术后残胃发生的癌，包括胃良性疾病术后5年以上残胃原发的癌及胃恶性肿瘤行胃切除术后10年以上，残胃出现的新发癌。对于不能手术切除的残胃癌，可参考胃癌的治疗方法。但对于残胃癌是否可以从免疫疗法中获益的临床证据有限。在本文中，回顾了一名MSI-H、体力状态较差的88岁男性晚期残胃癌患者在接受单药免疫治疗后，疗效达到部分缓解的过程，旨在分析总结病例，为今后该类患者的诊治提供借鉴。

关键词

残胃癌，微卫星不稳定，免疫治疗，PD-L1

A Case Report and Literature Review of Patients with Advanced Residual Gastric Cancer with MSI-H Receiving Immunotherapy

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Abstract

Gastric cancer (GC) is the fifth most common malignant tumor worldwide and the fourth leading cause of cancer-related deaths. At present, chemotherapy and targeted therapy are the main treatment methods for advanced gastric cancer. Immunotherapy has also become a new treatment option for gastric cancer. In 2017, pembrolizumab was approved by the US FDA for use in locally advanced or metastatic gastric cancer or gastroesophageal junction carcinoma (GC/GEJC) expressing PD-L1. In addition, patients with highly microsatellite instability high (MSI-H) in gastric cancer are more likely to experience overexpression of PD-L1, which shows better efficacy in immunotherapy. Gastric stump cancer (GSC) refers to the cancer of the remnant stomach after gastric surgery, including the primary cancer of the remnant stomach more than 5 years after the operation of benign gastric diseases and the new cancer of the remnant stomach more than 10 years after gastrectomy of gastric malignancies. For residual gastric cancer that cannot be surgically removed, reference can be made to the treatment methods for gastric cancer. However, there is limited clinical evidence on whether residual gastric cancer can benefit from immunotherapy. In this article, a review was conducted on an 88-year-old male patient with MSI-H and poor physical condition who achieved partial remission after receiving monotherapy immunotherapy for advanced gastric cancer. The aim was to analyze and summarize the case and provide reference for the diagnosis and treatment of this type of patient in the future.

Keywords

Residual Gastric Cancer, Microsatellite Instability, Immunotherapy, PD-L1

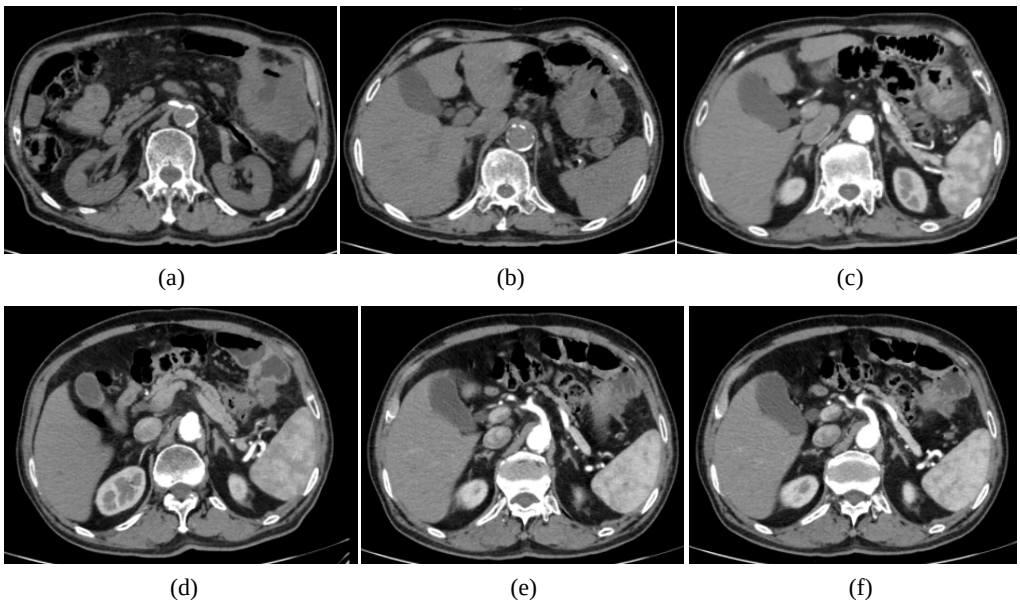
1. 引言

胃癌位居中国恶性肿瘤发病率和死亡率第 3 位，严重危害国人的生命和健康[1]。但胃癌早期症状不典型、筛查体系不完善，在中国约 70%患者确诊时胃癌多为局部进展期，预后较差[2]，MSI 是由于 DNA 错配修复系统缺陷(mismatch repair deficient, dMMR)导致微卫星片段出现的碱基对插入或丢失的现象，造成微卫星串联重复的长度发生改变，出现新的微卫星等位基因现象，是肿瘤的发生机制之一[3]。值得关注的是，最新证据表明 MSI-H 状态与胃癌的良好预后相关[4]。近几年来，免疫治疗在 MSI-H 实体瘤中的应用取得了令人兴奋的进展，MSI-H 胃癌免疫治疗的研究不断开展，但多关注于晚期胃癌[5]。对于 MSI-H 残胃癌是否可以从免疫疗法中获益的临床证据有限。本文中，一名 MSI-H、体力状态较差的 88 岁男性晚期残胃癌患者在接受单药免疫治疗后，疗效达到部分缓解，取得了令人满意的疗效。

2. 临床资料

患者男，88 岁，既往因胃穿孔行胃大部切除术，2022 年 6 月因腹痛 1 月余首次入院。查腹部 CT 平扫示：胃大弯外侧可见最大截面约 49 × 63 mm 的片团灶；脾门区可见直径 20 mm 的结节；左侧肾上腺结节样增粗(图 1)。2022 年 6 月行胃镜检查提示残胃癌(图 2)，病例活检结合免疫组化结果诊断为：低分化

腺癌。2022 年 6 月 30 于外院行 PET-CT 提示：胃体大弯侧局部伴软组织密度肿块，大小约 89 × 109 mm；脾胃间隙内数枚增大淋巴结，大者直径约 19.5 mm；左侧肾上腺外侧一直径约 8.5 mm 软组织密度结节，上考虑残胃癌并周围淋巴结转移、左侧肾上腺转移。后患者再次就诊于青岛市中心医院，2022 年 7 月 16 日微卫星序列不稳定性检测提示：MSI-H。遂于 2022 年 7 月 19 日接受恩沃利单抗免疫治疗，具体为：恩沃利单抗 150 mg ih qw。经过 3 月的治后复查腹部增强 CT，患者胃大弯侧肿物及脾门区淋巴结转移灶较前缩小(图 1)，后继续恩沃利单抗维持治疗，期间每 3 个月复查腹部增强 CT。2023 年 3 月 3 复查腹部增强 CT，胃大弯侧肿物及脾门区淋巴结转移灶较前明显缩小(图 1)，病灶稳定，评价疗效为部分缓解。

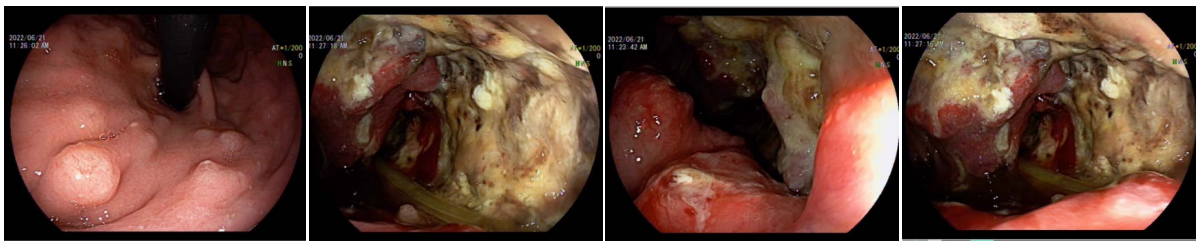


(a) (b) (c)

(d) (e) (f)

注：(a)为治疗前胃大弯侧病灶；(b)为治疗前脾门区淋巴结转移灶；(c)为治疗 3 月后胃大弯侧病灶；(d)为治疗 3 月后脾门区淋巴结转移灶；(e)为治疗 9 月后胃大弯侧病灶；(f)为治疗 9 月后脾门区淋巴结转移灶

Figure 1. Comparison of abdominal CT images before and after treatment
图 1. 治疗前后治疗前后腹部 CT 影像对比



(a) (b) (c) (d)

注：(a)为残胃体，可见散在数枚息肉样增生灶；(b)、(c)、(d)分别为鞍部、吻合口及输出襻，可见巨大不规则凹陷溃烂性病变，表面覆污苔，周围粘膜堤样隆起

Figure 2. Image of gastroscopy before treatment
图 2. 治疗前胃镜检查图像

3. 文献复习

胃癌是消化道常见的恶性肿瘤，在中国，胃癌的新发病例和死亡病例均占全世界的 40%以上[6]，是

中国第三常见的恶性肿瘤[1]。对于早期患者，诊断后及时根治性手术可在一定条件下有效控制甚至治愈，有研究报道，早期胃癌的5年生存率超过90% [7]。然而，由于起病隐匿，进展迅速，大多数胃癌患者在第一次诊断时就已经超出了早期阶段。即使采用手术和辅助化疗/放化疗，II期以上患者的5年生存率也急剧下降，仅有34%左右[8]。以5-氟尿嘧啶(5-fluorouracil, 5-FU)为基础联合铂类或紫杉醇化疗是晚期胃癌的常规治疗方法。然而，这些治疗的临床效果非常有限，中晚期胃癌常规化疗的中位生存期仅为8个月[9]。目前针对晚期胃癌靶向治疗的III期临床研究结果差强人意，靶向药物选择相对有限，只有曲妥珠单抗、雷莫芦单抗和阿帕替尼被证实有效[10] [11] [12]。残胃癌(gastric stump cancer, GSC)是指胃术后残胃发生的癌，包括胃良性疾病术后5年以上残胃原发的癌及胃恶性肿瘤行胃切除术后10年以上，残胃出现的新发癌[13]。对于不能手术切除的残胃癌，可参考胃癌的治疗方法。

以免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)为代表的肿瘤免疫治疗给晚期胃癌患者带来了新的希望[14]。II期研究KEYNOTE-059显示了帕博利珠单抗单药治疗的结果，帕博利珠单抗组的客观缓解率(objective response rate, ORR)为11.6%，中位无进展生存期(progress free survival, PFS)为2个月，中位总生存期(overall survival, OS)为5.6个月[15]。基于这项研究的结果，美国食品和药物管理局(Food and Drug Administration, FDA)于2017年9月批准帕博利珠单抗作为PD-L1联合阳性评分(combined positive score, CPS) ≥ 1的复发性局部晚期或转移性胃癌或胃食管结癌(GEJC)患者的三线治疗。然而，KEYNOTE-061研究、KEYNOTE-062研究为代表的III期临床研究表明与传统化疗相比，免疫治疗单药或者联合化疗一线或二线应用并没有表现出显著的生存获益[16] [17]。

免疫治疗在晚期胃癌的一线应用一直是临床研究的热点，KEYNOTE-062研究亚组分析结果表明，亚洲晚期胃癌患者患从一线免疫治疗中获益更加明显，OS优于总体人群，帕博利珠单抗组2年生存率高于单纯化疗组接近2倍(CPS ≥ 1, 45% vs 23%; CPS ≥10, 54% vs 27%) [17]。评估与FOLOFX或XELOX方案化疗相比，纳武利尤单抗联合化疗或伊匹木单抗用于治疗初治晚期或转移GC/GEJC/EAC患者的疗效CHECKMATE-649研究是一项全球多中心、随机对照、开发标签的临床研究，研究结果表明在PD-L1 CPS ≥ 5患者中，OS (14.4个月 vs 11.1个月，HR = 0.71，98.4% CI：0.59~0.86，$P < 0.001$)和PFS (7.7个月 vs 6.0个月，HR = 0.68，98% CI：0.56~0.81，$P < 0.001$)均观察到显著性差异[18]。在亚组分析中，中国人群观察到与总体人群一致的ORR、PFS和OS获益，并且死亡风险较全球人群降低更加显著(39% vs 20%)。针对中国人群ORIENT-16 III期临床研究表明对比XELOX方案，信迪利单抗联合化疗在CPS ≥ 5人群(18.4个月 vs 12.9个月，HR = 0.66，95% CI：0.51~0.86，$P = 0.0023$)及全人群(15.2个月 vs 12.3个月，HR = 0.77，95% CI：0.63~0.94，$P = 0.0090$)中均观察到OS显著获益[19]。

不同的免疫治疗药物在不同的研究中对不同阶段的胃癌患者疗效不同。这使得ICIs的临床疗效难以预测，因此有必要探索潜在的标志物来评估不同阶段可能对ICIs治疗有良好反应的患者。在III期KEYNOTE-062试验中，作为晚期胃癌的一线治疗，帕博利珠单抗联合化疗未能表现出优于单独化疗的OS。然而，当比较MSI-H肿瘤患者的生存期时，帕博利珠单抗联合化疗表现出更好的生存获益[17]。MSI是指因为DNA错配修复系统缺陷(dMMR)造成微卫星片段出现的碱基对插入或丢失的现象，导致微卫星串联重复的长度发生改变，从而出现新的等位基因，是肿瘤的发生机制之一[3]，MSI-H或dMMR肿瘤在多个基因中表现出频繁突变，有助于增强新抗原的表达，增加$CD8^+$T细胞浸润以及相关免疫检查点分子在肿瘤微环境中的表达[20]。近期新发表的一项纳入18例dMMR/MSI-H肿瘤患者的临床试验表明，使用恩沃利单抗胃癌患者的ORR达55.6%，疾病控制率达83.3%，且展现出良好的药物安全性[21]。遗憾的是，上述研究中关于MSI-H胃癌的数据均为亚组分析，样本量较少，且治疗效果并不如结肠癌理想，但这些研究结果为MSI-H胃癌免疫治疗的探索提供了重要的证据支持，展示出良好的治疗前景。

然而，在以上针对胃癌的研究中反复出现的问题是缺乏对残胃癌病例的报道，根据目前的文献，残胃癌的发病率占所有胃癌的 2%~6% [22] [23]，其发病率与胃切除手术后时间相关。一项国外的研究数据表明，与原发性胃癌相比，残胃癌 MSI 状态明显更高，这表明这些患者将是免疫治疗的良好候选者[24]。本例患者接受恩沃利单抗免疫治疗后，病灶达到部分缓解，至今已存活 11 月，目前仍继续随访。当前针对 MSI-H 晚期残胃癌患者免疫治疗的相关研究十分有限，本文旨在分析总结病例，为今后该类患者的诊治提供借鉴。

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