• 个案报道 •

纳武单抗联合放化疗治疗头颈部腺样囊性癌伴多发肝转移 1 例

尹清萍,陈方红,周行△,冯梅△,王鹤

637000 四川 南充,川北医学院 临床医学系(尹清萍);615000 四川 西昌,凉山彝族自治州第一人民医院 肿瘤科(陈方红);610041 成都,四川省肿瘤医院·研究所,四川省癌症防治中心,电子科技大学医学院 日间化疗(周行)、放疗科(尹清萍、冯梅、王鹤)

[摘要] **目的:** 提供免疫治疗在头颈部腺样囊性癌中的应用,为晚期腺样囊性癌的治疗提供参考。**方法:** 回顾性分析 1 例本院收治的头颈部腺样囊性癌伴多发肝转移的治疗过程,并查阅相关文献资料进行总结。**结果:** 经原发头颈部腺样囊性癌扩大切除术后,拟行辅助放化疗,但在化疗前患者出现多发肝转移,经多学科诊疗模式讨论后行常规放化疗联合免疫的综合个体化方案。但在第 5 周期治疗后患者出现 1 型糖尿病而停止治疗,遂后未接受任何抗肿瘤治疗,仅门诊定期复查。目前患者病情平稳,原发病灶控制良好,肝转移病灶几乎完全缓解。**结论:** 鉴于晚期头颈部腺样囊性癌缺乏具体的治疗共识,且出现多发肝转移的临床罕见,在常规放化疗的基础上联合免疫可能为晚期腺样囊性癌患者提供新的选择。

[关键词] 纳武单抗;头颈部;腺样囊性癌;肝转移

[中图分类号] R739.91 [文献标志码] B doi:10.3969/j.issn.1674-0904.2020.12.015

引文格式: Yin QP, Chen FH, Zhou H, *et al*. Treatment of head and neck adenoid cystic carcinoma with multiple hepatic metastases by nivolumab combined with radiotherapy and chemotherapy: A case report[J]. J Cancer Control Treat, 2020, 33(12):997-1001. [尹清萍,陈方红,周行,等. 纳武单抗联合放化疗治疗头颈部腺样囊性癌伴多发肝转移 1 例[J]. 肿瘤预防与治疗,2020,33(12):997-1001.]

腺样囊性癌是一种罕见的高度恶性肿瘤,通常起源于涎腺,也有文献报道在其他部位,如:皮肤、乳腺、宫颈等[1]。其每年的发病率为 3~4.5/100 万,占涎腺肿瘤的 10% 且仅占所有头颈部恶性肿瘤的 1%[2-3],约 58% 的头颈部腺样囊性癌原发于唾液腺[4]。其特点为生长缓慢、有侵袭性、易局部复发和远处转移[5-6]。常见的转移部位有肺、骨、肝、皮肤等,极少转移至颅脑[7-10]。手术为首选治疗,术后予以常规辅助治疗,但针对有远处转移的患者目前尚无具体的治疗共识。现将本院 2018 年收治的 1 例头颈部腺样囊性癌伴多发肝转移的治疗全过程报道如下,并结合相关文献进行复习、总结,为临床治疗提供参考。

1 临床资料

1.1 一般资料

患者,女,30 岁,因"右侧上腭包块伴疼痛 2 周"于 2018 年 5 月 31 日就诊于某三甲医院,行副鼻窦 CT 示:右侧软腭区团块状影,性质待定,建议进一步检查;双侧颈部多发淋巴结显示。为进一步诊疗于 2018 年 6 月 2 日入住本院头颈外科二病区,入院后完善相关检查,副鼻窦增强 CT 示:右软腭偏后份见软组织肿块占位,较大层面约 3.9 cm × 2.7 cm,增强后较明显不均性强化,病灶与右侧扁桃体分界欠清,后上方达右侧鼻腔后份并与右后下鼻甲分界不清,向右前与牙龈区分界不清,邻近骨质密度未见明显异常,考虑恶性肿瘤可能。双侧颈部颌下见稍大淋巴结,右侧颈部较大者约 0.6 cm × 1.0 cm。颈部彩超示:双颈查见小淋巴结,皮髓质分界清楚,未见明显血流信号。胸部平扫 CT、腹部彩超及全身骨扫描未见明显异常。综合诊断:右软腭占位,性质待定。

1.2 肿瘤治疗

排除禁忌后于 2018 年 6 月 7 日在全麻下行上颌骨肿块扩大切除术 + 临近皮瓣修复术 + 口腔修复膜修复术。术中见右上腭 2 cm 隆起,质硬,边界不清,活动度差,周围上颌骨骨质未见明显破坏,各壁完整,周围软组织受累,术中冰冻示:"右上腭肿块"腺样囊性癌。术后病检示:"右上腭肿块"腺样囊性癌,CD43(灶性阳性),CD117(+)(图 1)。综合诊

[收稿日期] 2019-10-28 [修回日期] 2020-06-05

[通讯作者] △周行,E-mail:2339929436@qq.com;△冯梅,E-mail:freda_fm@126.com

断为：右上颚腺样囊性癌（T3N0M0），术后予以补液、对症支持治疗后好转出院。术后 1 月拟返院行辅助放化疗。于 2018 年 7 月 10 日再次入院，腹部彩超示：右前叶肝实质内见两枚低回声结节，较大约 1.0 cm×0.9 cm，边界较清，形态较规则。其内未见明显血流信号，经肘正中静脉注入超声造影剂，较大结节动脉相快速不均匀高增强，造影后肝内见多个低回声结节，门脉相、延迟相均快速消退呈低增强，考虑继发性肝癌。遂进一步行全腹部增强 MRI 示：肝内多发结节，考虑肝转移瘤。另肝右后上段小血管瘤可能（图 2）。肝脏结节穿刺活检示：查见癌细胞，结合患者病史、影像学及病理综合诊断为：头颈部腺样囊性癌伴多发肝转移 IV 期。经全院多学科诊疗模式讨论，患者头颈部腺样囊性癌术后发现肝脏多发转移，PD-L1 表达阴性，但有强烈的治疗意向，参考治疗原则及国际晚期腺样囊性癌相关试验及结果拟行肝脏局部放疗联合全身化疗加免疫的综合个体化治疗。充分告知患者及家属病情，患者及家属签字要求使用免疫治疗。具体治疗为：于 7 月 10 日开始行全身化疗联合免疫治疗，方案为：纳武单抗（Opdivo）200 mg D0 + GP 化疗（吉西他滨 1 000 mg/m^2，D1，8；顺铂 75 mg/m^2，D1 ~ 3；21 天为一个周期）。于 7 月 24 日行肝脏局部放疗，放疗剂量为：4.0Gy/f×10f = 40Gy。

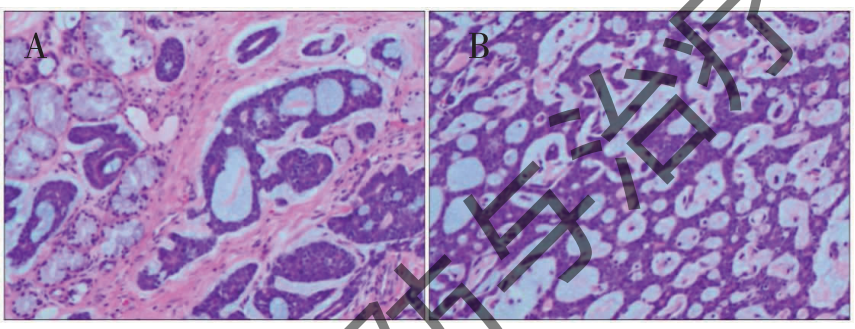

图 1　病理检查图示

Figure 1. Pathological Results

A. The tumor showed cribriform and invasive growth pattern in microscopic view; B. Hyperchromatic-angulated nuclei composed of myoepithelium and ductal epithelium（HE, ×100）.

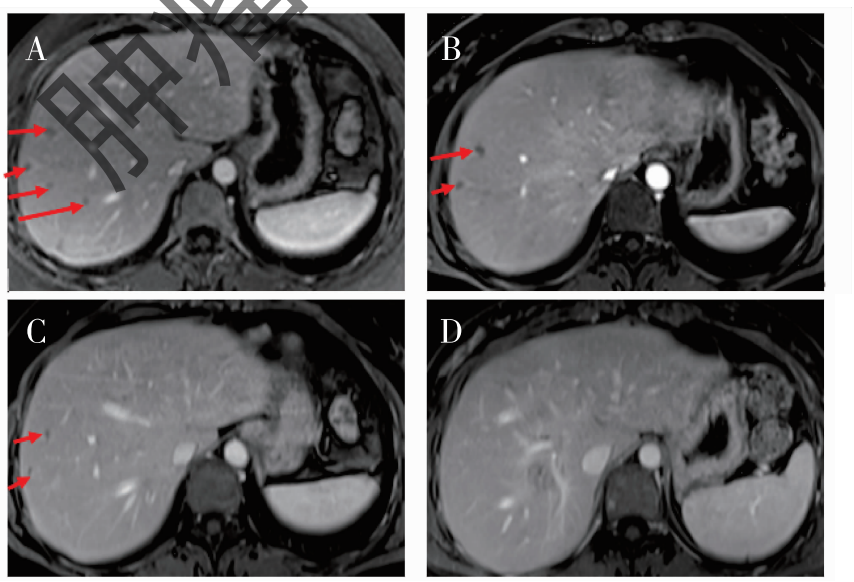

图 2　肝脏 MRI 变化情况

Figure 2. MRI of Liver Lesions

A. Before treatment (July 2, 2018, lesions as indicated by the red arrows); B. 4 cycles after treatment (September 30, 2018, lesions as indicated by the red arrows); C. 5 Cycles after treatment (October 23, 2018, lesions as indicated by the red arrows); D. 12 mouths after treatment (October 16, 2019).

1.3 治疗相关副反应

在第 5 周期治疗后，患者因“意识模糊 1 小时”急诊入当地医院 ICU，实验室检查见表 1，根据患者的症状、体征及实验室检查诊断为糖尿病酮症酸中毒。但患者既往无糖尿病病史及家族史，结合 GAD、IA-2Ab 及 HbA1c 等实验室指标诊断为 I 型糖尿病。最高血糖为 15.77 mmol/L，已达免疫相关不良反应 III 级，暂停免疫治疗，予以胰岛素控制血糖，目前患者血糖控制可。

表 1 ICU 实验室检查结果

Table 1. Laboratory Test Results in ICU

Laboratory test	Result	Reference value
HbA1c	8.2%	4.60 – 6.10
Glucose	24.8 mmol/L	3.90 – 6.10
Urinary ketone	(–)	
pH	7.23	7.35 – 7.45
pCO_2	49.1 mmHg	32 – 48
pO_2	71.5 mmHg	83 – 108
HCO_3	– 26.4 mmol/L	21 – 28
Anion gap	33.5 mmol/L	
Amylase	75 IU/L	30 – 110
Lipase	48.7 U/L	23 – 300
GAD antibody	1,165.82 U/ML	0.00 – 5.00
IA – 2Ab antibody	0.29 U/mL	1.00 – 2.00
ZnT8 antibody	Negative (–)	Negative (–)
Insulin autoantibody	0.25 U/mL	0.00 – 0.40

GAD: Glutamic acid decarboxylase.

2 讨 论

腺样囊性癌恶性程度高，远处转移是常见的死亡原因之一[11]，中位生存期仅为 13.8 个月[12]。已有一些头颈部腺样囊性癌伴肝转移的病例报道，但大多数案例是孤立性转移，对于这部分患者予以辅助化疗后行肝孤立性病灶切除术，术后疗效可。但对于头颈部腺样囊性癌伴多发肝转移目前报道罕见且无具体的治疗共识。此外，另一个病例报告：原发性肺腺样囊性癌伴肝转移经新型靶向药物埃克替尼治疗有效[13]。

当前，免疫疗法是肿瘤治疗的研究热点，鉴于免疫治疗对多种恶性肿瘤有效，特别是抗 PD 途径，因此整合已注册的腺样囊性癌或唾液腺癌相关的临床试验，见表 2，其中一些已经显示出令人鼓舞的结果。在一项 Ib 期 KEYNOTE-028 试验中，纳入了 26 名 PD-L1 阳性的晚期唾液腺癌患者，每 2 周给予帕博利珠单抗 10mg/kg。经过 20 个月的治疗随访，其客观缓解率为 12%，其中 3 例患者达到了部分缓解。疾病控制率为 58%，中位缓解时间为 4 个月[14]。在另一项正在进行的腺样囊性癌研究中显示：放化疗似乎会增加 CD8 + 的 T 效应细胞，减少 T 细胞的调节并促进全身免疫反应[11]。一项回顾性研究也表明，抗 PD 疗法与常规放化疗的结合能改善患者的总生存期，这对晚期腺样囊性癌也许是一种有希望的治疗策略[15]。

表 2　腺样囊性癌或唾液腺癌抗 PD 治疗的临床试验

Table 2. Some Clinical Trails on of Anti-PD Therapy ACC or SGC (https://www.clinicaltrials.gov/, 06/16/19)

Title	NCT number	Conditions	Interventions	Characteristics
Nivolumab and ipilimumab in treating patients with metastatic/recurrent ACC of all sites and non-ACC salivary gland cancer	NCT03146650	· Major SGC · Minor SGC · Recurrent SGC · Stage IV major SGC	· Biological: Ipilimumab · Biological: Nivolumab	· Study type: Interventional study · Phase: Phase 2 · Study design: Intervention model: Single group assignment Masking: None (open label) Primary purpose: Treatment
Nivolumab and ipilimumab in treating patients with rare tumors	NCT02834013	· Acinar cell carcinoma · ACC · Adrenal cortex carcinoma · Adrenal gland pheochromocytoma · ⩾75 cases	· Procedure: Biospecimen collection · Biological: Ipilimumab · Biological: Nivolumab	· Study type: Interventional study · Phase: Phase 2 · Study design: Intervention model: Single group assignment Masking: None (open label) Primary purpose: Treatment
Nivolumab in recurrent or metastatic salivary gland carcinoma of the head and neck	NCT03132038	· Salivary gland carcinoma · Metastatic cancer · Recurrent cancer	· Drug: Nivolumab	· Study type: Interventional study · Phase: Phase 2 · Study design: Intervention model: Single group assignment Masking: None (open label) Primary purpose: Treatment
Phase I study of enadenotucirev and PD-1 inhibitor in subjects with metastatic or advanced epithelial tumors	NCT02636036	· Colorectal cancer · Bladder carcinoma · HNSCC · SGC · NSCLC	· Biological: Enadenotucirev · Biological: Nivolumab	· Study type: Interventional study · Phase: Phase 2 · Study design: Intervention model: Single group assignment Masking: None (open label) Primary purpose: Treatment
Pembrolizumab with or without radiation in patients with recurrent or metastatic adenoid cystic carcinoma	NCT03087019	· Adenoid cystic carcinoma	· Radiation: Radiation · Drug: Pembrolizumab	· Study type: Interventional study · Phase: Phase 2 · Study design: Allocation: Randomized Intervention model: Parallel assignment Masking: None (open label) Primary purpose: Treatment
Pembrolizumab with chemotherapy for poorly chemo-responsive thyroid and salivary gland tumors	NCT03360890	· Thyroid cancer · Salivary gland cancer	· Drug: Pembrolizumab · Drug: Docetaxel	· Study type: Interventional study · Phase: Phase 2 · Study design: Allocation: Non randomized Intervention model: Parallel assignment Masking: None (open label) Primary purpose: Treatment
Study of pembrolizumab (MK-3475) in participants with advanced solid tumors (MK-3475-158/KEYNOTE-158)	NCT02628067	· Advanced cancer	· Biological: Pembrolizumab	· Study type: Interventional study · Phase: Phase 2 · Study design: Intervention model: Single group assignment Masking: None (open label) Primary purpose: Treatment

ACC: Adenoid cystic carcinoma; SGC: Salivary gland carcinoma; NCT: National Clinical Trial; PD-1: Programmed death 1; HNSCC: Head and neck squamous cell cancer; NSCLC: Non-small cell lung cancer.

本病例报道了头颈部腺样囊性癌术后伴多发肝转移,这种情况在文献中少有报道。根据美国国家综合癌症网络指南显示:一旦出现远处转移,应优先考虑参加临床试验,但目前中国无相关临床试验。

因此借鉴已注册的临床试验，经讨论后行常规的放化疗联合纳武单抗的综合、个体化治疗。在治疗后肝脏病灶逐渐缓解，疗效评价达到部分缓解甚至在影像学上达到完全缓解。更重要的是，患者在治疗过程中因免疫治疗的副作用而停止所有抗肿瘤治疗后仍可保持疾病稳定期长达 16 个月及以上，这较晚期腺样囊性癌患者中位生存期明显延长。这为免疫治疗在晚期腺样囊性癌中的应用提供了新的选择。然而，仍需进一步的临床研究以更好地评估免疫治疗的疗效和安全性。

[参考文献]

[1] Qin YW, Xiao S, Yong CL, *et al*. Adenoid cystic carcinoma in ventricle of larynx: An interesting case[J]. Medicine (Baltimore), 2018, 97(50): e13622.

[2] Coca-Pelaz A, Rodrigo JP, Bradley PJ, *et al*. Adenoid cystic carcinoma of the head and neck-An update[J]. Oral Oncol, 2015, 51(7): 652-661.

[3] Laurie SA, Ho AL, Fury MG, *et al*. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: A systematic review[J]. Lancet Oncol, 2011, 12(8): 815-824.

[4] Ellington CL, Goodman M, Kono SA, *et al*. Adenoid cystic carcinoma of the head and neck: Incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data[J]. Cancer, 2012, 118(18): 4444-4451.

[5] Harish K, Gouri SRM. Adenoid cystic carcinoma of the parotid metastasizing to liver: case report[J]. BMC Cancer, 2004, 4: 41.

[6] Zemni I, Tounsi N, Bouraoui I, *et al*. A single liver metastasis from adenoid cystic carcinoma of the parotid gland: Case report[J]. Investig Med High Impact Case Rep, 2019, 7(2): 2324709619879631.

[7] Spiro RH. Distant metastasis in adenoid cystic carcinoma of salivary origin[J]. Am J Surg, 1997, 174(5): 495-498.

[8] Balducci G, Sagnotta A, Muroni M, *et al*. An unusual case of exclusive liver metastases from adenoid cystic carcinoma of the submandibular gland: A role for surgery? Report of a case[J]. Surg Today, 2011, 41(4): 596-599.

[9] Dillon PM, Chakraborty S, Moskaluk CA, *et al*. Adenoid cystic carcinoma: A review of recent advances, molecular targets, and clinical trials[J]. Head Neck, 2016, 38(4): 620-627.

[10] Chang CF, Hsieh MY, Chen MK, *et al*. Adenoid cystic carcinoma of head and neck: A retrospective clinical analysis of a single institution[J]. Auris Nasus Larynx, 2018, 45(4): 831-837.

[11] Sridharan V, Liao X, Chau NG, *et al*. Immune profiling of adenoid cystic carcinoma: PD-L2 expression and associations with tumor-infiltrating lymphocytes[J]. Cancer Immunol Res, 2016, 4(8): 679-687.

[12] Alsaab HO, Sau S, Alzhrani R, *et al*. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: Mechanism, combinations, and clinical outcome[J]. Front Pharmacol, 2017, 8: 561.

[13] Song Z, Wu W, Zhang Y. Effective treatment with icotinib in primary adenoid cystic carcinoma of the lung with liver metastasis[J]. J Thorac Oncol, 2014, 9(9): e67-e69.

[14] Cohen RB, Delord JP, Doi T, *et al*. Pembrolizumab for the treatment of advanced salivary gland carcinoma: Findings of the phase 1b KEYNOTE-028 study[J]. Am J Clin Oncol, 2018, 41(11): 1083-1088.

[15] Sridharan V, Liao X, Chau NG, *et al*. Immunologic profiling of adenoid cystic carcinoma (acc)[J]. J Immunotherapy Cancer, 2015, 3(S2): 105.