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·防治实践·

卡瑞利珠单抗致牙龈及唇化脓性肉芽肿1例报道及文献回顾

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【摘要】 目的 探讨卡瑞利珠单抗致口腔颌面部化脓性肉芽肿的临床表现、病理特征及治疗。**方法** 报道1例卡瑞利珠单抗致牙龈及唇化脓性肉芽肿病例并结合文献进行系统性回顾分析。**结果** 患者使用卡瑞利珠单抗治疗肝癌4个月后，出现全身反应性毛细血管增生症（reactive capillary hemangiomas，RCH），随后出现下唇及牙龈多发肿物，患者行牙周基础治疗后，切除下唇及牙龈肿物并停用卡瑞利珠单抗，病理结果为牙龈化脓性肉芽肿/肉芽肿型血管瘤，术后随访口腔内未见新生肿物。文献回顾表明，RCH是卡瑞利珠单抗最常见的药物不良反应，发生于口腔者较少。目前尚未明确RCH病因，有研究表明卡瑞利珠单抗可能通过激活血管内皮细胞使其增殖为血管瘤；联合使用卡瑞利珠单抗安全性优于单用；RCH有自限性，大多数停药后可自行消退；若肿物引起功能障碍，可行手术切除。**结论** 卡瑞利珠单抗可致口腔颌面部反应性毛细血管增生症并发化脓性肉芽肿。

【关键词】 卡瑞利珠单抗；程序性细胞死亡受体-1；恶性肿瘤；免疫治疗；药物不良反应；口腔；反应性毛细血管增生症；血管瘤；血管内皮细胞；化脓性肉芽肿
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Pyogenic granuloma of the gums and lips caused by camrelizumab: case report and literature review

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【Abstract】 Objective To investigate the clinical manifestations, pathological features, and treatment of oral and maxillofacial pyogenic granulomas induced by camrelizumab. **Methods** A case of pyogenic granuloma of the gums and lips caused by camrelizumab was reported along with a literature review. **Results** After 4 months of treatment with camrelizumab for liver cancer, the patient developed systemic reactive capillary hyperplasia (RCH), followed by multiple masses on the lower lip and gingiva. After periodontal therapy, the masses on the lower lip and the gingiva were removed, and camrelizumab administration was stopped. The pathological result was gingival pyogenic granuloma/granulomatous hemangioma. No new masses were found in the oral cavity during postoperative follow-up. A review of the literature showed that RCH is the most common adverse drug reaction to camrelizumab but it occurs infrequently in the oral cavity. At present, the etiology of RCH has not been clarified, but the research has shown that camrelizumab may trigger tissue proliferation into hemangiomas by activating vascular endothelial cells, and the combined use of camrelizumab is safer than single use. RCH is self-limiting and most cases resolve spontaneously after discontinuation of the drug. If the mass

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causes dysfunction, surgical excision is feasible. **Conclusion**　Camrelizumab can cause oral and maxillofacial reactive capillary hyperplasia complicated by pyogenic granuloma.

【Key words】 camrelizumab; PD-1; malignant tumor; immunotherapy; adverse drug reaction; oral cavity; reactive capillary hemangiomas; hemangioma; vascular endothelial cells; pyogenic granuloma
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免疫治疗是目前最受关注的肿瘤治疗方法之一，在多种实体恶性肿瘤中有显著疗效。卡瑞利珠单抗（SHR-1210）是目前常用的国产程序性细胞死亡受体-1（programmed cell death-1，PD-1）抑制剂，其最常见的免疫相关不良事件是反应性毛细血管增生症（reactive capillary hemangiomas，RCH），主要发生在头部、面部和躯干的皮肤表面，但发生于口腔黏膜的不良反应少有报道。本文报道1例应用卡瑞利珠单抗治疗肝癌的患者，治疗期间除发生全身皮肤的反应性毛细血管增生外，下唇及牙龈黏膜出现了化脓性肉芽肿病变，并对相关文献进行复习，以期为临床提供参考。

1　临床资料

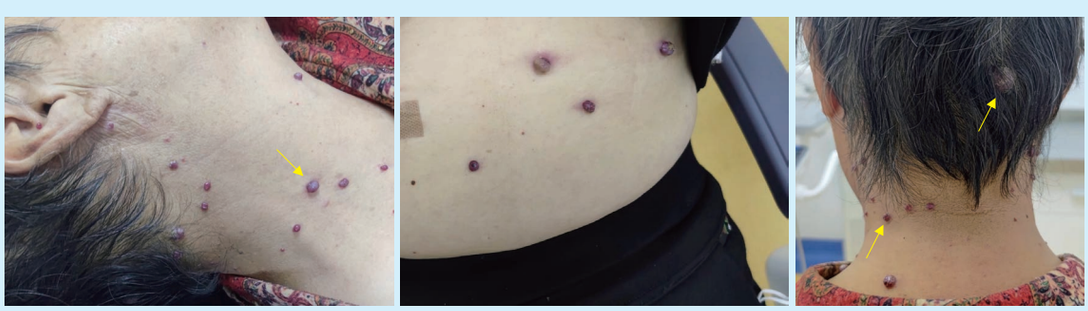
1.1　病史及检查

患者，女，62岁，1个月前发现上颌牙龈肿物，约“蚕豆”大小，下唇肿物约“黄豆”大小，无疼痛、易出血，自行涂抹中药粉剂，具体成分及用量不详，无效果。肿物生长迅速，影响进食，于2021年12月14日来本院口腔颌面外科就诊。该患者肝癌病史5年，行经导管肝动脉化疗栓塞术治疗8次后，于6个月前开始应用卡瑞利珠单抗（生产批号：S20190027，苏州盛迪亚生物有限医药有限公司，中国），用法为200 mg静脉注射，3周1次，同时口服瑞戈非尼（患者自行国外代购碧康制药股份有限公司药品，产地：孟加拉国），160 mg/d。2个月前患者发现腹部皮肤有多个“红斑”，迅速突起于皮肤表面，遍及全身皮肤。

查体：全身多发肿物（图1），呈紫红色，大小不一，部分肿物表面破溃。上颌腭侧牙龈及下唇多发肿物（图2）。左上颌前牙区腭侧牙龈肿物（图2a）约2.0 cm × 1.0 cm × 1.0 cm，质韧，有蒂，触之易出血。下唇多个肿物，约0.5 cm × 0.5 cm × 0.5 cm，圆形，表面破溃、结痂（图2b），口腔卫生状况一般，部分龈缘充血。21～23牙齿无明显松动。

1.2　牙龈及唇化脓性肉芽肿治疗及随访结果

牙周基础治疗后，给予聚维酮碘漱口液漱口，口服抗生素，经患者同意后在局麻下行左上颌前牙区腭侧牙龈肿物（图2c）及下唇肿物（图2d）切除术，牙周支持治疗。术后病理诊断：左上颌前牙区腭侧牙龈肿物为化脓性肉芽肿/肉芽肿型血管瘤，下唇为化脓性肉芽肿/肉芽肿型血管瘤伴灶性出血坏死。病理检查显示：病变由纤维性间隔分隔，呈分叶状。由增生的内皮细胞构成的小叶组成，小叶内含较小、多少不一的血管腔隙，内皮细胞呈多边形或短梭形，细胞界限不清。表皮形成围领状，



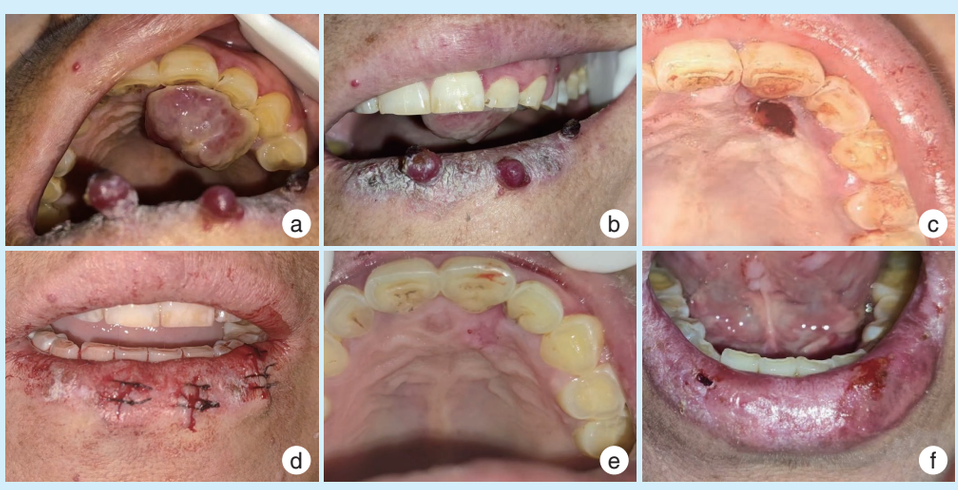
Multiple capillary hemangiomas of the skin were found (arrows)

Figure 1　A patient with hepatocellular carcinoma developed systemic cutaneous reactive capillary hemangiomas after 4 months of camrelizumab administration

图1　肝癌患者使用卡瑞利珠单抗4个月后出现全身反应性毛细血管增生症

部分包绕病变。间质水肿，富于炎细胞。表皮呈化脓性改变（图3）。

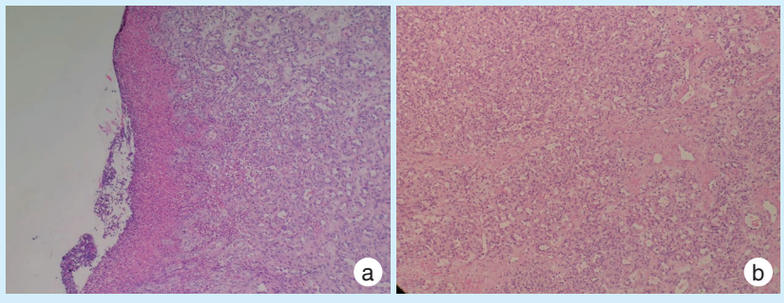
术后2个月复诊，左上颌前牙区腭侧牙龈肿物切除术后愈合较好，牙龈颜色、质地正常（图2e）；下唇愈合良好（图2f）。但因全身皮肤病变的不断形成，患者心理难以承受，与其肿瘤科医生沟通后，已停止免疫治疗2个月，目前仅使用瑞戈非尼靶向药物，患者口内未发现新生肿物，全身皮肤肿物也有所减少。



a: the gingival mass is "tumor-like", growing rapidly, purple - red, tough and pedunculatel. b: "pearl - like" mass on the lower lip, multiple, easy to break and bleed, and the surface was covered with scabs. c: the gingival mass was excised by a high frequency electrotome. d: the lower lip was sutured after resection of the mass. e: the gingival mucosa healed 2 months after resection. f: the mucosa of the lower lip was smooth and no new mass was seen 2 months after resection

Figure 2　A patient with hepatocellular carcinoma developed pyogenic granulomatous lesions in the mouth after 4 months of camrelizumab administration

图2　肝癌患者使用卡瑞利珠单抗4个月后口腔出现化脓性肉芽肿性病变



a: lip biopsy. b: gingiva biopsy. The lesions were separated by fibrous septa and were lobulated. The lobules were composed of proliferating endothelial cells. The lobules contained smaller, more or less variable vascular cavities with polygonal or short spindle-shaped endothelial cells. The epidermis formed a collar that partially surrounded the lesion. Interstitial edema, rich in inflammatory cells. The epidermis was purulent. HE (×100)

Figure 3　Histopathological findings of the lower lip and gingiva biopsies

图3　下唇及牙龈化脓性肉芽肿活检组织病理学观察

2　讨　论

肿瘤可诱导T淋巴细胞和B淋巴细胞等免疫细胞表面PD-1信号传导[1-2]，同时肿瘤细胞过度表达其配体（主要是PD-L1）[3]，二者结合后引起免疫抑制[4]，进而利于肿瘤细胞的生长和繁殖。免疫治疗是指恢复免疫系统和肿瘤细胞之间的平衡，主要包括单克隆抗体类免疫检查点抑制剂（immune checkpoint inhibitor，ICIs）、治疗性抗体、癌症疫苗、细胞治疗[5]。免疫检查点抑制剂与细胞毒性或靶向药物的抗肿瘤机制不同，其通过阻断负调节因子来激活内源性免疫细胞以杀死肿瘤细胞[6-7]。PD-1和PD-L1通路的免疫检查点阻断已成为乙肝病毒导致的晚期肝细胞癌（hepatocellular carcinoma，HCC）、肺癌、黑色素瘤、肾细胞癌、头颈部鳞状细胞癌等癌症中最具潜力的治疗策略之一[1, 8-10]。2019年5月31日，经国家药品监督管理局批准，我国自主研发的PD-1抑制剂卡瑞利珠单抗（SHR-1210，Camrelizumab，艾瑞卡）获批上市。该药物可用于多种恶性肿瘤的治疗，包括肝癌、食管鳞癌、胃/胃食管交界处癌、鼻咽癌、霍奇金淋巴瘤、B细

胞淋巴瘤和非鳞状、非小细胞肺癌[11-12]。

随着卡瑞利珠单抗应用越来越多，临床上发现RCH是其最常见特殊不良反应，并且仅在接受卡瑞利珠单抗治疗的患者中发现[6]，主要发生在头部、面部和躯干的皮肤上，皮肤RCH的发病率约为80%[13-15]，仅在少数情况下，可并发其他部位的RCH[16]，发生于口腔甚少。Wang等[16]报道全国范围内的多中心2期卡瑞利珠单抗治疗晚期肝癌试验，217例受试者中RCH在口腔中的发生率为1.4%（口腔黏膜2例，牙龈1例），按形态可分为“红痣样”、“珍珠样”、“桑椹样”、“斑块样”、“瘤样”。本研究报道病例中，肿物组织病理学改变均表现为化脓性肉芽肿/肉芽肿型血管瘤，通过检索相关文献，目前未见报道。单纯的口腔化脓性肉芽肿发病机制涉及多种因素，但确切原因尚不清楚，目前认为损伤可能导致促血管生成因子和抗血管生成因子失衡，轻微创伤引起的反应性肉芽组织可能是促成因素，其他可能的诱发因素包括感染和先前存在的血管畸形[17]。因此考虑：口腔黏膜的RCH容易因进食受到损伤，合并细菌感染，致使患者口腔RCH在细菌感染的基础上发生化脓性肉芽肿性病理变化。本研究未进行肿物细菌、真菌的感染监测及皮肤肿物活检，未来仍需针对RCH的病理特征进一步研究分析。

目前RCH的病因尚未明确，Finlay等[18]通过实验发现卡瑞利珠单抗（SHR-1210）是人类血管内皮生长因子受体2（vascular endothelial growth factor receptor 2，VEGFR2）的有效激动剂，可能通过激活血管内皮细胞使其增殖为血管瘤。也有研究认为卡瑞利珠单抗可能与皮肤中的PD-1表达细胞靶向结合，而这些细胞又可能通过释放趋化因子产生VEGF[19]。在一项对晚期原发性肝癌、胃癌和胃食管交界癌的1期研究中，卡瑞利珠单抗联合阿帕替尼治疗的患者反应性皮肤毛细血管增生症（reactive cutaneous capillary endothelial proliferation，RCCEP）发生率为12.1%（4/33）[20]。阿帕替尼是抗肿瘤血管生成的药物，是VEGFR2的受体拮抗剂[21]，可能有抑制卡瑞利珠单抗与VEGFR2结合的作用[22]，卡瑞利珠单抗联合阿帕替尼治疗可降低RCH的发生率[23-24]。抗血管生成类药物与PD-1/PD-L1有协同作用[25-26]。该例患者在使用卡瑞利珠单抗治疗的同时，一直使用与阿帕替尼同类型的VEGFR抑制剂瑞戈非尼，其对各种促血管生成受体的抑制作用较强[27]，但该患者RCH症状并未减轻，有待深入探索其发生机制。另据报道，在以铂类为基础的化疗中添加抗PD-1/PD-L1药物临床疗效较好，并且不会导致治疗非小细胞肺癌和小细胞肺癌的意外毒性[28]，可能需要进一步大样本随机对照研究为临床提供循证医学证据。Wang等[29]通过系统性回顾及分析发现在任何级别的不良事件中，联合使用卡瑞利珠单抗的安全性优于单用。

RCH大多数不需要治疗，停药后多可自行消退[13]。最近有研究发现沙利度胺对于RCH的预防可能有效[30]。本例患者牙龈及下唇RCH发生肉芽肿性病变，生长迅速，影响进食及口腔功能，应首选手术切除。术后复诊，牙龈及下唇均已愈合，术前进行对应牙齿的洁治可有效防止病变的复发，因此建议在免疫治疗前进行口腔检查，去除口腔黏膜的炎性刺激因素并定期进行口腔卫生维护治疗。

【Author contributions】 Li YZ collected the data and wrote the article. Wang SY, Bu LX, Pang BX revised the article. Liu FZ, Yang N, Chen C were responsible for data collection. Wang Y was responsible for the pathological analysis.

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