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·防治实践·

三氧化二砷治疗急性早幼粒细胞白血病致颌骨坏死1例及文献复习

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【摘要】　目的　探讨三氧化二砷致颌骨坏死的病因、临床表现、治疗及预防，为临床诊疗提供参考。**方法**　对1例三氧化二砷治疗急性早幼粒细胞白血病致颌骨坏死患者的临床资料及相关文献进行回顾。**结果**　该病例因静脉注射三氧化二砷(每日1次，每次10 mg，治疗1个月)治疗急性早幼粒细胞白血病，治疗后约20 d，出现右上颌疼痛伴有牙龈红肿及黏膜溃疡，14-17牙颊侧和腭侧牙槽骨暴露，牙龈黏膜缺失，牙龈组织缺损至前庭沟底部，腭部软组织缺损至腭中缝5～8 mm；该患者因患急性早幼粒细胞白血病，病情不稳定，予以患者口服维生素及康复新液含漱，保持口腔卫生清洁等保守治疗。文献报道的药物性颌骨坏死可见于双膦酸盐类药物引起，三氧化二砷亦可引起局部颌骨坏死，临床上常表现为伤口长期不愈合、脓液、牙槽骨或颌骨外露、死骨形成，伴有疼痛、牙齿松动、面部红肿等症状。抗炎、清创、手术切除死骨是常用的治疗方法。**结论**　临床上需要警惕药物性颌骨坏死并加强预防。

【关键词】　急性早幼粒细胞白血病；　三氧化二砷；　双膦酸盐；　颌骨坏死；　死骨；　清创术
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Osteonecrosis of the jaw induced by arsenic trioxide therapy in acute promyelocytic leukemia patient: a case report and literature review

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【Abstract】　Objective　To investigate the etiology, clinical manifestations, treatment and prevention of jaw necrosis caused by arsenic trioxide to provide a reference for clinical diagnosis and treatment. **Methods**　To analyze the clinical data and related literature of patients with jaw necrosis caused by acute promyelocytic leukemia treated with arsenic trioxide. **Results**　We report a case of jaw necrosis caused by the use of arsenic trioxide (10 mg once a day for one month) during the treatment of acute promyelocytic leukemia. About 20 days after treatment, the patient developed right maxillary pain accompanied by gingival redness and swelling and mucosal ulcer, 14-17 teeth had buccal and palatal alveolar bone exposed, gingival mucosa was missing, gingival tissue was damaged to the bottom of vestibular groove, and palatal soft tissue was damaged to 5-8 mm of palatal suture. Due to the unstable condition of acute promyelocytic leukemia, the patient was given conservative treatment such as oral vitamin and Kangfuxin liquid gargle to keep his mouth clean. Drug induced jaw necrosis reported in the literature can be caused by bisphosphonates. Arsenic trioxide can also cause local jaw necrosis. Clinically, it is often manifested as long-term wound nonunion, pus, alveolar bone or jaw bone exposure, dead bone formation, accompanied by pain, loose teeth, facial swelling and other symptoms. Anti inflammation, debridement and surgical removal of dead bone are commonly used treatment methods. **Conclusion**　In clinical practice, we should be alert to drug-induced jaw necrosis and strengthen prevention.

【Key words】　acute promyelocytic leukemia;　arsenic trioxide;　bisphosphonates;　osteonecrosis of the jaw;　sequestrum;　debridement

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颌骨坏死是较常见的药物不良反应，它主要与两种不同的药物有关：抑制骨质吸收和抗血管生成药物[1-2]。抑制骨质吸收药物用于治疗骨吸收严重的疾病，如骨质疏松症和骨转移，临床上常用的药物是双膦酸盐（bisphosphonates，BP）和地诺单抗。抗血管生成药物主要用于治疗各种胃肠道肿瘤，其中一种重要的药物是贝伐单抗[3-4]。然而，并非所有颌骨坏死病例都是由这两类药物引起的。三氧化二砷广泛用于肿瘤学、血液学和口腔科，局部或全身应用三氧化二砷可引起颌骨坏死，其中以下颌骨最为常见。临床上常表现为伤口长期不愈合、牙槽骨外露、死骨形成、疼痛、牙齿松动，并伴有面部红肿等症状[5-7]。本文通过分析1例三氧化二砷治疗急性早幼粒细胞白血病致颌骨坏死患者的临床资料，并复习文献，总结该并发症的病因、临床表现、治疗及预防。

1　病例资料

患者，男性，41岁，工人，因“右上颌牙齿区域的疼痛和不适3月余”就诊。1年前在外院诊断出患有急性早幼粒细胞白血病（acute promyelocytic leukemia，APL），静脉注射三氧化二砷治疗（每日1次，每次10 mg，治疗1个月），治疗后约20 d，出现右上颌疼痛伴有牙龈红肿及黏膜溃疡，并于半年前拔除右上疼痛牙，未予其他治疗。临床检查：14-17牙颊侧和腭侧牙槽骨暴露，牙龈黏膜缺失，牙龈组织缺损至前庭沟底部，腭部软组织缺损至腭中缝5～8 mm（图1a、1b）。影像学检查：14-17牙槽骨骨密度降低，拔牙窝处骨质溶解、死骨中存在未重塑骨，骨折线明显（图1c）。结合影像学表现临床诊断：颌骨坏死。

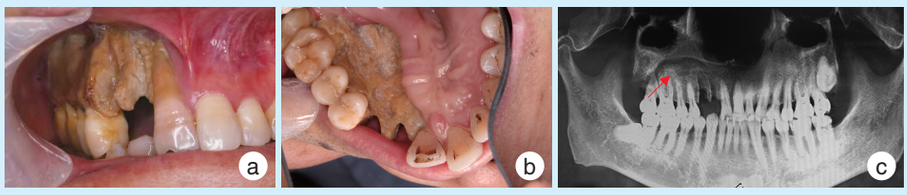
因患者有急性早幼粒细胞白血病，现病情不稳定，清创术和手术切除病灶都不适用，采用了保守的治疗方法，予以患者口服维生素及康复新液含漱，保持口腔卫生清洁。

2　讨　论

2.1　药物致颌骨坏死

2.1.1　砷制剂药物致颌骨坏死　1492年，Haly Abbas首次提出牙科中使用三氧化二砷作为失活剂治疗牙髓炎。此类化合物渗入牙周组织会导致牙龈损伤和骨坏死[8]。Marty等[9]报道了由于使用三氧化二砷作为失活剂而导致下颌骨坏死的儿童病例1例。总之，不管在成人或儿童，如果发生三氧化二砷渗漏或使用不慎，可能会对邻近的牙周组织和牙槽骨组织造成有害的影响[10]。1970年三氧化二砷被用来治疗APL，并于2000年被美国食品药品监督管理局批准作为治疗急性粒细胞白血病的一线药物[11]。三氧化二砷治疗APL效果好、生存率高，但最近的表明，在成人APL治疗中，使用全反式维甲酸（all trans retinoic acid，ATRA）和三氧化二砷进行全身化疗会导致颌骨坏死[12-13]。

2.1.2　双膦酸盐类药物致颌骨坏死　颌骨坏死是双膦酸盐静脉注射治疗过程中可能发生的并发症之一。2007年，美国口腔颌面外科医师协会将这一并发症命名为双膦酸盐相关性颌骨坏死（bisphosphonate related osteo-necrosis of the jaws，BRONJ）[14]。据统计，BRONJ发病平均年龄为（66.5 ± 4.7）岁，男女比例为1∶2，发生部位为下颌骨（约2/3以上），但发生在上颌骨的病变多较为严



a: the buccal side; b: the palatal side; a & b: the gingival tissue is missing, and the alveolar bone and jaw are exposed; c: X-ray panorama, the bone mineral density of 14-17 alveolar bone decreased, the bone in the extraction fossa was dissolved, there was unreformed bone in the dead bone, and the fracture line was obvious as showed by red arrow

Figure 1　Oral photograph and X-ray panorama of the patient with osteonecrosis of the jaw induced by arsenic trioxide therapy in acute promyelocytic leukemia

图1　三氧化二砷治疗急性早幼粒细胞白血病致颌骨坏死患者临床及影像结果

重[15]。一项系统评价显示，口服双膦酸盐类药物治疗者BRONJ发病率约0.47%，而静脉途径双膦酸盐类药物治疗者的BRONJ发病率为6.9%[16]。

2.2　病因学

尽管据报道砷是有毒的，但作为治疗剂使用它是相对安全的，常见的不良反应包括皮肤毒性（干燥、瘙痒）、头痛、肝毒性、胃肠道毒性和神经毒性，对骨骼的不利影响并不常见[17]。三氧化二砷俗称砒霜，其可以诱导细胞凋亡，临床上可见于牙髓炎、多发性骨髓瘤、急性粒细胞性白血病等的治疗用药。在牙髓炎的治疗中，三氧化二砷通过根尖孔或因封药失败造成泄露，导致剧毒砷与牙槽骨直接接触[18]。在APL的治疗中，颌骨坏死的作用机制并未被阐述。研究者发现颌骨坏死患者在接受三氧化二砷治疗前牙齿均有炎症或龋坏，并且患者同时服用了其他抗感染药物，因此，笔者推测牙齿的健康状况是影响APL治疗时颌骨坏死情况出现的关键。颌骨坏死是三氧化二砷的单一作用或多种药物的综合作用，但具体的作用机制尚未阐明，是未来的研究方向。

双膦酸盐类药物导致颌骨坏死的原因尚不清楚，主要与以下几方面相关。双膦酸盐类药物可抑制破骨细胞骨吸收，并诱导其凋亡；同时，它可作用于血管，降低骨骼血管数量，造成局部缺血、缺氧微环境[19]。经体外研究发现，双膦酸盐类药物可通过诱导活性氧的产生而影响成纤维细胞的形成与功能，导致口腔黏膜层的完整性及黏膜免疫系统受损。

2.3　治疗

对于药物引起的颌骨坏死，目前尚无明确的治疗策略。临床治疗分为两大类，即保守治疗（如漱口水、使用抗生素）和手术治疗（清创术或死骨切除术）[20-21]，治疗目标应主要是控制疼痛，减轻软组织和硬组织感染，减少骨坏死的进展或发生。保守治疗主要是指局部使用0.12%抗菌洗必泰冲洗[22]。当有局部炎症或感染时，建议使用广谱抗生素或抗菌药，如青霉素、阿莫西林和甲硝唑，同时可予以止痛、营养支持等对症支持治疗[23]。软组织清创术和死骨切除术是常用的手术方法，局麻下行患牙拔除术，牙槽骨部分切除术。术中彻底清除死骨，以骨创面有渗血为止。对于有足够牙龈组织瓣者，创面放置碘仿纱条包扎缝合；若无龈瓣覆盖者，可行皮瓣滑行移植术，使创口缩小后再放碘仿纱条包扎缝合。富含血小板的纤维蛋白或富含血小板的血浆能显著增强成纤维细胞和成骨细胞的增殖能力，促进牙龈的有效愈合和新骨的形成[24-25]。此外，对于暴露的骨坏死区域或保守治疗后进展不理想的患者，无论疾病处于何种阶段，都可能需要进行二次手术以去除坏死骨临近区域和/或骨隔离区域，直到肉芽组织覆盖创面愈合为止[26]。对于APL患者，应与主治医师仔细权衡利弊，治疗原发病，综合考虑是否可以暂停使用诱导药物，再考虑对颌骨坏死的进一步治疗。

2.4　预防

对于颌骨坏死的治疗结果，牙槽骨及附着牙龈的损失是不可避免的，因此预防尤为重要。已经发现，骨坏死病变通常起源于牙槽突，并且经常受到牙源性感染的影响，这些感染可以通过根尖孔和副管或通过感染的牙周组织有效地渗透到牙槽中。因此，对于局部用药，三氧化二砷作为根管治疗药物应密封，严禁与外部软硬组织接触。同时，要保证密封时间不要过长，一般封药时间为不超过48 h，告知患者在规定时间内按时复诊，以防砷制剂外泄。对于全身用药，如三氧化二砷用作APL治疗药物或双膦酸盐类药物等，准备接受相关药物治疗的患者应在开始治疗前进行全面的口腔检查和放射学评估，患者应尽早治疗，无法修复的牙齿应尽快拔除，评估口腔内的所有修复体，以消除对周围软组织造成创伤的潜在因素，同时应系统地对患者进行口腔卫生教育。

3　小　结

综上，药物相关颌骨坏死虽不常见，但带给患者的伤害不容小觑。相关治疗主要是对症治疗，至今没有公认有效的治疗方法，仍处于探索讨论阶段，因此预防尤为重要。建议在使用双膦酸盐类药物或三氧化二砷之前，详问病史，要保证口腔卫生，去除口腔安全隐患，避免非紧急的拔牙，规避发生颌骨坏死的相关危险因素。

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