病，也可能导致明显的充血和随后的骨骼破坏[1]，他们还发现在骨吸收区域，破骨细胞的活性增强，数量却并未见明显增加，即使溶骨过程不再继续进展，也无新骨形成。而其他学者认为：溶骨症的发生可能与白细胞介素（interleukin，IL）-6、肿瘤坏死因子（tumor necrosis factor，TNF）-α、血管内皮生长因子（vascular endothelial growth factor，VEGF）的生物化学作用有关[13-15]，这些因子激发了破骨细胞的活性，同时又促进了病理性淋巴管的增生[16-17]，进而加快了骨破坏。在此基础之上，Zhu等[18]提出了核因子κB受体活化因子配体（receptor activator of nuclear factor κB ligand，RANKL）/核因子κB受体（receptor activator of nuclear factor κB，RANK）系统理论。RANKL/RANK系统与多种骨疾病的发病机制有关，如绝经后骨质疏松症[19]和炎症性骨丧失[20]。RANK是TNF受体（TNF receptor，TNFR）家族的成员，因其缺乏细胞内结构域固有酶活性，所以RANK与RANKL结合后，需招募衔接蛋白，比如死亡结构域蛋白（Fas和TNFR相关死亡结构域蛋白）及TNFR相关因子（TRAF-1~6）等引起信号转换，激活核因子（nuclear factor，NF）-κB、Akt/PKB、JNK、ERK及p38等下游信号通路，调控破骨细胞的生成、分化、功能及存活[21-23]。但是，对于溶骨症发生的具体机制仍不是很清楚。

2 临床表现

溶骨症的临床表现呈多样性，患者可能一直处于潜伏期，溶骨过程无痛，又无其他症状伴发，直至出现病理性骨折时才被发现。骨组织可自发性、进行性吸收直至整块骨被累及，甚至侵及临近软组织[24]，因此颌面部溶骨症会出现面部畸形、受累牙疼痛松动、咬合紊乱及张口受限等症状。患者虽有牙痛病史，但无炎症反应，此刻需引起重视。但也有一部分溶骨症患者具有自限性，可能一直处于静止期，即骨吸收稳定，不再进展[25]。溶骨症的实验室检查可显示为无明显异常[26-27]，一些核医学成像如骨闪烁扫描等，有助于诊断和评估疾病的延伸和活动情况[28]。曲面断层和CT检查可见大面积骨吸收，边缘粗糙，有病理性骨折线，无骨膜反应及新骨形成[14]。病理检查则以骨小梁破坏及薄壁血管和淋巴管的增生为主要特征，无恶性肿瘤细胞[27,29]。免疫组化分析发现：血管内皮标记物CD31、CD34表达阳性[29-30]，淋巴内皮标记物D2-40阳性[30-31]，Ki染色仅能看到边缘细胞的活动，进一步证明了无恶性增生[31]。而且在内皮细胞中可见CD105呈高水平表达[32]。在临床上，需综合以上溶骨症的这些临床特点，才能做出诊断。

3 诊断及鉴别诊断

因溶骨症在临床上非常罕见，且其发病机制尚未完全明确，所以初期诊断较为困难[33]。临床表现、放射线检查结合病理结果，可以诊断为溶骨症。但在诊断之前，也有一些类似的临床表现会干扰诊断结果，如颌骨慢性骨髓炎、骨化性纤维瘤、颌骨的恶性肿瘤和广泛性淋巴异常（generalized lymphatic anomaly，GLA）[27]。

颌骨慢性骨髓炎是由细菌感染以及物理或化学因素使颌骨产生炎性病变，而且多数可穿透黏膜或皮肤形成瘘管，X线检查可见死骨形成，但溶骨症未见死骨形成，且无明显的炎症反应。

颌骨恶性肿瘤以鳞状细胞癌多见，早期可能无自觉症状，后期可出现局部疼痛，并相继出现下唇麻木，影像学检查可见骨质呈不规则虫蚀状破坏，而溶骨症一般颌骨呈广泛性吸收，累及范围较大，但很少出现下唇麻木的症状。发生于颌骨的骨化性纤维瘤，可出现颌骨膨隆，质地坚硬，导致面部畸形及牙移位，咬合错乱，但牙一般不松动，影像学检查骨密质内侧和髓腔的溶骨病变可被一清晰的骨硬化线所包绕，而溶骨症表现为骨质广泛吸收导致的颌骨萎缩、变形。

GLA是一种影响骨骼的多系统性疾病，主要特点是病理性的淋巴管扩张，而溶骨症是以薄壁血管增生为主的导致骨吸收破坏的血管异常紊乱，针对两者的鉴别，主要从临床资料、影像学检查及组织病理方面入手。溶骨症主要发生在颅骨、颈椎和锁骨，而GLA主要在胸椎、肱骨和肩胛骨。有报道[27]指出：溶骨症和GLA之间存在显著的放射学差异，尽管有一些重叠的特征，主要特点是在溶骨症中可观察到进行性骨溶解，而GLA的结果则提示为更广泛的破坏，特别是附属骨骼，存在椎间盘淋巴畸形和内脏器官的损伤。

血管瘤与溶骨症是相似的，因溶骨症在起始也有可能是不明病因的血管瘤型。此外，血管瘤病和溶骨症在扩散、病程和预后方面非常相似，

但不同之处在于，溶骨症一般是非家族性的，通常是单中心的[34]。

4 发生于全身其他部位的溶骨症

溶骨症不仅发生于颌面部，全身其他部位也有可能发生，包括肱骨、肩胛骨、锁骨、肋骨、胸骨、股骨、脊柱和手腕等[35]。其可能的发病机制包括：淋巴血管增生、破骨细胞数量或活性的增加、成骨细胞活性降低，其主要临床表现：肿胀及触诊疼痛，运动受限，功能障碍，病理性骨折，软组织萎缩或畸形等，进行性骨质溶解可引起脊柱后凸及侧凸、半脱位或甚至脱位。对相邻软组织的浸润也是破坏性的，但是并没有发现恶性肿瘤的迹象[10]。X线片及CT片：明显界限的低密度骨吸收区域，但在骨缺损区域无钙化骨及死骨形成[4,36]。病理及免疫组化检查：薄壁血管的增生，但无细胞的异型性，骨内增生血管，在增殖血管内皮细胞内CD31、CD34和D2-40阳性表达，免疫组化染色还显示了VEGF和VEGFR-3的表达。因此，该病的诊断需要结合临床表现、影像学检查和病理组织学结果，并且排除原发性或继发性骨质溶解的任何其他原因[37]。

5 治疗

溶骨症的骨质广泛性吸收破坏，因此针对该疾病的治疗是比较困难的，关于溶骨症的最有效的治疗方法尚未达成共识，但目前仍有许多手段来治疗，这些治疗方法主要包括药物治疗、放射治疗及手术。

溶骨症的病理分期可分为2期：第1期以血管增生为主，即活跃期；第2期以纤维增生为主，即骨吸收静止稳定，因此手术相对来说是比较好的治疗，即去除破坏的骨组织及行假体或腓骨、髂骨等移植，有患者行手术治疗后骨吸收停止，即使病变处于稳定期[38-39]，但手术治疗的缺点是，部分患者短期内骨吸收继续进行，甚至整个颌骨完全被吸收，这会导致手术治疗失败[40]。手术治疗的预后情况主要取决于手术移植时溶骨症是否处于活跃期[41]。也有报道[42]称，神经功能缺损的修复不在手术治疗方案内，这也是手术治疗的缺点之一。

针对该疾病的药物有双膦酸盐、降血钙素、贝伐单抗、干扰素-α[7]等。双膦酸盐主要是通过以下3点来抑制骨吸收：1）调节血清中IL-6的水平，使其处于正常范围，从而减少破骨细胞的活性[43-45]；2）直接抑制破骨细胞的活性；3）诱导破骨细胞凋亡，从而干扰破骨细胞的吸收，但其会引起严重的肾损害及下颌骨损害等，这使其应用受到了限制。贝伐单抗和干扰素-α[46]主要是下调循环血液中VEGF的水平来抑制血管增生的[47-48]。然而这些药物基本上对骨吸收没有明显改善，也没有达到控制疾病不再进展的效果。

合适剂量的放射治疗可以有效地降低溶骨活动，达到较好的临床效果；但当涉及多个椎骨时，因其严重的不良反应而不能被使用；而且该治疗的预后尚未明确，何时使用放射治疗也存在争议[49]。在临床治疗中，联合应用手术、药物及放射治疗，可能会产生加法效应。

6 参考文献

[1] Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone); its relation to hemangiomatosis[J]. J Bone Joint Surg Am, 1955, 37-A(5): 985-1004.

[2] Dellinger MT, Garg N, Olsen BR. Viewpoints on vessels and vanishing bones in Gorham-Stout disease [J]. Bone, 2014, 63: 47-52.

[3] Patel DV. Gorham's disease or massive osteolysis[J]. Clin Med Res, 2005, 3(2): 65-74.

[4] Shi J, Zhang Z, Li Y, et al. Reossification in Gorham's disease of the hand and wrist with unusual CT and MR imaging features[J]. Skeletal Radiol, 2015, 44 (7): 1033-1038.

[5] Yalniz E, Alicioglu B, Benlier E, et al. Gorham-Stout disease of the humerus[J]. JBR-BTR, 2008, 91(1): 14-17.

[6] 游云华, 汪跃平, 梁军, 等. 上颌骨溶骨症一例报告并文献复习[J]. 中华肿瘤防治杂志, 2010, 17(14): 1131-1133.
You YH, Wang YP, Liang J, et al. Massive osteolysis of maxillary bone: report of one case and literature review[J]. Chin J Cancer Prev Treat, 2010, 17 (14): 1131-1133.

[7] 李运良, 刘京兵, 朱兆夫. 颅、颌骨溶解症2例报道[J]. 口腔颌面外科杂志, 2002, 12(2): 183-184.

Li YL, Liu JB, Zhu ZF. Report of 2 cases of jaw osteolysis[J]. J Oral Maxillofac Surg, 2002, 12(2): 183-184.

[8] Escande C, Schouman T, Françoise G, et al. Histological features and management of a mandibular Gorham disease: a case report and review of maxillofacial cases in the literature[J]. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2008, 106(3): e30-e37.

[9] Perschbacher SE, Perschbacher KA, Pharoah MJ, et al. Gorham's disease of the maxilla: a case report[J]. Dentomaxillofac Radiol, 2010, 39(2): 119-123.

[10] Maillot C, Cloche T, Le Huec JC. Thoracic osteotomy for Gorham-Stout disease of the spine: a case report and literature review[J]. Eur Spine J, 2014. [Epub ahead of print].

[11] Hardegger F, Simpson LA, Segmueller G. The syndrome of idiopathic osteolysis. Classification, review, and case report[J]. J Bone Joint Surg Br, 1985, 67 (1): 88-93.

[12] Busilacchi A, Ramazzotti D, Ulisse S, et al. Gorham-Stout disease as a complication of posterior shoulder capsulorrhaphy[J]. J Shoulder Elbow Surg, 2012, 21(9): e1-e7.

[13] Devlin RD, Bone HG 3rd, Roodman GD. Interleukin-6: a potential mediator of the massive osteolysis in patients with Gorham-Stout disease[J]. J Clin Endocrinol Metab, 1996, 81(5): 1893-1897.

[14] Hirayama T, Sabokbar A, Itonaga I, et al. Cellular and humoral mechanisms of osteoclast formation and bone resorption in Gorham-Stout disease[J]. J Pathol, 2001, 195(5): 624-630.

[15] Spieth ME, Greenspan A, Forrester DM, et al. Gorham's disease of the radius: radiographic, scintigraphic, and MRI findings with pathologic correlation. A case report and review of the literature[J]. Skeletal Radiol, 1997, 26(11): 659-663.

[16] Venkatramani R, Ma NS, Pitukcheewanont P, et al. Gorham's disease and diffuse lymphangiomatosis in children and adolescents[J]. Pediatr Blood Cancer, 2011, 56(4): 667-670.

[17] Dupond JL, Bermont L, Runge M, et al. Plasma VEGF determination in disseminated lymphangiomatosis-Gorham-Stout syndrome: a marker of activity? A case report with a 5-year follow-up[J]. Bone, 2010, 46(3): 873-876.

[18] Zhu X, Gao JJ, Landao-Bassonga E, et al. Thonzonium bromide inhibits RANKL-induced osteoclast formation and bone resorption *in vitro* and prevents LPS-induced bone loss *in vivo*[J]. Biochem Pharmacol, 2016, 104: 118-130.

[19] Eghbali-Fatourechi G, Khosla S, Sanyal A, et al. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women[J]. J Clin Invest, 2003, 111(8): 1221-1230.

[20] Kong YY, Feige U, Sarosi I, et al. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand[J]. Nature, 1999, 402(6759): 304-309.

[21] Darnay BG, Ni J, Moore PA, et al. Activation of NF-kappaB by RANK requires tumor necrosis factor receptor-associated factor (TRAF) 6 and NF-kappa B-inducing kinase. Identification of a novel TRAF6 interaction motif[J]. J Biol Chem, 1999, 274(12): 7724-7731.

[22] Armstrong AP, Tometsko ME, Glaccum M, et al. A RANK/TRAF6-dependent signal transduction pathway is essential for osteoclast cytoskeletal organization and resorptive function[J]. J Biol Chem, 2002, 277(46): 44347-44356.

[23] Feng X. RANKing intracellular signaling in osteoclasts[J]. IUBMB Life, 2005, 57(6): 389-395.

[24] Kai B, Ryan A, Munk PL, et al. Gorham disease of bone: three cases and review of radiological features [J]. Clin Radiol, 2006, 61(12): 1058-1064.

[25] Zhao SF, Wang YX, Yang XD, et al. Gorham disease of the mandible[J]. J Craniofac Surg, 2015, 26(2): e160-e162.

[26] Yang RH, Chen PC, Chang CP, et al. Gorham's disease: the disappearing bone[J]. Clin Nucl Med, 2013, 38 (5): 361-364.

[27] Lala S, Mulliken JB, Alomari AI, et al. Gorham-Stout disease and generalized lymphatic anomaly—clinical, radiologic, and histologic differentiation[J]. Skeletal Radiol, 2013, 42(7): 917-924.

[28] Alves VM, Vieira TS, Amorim NS, et al. 99mTc(V)-DMSA SPECT-CT findings in a case of Gorham-Stout disease[J]. Nucl Med Rev Cent East Eur, 2015,

18(2): 97-101.

[29] Liu Y, Zhong DR, Zhou PR, et al. Gorham-Stout disease: radiological, histological, and clinical features of 12 cases and review of literature[J]. Clin Rheumatol, 2016, 35(3): 813-823.

[30] Suero Molina EJ, Niederstadt T, Ruland V, et al. Cerebrospinal fluid leakage in Gorham-Stout disease due to dura mater involvement after progression of an osteolytic lesion in the thoracic spine[J]. J Neurosurg Spine, 2014, 21(6): 956-960.

[31] Choi BS, Hong SJ, Chu MA, et al. Gastrointestinal tract involvement of Gorham's disease with expression of D2-40 in duodenum[J]. Pediatr Gastroenterol Hepatol Nutr, 2014, 17(1): 52-56.

[32] Franchi A, Bertoni F, Bacchini P, et al. CD105/endoglin expression in Gorham disease of bone[J]. J Clin Pathol, 2009, 62(2): 163-167.

[33] Kuriyama DK, McElligott SC, Glaser DW, et al. Treatment of Gorham-Stout disease with zoledronic acid and interferon-α: a case report and literature review[J]. J Pediatr Hematol Oncol, 2010, 32(8): 579-584.

[34] Edwards JR, Williams K, Kindblom LG, et al. Lymphatics and bone[J]. Hum Pathol, 2008, 39(1): 49-55.

[35] Chattopadhyay P, Bandyopadhyay A, Das S, et al. Gorham's disease with spontaneous recovery[J]. Singapore Med J, 2009, 50(7): e259-e263.

[36] Shimizu T, Sato K, Yoshida T, et al. A case report of Gorham-Stout syndrome remission[J]. J Orthop Sci, 2012, 17(2): 199-204.

[37] Lala S, Mulliken JB, Alomari AI, et al. Gorham-Stout disease and generalized lymphatic anomaly—clinical, radiologic, and histologic differentiation[J]. Skeletal Radiol, 2013, 42(7): 917-924.

[38] Ruggieri P, Montalti M, Angelini A, et al. Gorham-Stout disease: the experience of the Rizzoli Institute and review of the literature[J]. Skeletal Radiol, 2011, 40(11): 1391-1397.

[39] Aizawa T, Sato T, Kokubun S. Gorham disease of the spine: a case report and treatment strategies for this enigmatic bone disease[J]. Tohoku J Exp Med, 2005, 205(2): 187-196.

[40] Paley MD, Lloyd CJ, Penfold CN. Total mandibular reconstruction for massive osteolysis of the mandible (Gorham-Stout syndrome)[J]. Br J Oral Maxillofac Surg, 2005, 43(2): 166-168.

[41] Sekharappa V, Arockiaraj J, Amritanand R, et al. Gorham's disease of spine[J]. Asian Spine J, 2013, 7(3): 242-247.

[42] Lehmann G, Pfeil A, Böttcher J, et al. Benefit of a 17-year long-term bisphosphonate therapy in a patient with Gorham-Stout syndrome[J]. Arch Orthop Trauma Surg, 2009, 129(7): 967-972.

[43] Möller G, Priemel M, Amling M, et al. The Gorham-Stout syndrome (Gorham's massive osteolysis). A report of six cases with histopathological findings[J]. J Bone Joint Surg Br, 1999, 81(3): 501-506.

[44] Kuriyama DK, McElligott SC, Glaser DW, et al. Treatment of Gorham-Stout disease with zoledronic acid and interferon-α: a case report and literature review[J]. J Pediatr Hematol Oncol, 2010, 32(8): 579-584.

[45] Grunewald TG, Damke L, Maschan M, et al. First report of effective and feasible treatment of multifocal lymphangiomatosis (Gorham-Stout) with bevacizumab in a child[J]. Ann Oncol, 2010, 21(8): 1733-1734.

[46] Takahashi A, Ogawa C, Kanazawa T, et al. Remission induced by interferon alfa in a patient with massive osteolysis and extension of lymph-hemangiomatosis: a severe case of Gorham-Stout syndrome[J]. J Pediatr Surg, 2005, 40(3): E47-E50.

[47] Dupond JL, Bermont L, Runge M, et al. Plasma VEGF determination in disseminated lymphangiomatosis-Gorham-Stout syndrome: a marker of activity? A case report with a 5-year follow-up[J]. Bone, 2010, 46(3): 873-876.

[48] 黄慧, 徐作军, 王立, 等. Gorham-Stout综合征五例临床分析并文献复习[J]. 中华内科杂志, 2009, 48(1): 23-27.
Huang H, Xu ZJ, Wang L, et al. Clinical features of Gorham-Stout syndrome and literature review[J]. Chin J Int Med, 2009, 48(1): 23-27.

[49] Heyd R, Micke O, Surholt C, et al. Radiation therapy for Gorham-Stout syndrome: results of a national patterns-of-care study and literature review[J]. Int J Radiat Oncol Biol Phys, 2011, 81(3): e179-e185.

（本文编辑 张玉楠）