·病例报告·

注射用骨肽致过敏性休克、肺水肿和急性胰腺炎

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【摘要】 1例77岁女性患者因腰椎间盘突出症行椎管减压植骨融合内固定术，术后给予注射用骨肽50 mg入0.9%氯化钠注射液100 ml静脉滴注、1次/d。首次静脉滴注该药约5 min时患者诉胸闷、呼吸困难、出冷汗、上腹部疼痛，并出现口唇紫绀、寒战、全身红色皮疹伴瘙痒，血压74/45 mmHg（1 mmHg=0.133 kPa）。立即停药，给予地塞米松10 mg静脉注射、肾上腺素0.5 mg肌内注射、补液及吸氧等。约2 h后血压95/50 mmHg，皮疹消退，腹痛、胸闷、气急无缓解，血淀粉酶626 U/L，胸腹部CT平扫示肺水肿、双侧胸腔积液，立即给予注射用甲泼尼龙琥珀酸钠40 mg静脉注射，人血白蛋白注射液20 g静脉滴注，生长抑素0.25 mg/h持续静脉泵入，禁食。约4 h后血压110/60 mmHg，腹痛、胸闷、气急缓解。第2天患者诉上述症状再次加重，血淀粉酶915 U/L，给予注射用甲泼尼龙琥珀酸钠40 mg/d，2 h后症状缓解。第9天血淀粉酶68 U/L，胸部CT未见肺水肿，病情平稳。

【关键词】 过敏反应；　休克；　肺水肿；　胰腺炎；　骨肽
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Anaphylactic shock, pulmonary edema, and acute pancreatitis caused by ossotide injection

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【**Abstract**】 A 77-year-old female patient received an IV infusion of ossotide injection 50 mg dissolved in 0.9% sodium chloride injection 100 ml once daily after spinal canal decompression, bone grafting, fusion, and internal fixation due to lumbar disc herniation. About 5 minutes on the first infusion of the drug, the patient complained of chest tightness, dyspnea, cold sweat, and upper abdomen pain; cyanosis, chills, and red rash with itching all over the body appeared. Her blood pressure was 74/45mmHg. Ossotide injection was discontinued immediately and intravenous injection of dexamethasone 10 mg, intramuscular injection of epinephrine 0.5 mg, fluid infusion, and oxygen inhalation were given. About 2 hours later, her blood pressure was 95/50 mmHg, red rash was subsided, but the abdominal pain, chest tightness, and shortness of breath were not relieved. The blood amylase level was 626 U/L. The chest and abdomen CT scan showed pulmonary edema and bilateral pleural effusion. Intravenous injection of methylprednisolone 40 mg, intravenous infusion of human serum albumin 20 g, continuous intravenous pumping of somatostatin 0.25 mg per hour, and fasting were given immediately. About 4 hours later, the blood pressure increased to 110/60 mmHg, and the abdominal pain, chest tightness, and shortness of breath were relieved. On the second day, the patient complained of abdominal pain, chest tightness, and shortness of breath again, blood amylase level was 915 U/L. Intravenous injection of methylprednisolone 40 mg once daily was given. And 2 hours later, these symptoms were relieved. On the 9th day, abdominal pain disappeared, blood amylase level was 68 U/L, chest CT showed no pulmonary edema, and her condition was stable.

【**Key words**】 Anaphylaxis;　Shock;　Pulmonary edema;　Pancreatitis;　Ossotide
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患者女，77岁，因左下肢酸胀痛、跛行3个月，于2020年12月2日收入我院骨二科。患者3个月前无明显诱因出现左下肢酸胀痛，进行性加重，导致跛行。就诊于外院，腰椎磁共振检查示腰3~4椎间盘膨出，腰4~5和腰5~骶1椎间盘

突出，椎管狭窄，腰椎退行性变，给予活血化瘀、止痛和中药外敷治疗（具体不详），症状未见好转，为行手术治疗来我院就诊。否认冠状动脉粥样硬化性心脏病（冠心病）、糖尿病、高血压病、慢性胰腺炎等病史，否认药物和食物过敏史。

入院体检：体温36.3 ℃，脉搏68次/min，呼吸19次/min，血压133/71 mmHg（1 mmHg=0.133 kPa）。神志清楚，营养一般，言语正常，自动体位，心、肺、腹部检查未见明显异常。下肢呈破行步态，腰部屈伸活动受限，下腰部叩击痛（+），腰4~5、腰5~骶1棘间有压痛，腰5~骶1左侧椎旁压痛，直腿抬高试验左侧60°（+），左小腿背伸肌力稍减弱，肌张力及感觉正常；右下肢检查未见异常。入院后实验室检查血常规、肝肾功能、血糖、血脂、血淀粉酶等均无明显异常。胸部X线检查示慢性支气管炎、主动脉硬化、胸腰椎退行性变；超声心动图示二尖瓣及三尖瓣轻度关闭不全、左心舒张功能减退。入院诊断：腰椎间盘突出症。2020年12月8日8:00在全麻下行腰后路椎管减压植骨融合内固定术。麻醉及手术过程顺利，术中出血300 ml，术后给予枸橼酸舒芬太尼注射液以8 μg/h速度持续静脉泵入。10:30安返病房，生命体征平稳。医嘱给予注射用骨肽50 mg溶于0.9%氯化钠注射液100 ml静脉滴注、1次/d。15:30首次静脉滴注注射用骨肽约5 min，患者诉胸闷、呼吸困难、出冷汗、中上腹疼痛，全身出现红色皮疹伴瘙痒、寒战、口唇发绀，测血压74/45 mmHg，脉搏102次/min，呼吸28次/min，两肺闻及湿啰音和少许哮鸣音。立即停用注射用骨肽，更换输液器，给予0.9%氯化钠注射液500 ml维持静脉通道，吸氧6 L/min，同时给予肾上腺素注射液0.5 mg肌内注射、地塞米松10 mg静脉注射，先后静脉滴注乳酸钠林格注射液500 ml、注射用艾司奥美拉唑钠40 mg溶于0.9%氯化钠注射液100 ml、0.9%氯化钠注射液500 ml。17:30，患者血压95/50 mmHg，脉搏92次/min，呼吸24次/min，体温36.6 ℃，皮疹消退，诉仍中上腹持续疼痛，胸闷、气急无缓解。实验室检查：动脉血氧分压82 mmHg（氧合指数约182 mmHg），血淀粉酶626 U/L，白蛋白28.9 g/L，血红蛋白100 g/L，D-二聚体2 460 mg/L，白细胞计数、血小板计数、肝肾功能、B型脑钠肽、肌钙蛋白I、C反应蛋白、癌糖类抗原19-9均未见异常。胸腹部CT示肺水肿、双侧胸腔积液，胰腺未见异常、未见腹腔积液和腹膜后血肿。诊断为注射用骨肽致过敏性休克、肺水肿、急性胰腺炎。给予注射用甲泼尼龙琥珀酸钠40 mg静脉注射，人血白蛋白注射液20 g静脉滴注和生长抑素以0.25 mg/h速度持续静脉泵入，禁食。19:00，患者血压恢复至110/60 mmHg，腹痛、胸闷、气急症状缓解。12月9日10:00，患者腹痛、胸闷、气急再次加重，血压95/56 mmHg，脉搏88次/min，呼吸24次/min，急查血淀粉酶915 U/L，血白蛋白26.6 g/L，C反应蛋白22 mg/L，其余均正常。给予注射用甲泼尼龙琥珀酸钠40 mg静脉注射、1次/d，人血白蛋白10 g静脉滴注、1次/d，继续禁食，胃肠减压，同时给予脂肪乳氨基酸（18）注射液、脂溶性/水溶性维生素注射液、多种微量元素注射液等肠外营养支持治疗。12:00，患者上述症状缓解，血压115/65 mmHg，脉搏70次/min，呼吸20次/min。12月11日，患者腹痛、胸闷、气急症状完全消失，停用注射用甲泼尼龙琥珀酸钠。12月17日，血淀粉酶68 U/L，血白蛋白38.8 g/L，胸腹部CT未见肺水肿、胸腔积液，胰腺形态大小正常。12月25日患者出院，嘱患者以后避免使用注射用骨肽。

讨论　本例患者因腰椎间盘突出症术后按说明书规定剂量静脉滴注注射用骨肽过程中出现胸闷、呼吸困难、皮疹和血压下降，符合过敏性休克的诊断；发生过敏反应后，行胸部CT检查示肺水肿、双侧胸腔积液，考虑与患者过敏反应后发生低白蛋白血症有关；患者有持续腹痛症状，实验室检查发现血淀粉酶升高，符合急性胰腺炎的诊断。患者同期持续静脉使用枸橼酸舒芬太尼注射液镇痛，因过敏性休克、肺水肿、急性胰腺炎发生前、中和治愈后均未停止使用该药，故上述不良反应可排除由枸橼酸舒芬太尼注射液引起，考虑为注射用骨肽所致。

已有文献报道骨肽类注射剂可导致多种不良反应[1]，其中主要为过敏反应[2]，严重者可发生过敏性休克[3]，检索PubMed和中国期刊全文数据库（截至2020年12月31日），未见骨肽类注射剂同时导致过敏性休克、肺水肿和急性胰腺炎的报道。注射用骨肽是由新鲜或冷冻的猪四肢骨提取的骨肽溶液制成的无菌冻干品，辅料为甘露醇，含有多种骨代谢的活性肽类。这些成分易成为过敏原，导致过敏反应。本例可能由Ⅰ型和Ⅲ型超敏反应同时参与，使外周小血管扩张，血管通透性增加，大量血浆渗出，导致低白蛋白血症，因而发生过敏性休克和肺水肿。有研究发现，肥大细胞在过敏反应中起重要作用[4]，且自身免疫性胰腺炎患者多有过敏性疾病[5-6]。过敏反应可导致血清IgE水平升高，致敏的肥大细胞释放组织胺、5-羟色胺等物质，可导致水肿型胰腺炎。

2020年1月6日，国家药品监督管理局发布《骨肽类注射剂[骨肽注射液、骨肽氯化钠注射液、注射用骨肽和注射用骨肽（Ⅰ）]说明书修订要求》[7]，要求增加该类药物可导致严重过敏反应的警示。本例提示，骨肽注射液不仅可引起严重过敏反应，还可能因过敏反应诱发肺水肿、急性胰腺炎等多器官损伤，应予高度重视。

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安罗替尼致肾脏血栓性微血管病

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【摘要】 1例64岁女性患者因直肠腺癌伴双肺多发转移行直肠癌根治术，术后接受奥沙利铂联合卡培他滨治疗无效，改用安罗替尼12 mg/d口服，治疗2周，停药1周，3周为1个周期。在安罗替尼第2周期治疗期间出现水肿、蛋白尿、高血压和低白蛋白血症，血清肌酐正常，肾脏穿刺病理学提示肾脏血栓性微血管病，符合抗血管内皮生长因子药物相关肾损伤的临床和病理表现。停用安罗替尼，给予降压及对症治疗，水肿逐渐消退，尿蛋白逐渐减少，3个月后尿蛋白转阴，血白蛋白恢复正常。

【关键词】 抗肿瘤药；　血栓性微血管病；　安罗替尼
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Anlotinib-induced renal thrombotic microangiopathy

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【Abstract】 A 64-year-old female patient received postoperative adjuvant chemotherapy with oxaliplatin and capecitabine after radical resection of rectal cancer for rectal adenocarcinoma with multiple lung metastases. Due to poor therapeutic effect, the patient was switched to anlotinib treatment at a dose of 12 mg/d orally for 2 weeks with a 1-week break and 3 weeks was one cycle. During the second cycle of anlotinib treatment, the patient developed edema, proteinuria, hypertension, and hypoalbuminemia, with normal serum creatinine. The renal pathology suggested renal thrombotic microangiopathy, which was in line with the clinical and pathological manifestations of drug-related renal injury due to anti-vascular endothelial growth factor. After discontinuation of anlotinib and receiving symptomatic treatment such as blood pressure control, the edema gradually subsided along with remission of proteinuria. Three months later, the patient had no proteinuria and the serum albumin was normal.

【Key words】 Antineoplastic agents;　Thrombotic microangiopathies;　Anlotinib