

临床病理讨论

Clinicopathological Conference

Anticoagulant therapy for lung cancer concomitant with multiple thrombosis: a 60-year-old male case report

(the 43rd case)

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Case presentation

The patient, a 60-year-old male, was admitted to the Chinese PLA General Hospital on Jun 1, 2009, because of "cough, dyspnea and left chest pain for 2 months". He was diagnosed as poorly differentiated adenocarcinoma of left lung, with pleural and mediastinal lymph nodes, and bony metastasis. Chemotherapy was administered through retained peripherally inserted central catheters (PICC) at left brachiocephalic artery. On June 22, 2009, the patient developed left upper limb edema. Ultrasound examination displayed venous thrombosis from ulnar vein to subclavian vein. Low molecular weight heparin (LMWH) was given (5000 U/12 h) to maintain activated partial thromboplastin time (APTT) at 45-50 s. Then the left upper limb edema was alleviated gradually and no exacerbation was reported.

On July 5, 2009, the patient suddenly suffered severe waist and lower limbs pain and numbness after washing bowls, especially at the right side. Both lower extremities had low skin temperature with absent pulsation of dorsal artery of feet. Acute embolism of common iliac artery was highly suspected. The patient received emergency operation, and was diagnosed with aortic overriding embolism and right popliteal artery embolism, and embolectomy was performed. The patient was then transferred to intensive care unit (ICU) after operation. Anticoagulation therapy (heparin 3-8 mg/h) was given continuously to maintain APTT at 80s. On July 7, the patient developed conjunctival hemorrhage, then heparin was down-regulated to maintain APTT at 50s. Ultrasound reexamination suggested that thrombus in left subclavian vein, axillary vein and brachial vein do not show any

change. Considering that the thrombosis and infection were related to retained PICC, PICC was then extracted at 11:00, July 8. However, at 13:15, the patient suddenly developed hypoxemia, tachycardia, high D-dimer and the electrocardiogram (ECG) displayed a S1Q3 pattern. Pulmonary embolism was considered for the patient. Heparin dose was elevated to maintain APTT at 60-70 s. The patient's condition got better gradually. Pathological examination indicated thrombus instead of cancer embolus. Considering that long-term heparin utilization can induce thrombocytopenia, heparin was replaced by dalteparin sodium (5000 U/12 h) on July 13, and APTT was maintained at 45-50s. The patient's condition remained stable and he was discharged from ICU on July 20.

Clinical discussion

Dr. YUE Hui: This patient is an old male, admitted to hospital because of "cough, dyspnea and left chest pain for 2 months". He was diagnosed with lung cancer and received chemotherapy. He developed venous thrombosis, artery thrombosis and pulmonary embolism successively, which might be related to advanced age, lung cancer and chemotherapy. Anticoagulation therapy was given with unfractionated heparin (UFH, 3-8 mg/h) to maintain APTT at 80s. The patient developed pulmonary embolism after PICC extraction and his condition got better after elevation of UFH dose. Then he was discharged from ICU. The anticoagulant therapy with UFH was effective and correct, which proved to be the key point to postpone the thrombus progression and improve the patient's condition.

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Dr. ZHOU Feihu: The anticoagulant therapy with UFH was effective for this case. Heparin of 3-8 mg/h maintained APTT at 80s. Because of conjunctival hemorrhage, UFH was down-regulated to maintain APTT at 50s. Pulmonary embolism appeared after PICC extraction. It can not be excluded that pulmonary embolism was associated with UFH down-regulation. But it deserves attention that conjunctival hemorrhage is not a proper indicator for UFH modulation. Additionally, PICC extraction should be performed in a gradual manner rather than a just-for-once way in case of venous thrombosis.

Dr. SONG Qing: Cancer patients have higher risk of developing venous thrombosis and pulmonary thrombolism. Their characteristics conditons, for example, advanced age and frequent hospitalization, make them more feasible to thrombosis. Chemotherapy further increased these likelihood. Cancer patients often present with a hypercoagulable state, pro-thrombotic changes, and fibrinolytic system disturbance. All these are involved in thrombosis in cancer patients. The artery thrombosis was also associated with abnormalities of endothelial cells, platelet function, coagulation factors, antithrombotic and fibrinolytic factors. The patient developed venous thrombosis of upper limb, artery thrombosis and pulmonary embolism successively following chemotherapy, indicating that he had high thrombosis risk, which is the characteristics of this case. Both UFH and LMWH are recommended for treatment of thrombosis. LMWHs has an advantage of lower bleeding risk. But as for

patient with high thrombosis risk, artery thrombosis may be avoided if UFH was used during the treatment of the upper limb venous thrombosis. And also, conjunctival hemorrhage was not an indicator of down-regulation of UFH dose during anticoagulation therapy. It's not recommended to remove PICC in a just-for-once way. During anticoagulation therapy for patients with high thrombosis risk, UFH dose should be modulated to maintain APTT at 80s. UFH is lower cost, definitely effective, and easy to monitor and has antagonist. LMWH can be used in prophylaxis or after acute phase of thrombosis to decrease risks of heparin related thrombocytopenia and bleeding.

Summary

Cancer patients are at increased risk of thrombosis due to the disease, the treatment and the patient-related factors. LMWH should be given prophylactically to patients with high thrombosis risk as early as possible. Comparatively, UFH is more effective and easier to monitor than LMWH in treatment of thrombosis. APTT should be closely monitored and maintained at 80s, which can postpone the thrombus progression and improve the prognosis. In clinical practice, thrombosis prophylaxis and careful regulation of UFH dose deserve great attention, which are very important to balance thrombus recurrence and bleeding risk.

(Translator: YUE Hui)

肺癌合并多发血栓患者抗凝治疗 1 例

1 病历摘要

患者,男性,60岁,主因“咳嗽、胸闷不适、左侧胸痛2个月”于2009年6月1日入院。入院后完善检查诊断为左肺低分化腺癌 胸膜、纵隔淋巴结、多发骨转移,并予化疗。为行化疗左侧头臂动脉留置PICC导管,于2009年6月22日开始左上肢肿胀明显,超声检查发现静脉血栓从肘静脉延续至锁骨下静脉,给予低分子肝素钙抗凝治疗(5000 U/12 h, APTT45~50 s),肢体肿胀逐渐好转,复查无进展。

2009年7月5日洗碗后突然出现腰部及双下肢剧烈疼痛,伴麻木感,以右侧为著。双下肢皮温减低,双侧足背动脉搏动消失,考虑髂总动脉急性

栓塞可能性大。行急诊手术,术中诊断主动脉骑跨栓、右腘动脉栓塞,行主一髂动脉、腘动脉取栓术。术后入ICU,应用肝素抗凝(3~8 mg/h),APTT维持在80 s左右。7月7日出现眼结膜出血,肝素用量下调,维持APTT在50 s左右。复查血管超声提示左侧锁骨下、腋静脉及肱静脉血栓无明显变化。因考虑血栓及感染与PICC置管有关,遂于7月8日上午11:00拔出PICC导管,下午13:15突然出现突发低氧血症和快速心律失常,D-二聚体高,ECG出现S1Q3,而且Q3加深,考虑肺栓塞。加强肝素抗凝,APTT维持在60~70 s,病情逐渐改善。7月13日考虑患者应用肝素抗凝已7 d,取栓术后血栓病理为红白血栓,并非癌栓,长期应用肝素容易耐受

及引起血小板减低,更换为达肝素钠 5000 U/12 h,此后病情平稳,APTT45~50 s,于7月20日转出ICU。

2 临床病例讨论

岳慧医师:患者老年男性,本次以“咳痰、胸闷不适、左侧胸痛2个月”入院,入院后确诊肺癌,并化疗,住院过程中先后出现静脉、动脉血栓及肺栓塞,考虑与高龄、肺癌及化疗有关。给予抗凝治疗,应用肝素抗凝(3~8 mg/h),APTT维持在80 s左右。之后因拔除PICC过程中出现肺栓塞,加强肝素用量后,患者好转转出ICU病房。治疗过程中,肝素抗凝治疗方案正确有效,是延缓血栓进展、病情好转的关键。

周飞虎副主任医师:在患者治疗过程中,肝素治疗方案有效。应用肝素3~8 mg/h,APTT维持在80 s左右,后因出现眼结膜出血,肝素用量下调,维持APTT在50 s左右。拔除PICC管后出现肺栓塞,不除外与肝素用量下调有关,但应注意不应以眼结膜出血为肝素下调的指标,并且拔除发生静脉血栓的PICC管应循序渐进,避免一次拔除。

宋青主任医师:同意以上两位医师的分析。癌症患者静脉血栓及肺栓塞的风险相应增加。癌症患者的特征如老龄、反复住院也同时是易发生血栓的因素。在接受癌症治疗、如化疗的患者,血栓风险进一步升高。癌症患者易发生血栓与癌症导致高凝状态及引起促血栓形成的改变有关,也与纤溶系统的异常有关。动脉血栓也与内皮细胞、血小板功能、凝血因子、抗血栓及纤溶因素的异常有关。

该患者癌症化疗后先后出现上肢静脉血栓,动脉血栓以及肺栓塞,为血栓高发病例,这是本病例的特殊之处。在血栓治疗中,肝素及低分子肝素都推荐应用,低分子肝素有出血风险小的优势。但对于血栓高危患者,在早期上肢静脉血栓的治疗当中,如给予肝素抗凝治疗,有可能避免动脉血栓的发生。并且在肝素治疗血栓过程中,不宜因眼结膜出血而将肝素减量,也不宜一次拔除有血栓的PICC管,以避免出现肺栓塞。因此,在血栓高危患者的治疗当中,应以APTT在80s左右为最佳抗凝剂量。肝素抗凝的优点在于价格实惠,效果明确,便于监测,可以拮抗。而在血栓预防及栓塞急性期后,可给予低分子肝素抗凝,减少肝素相关血小板减少及出血风险。

3 总结

癌症患者血栓风险增加,与一系列疾病、治疗、患者相关的因素有关。对于癌症并血栓高危患者,应尽早给予低分子肝素预防治疗。在血栓治疗中,肝素较低分子肝素有效果更明确、更易于监测等优点。在肝素应用时严密监测APTT指标,维持在80 s左右,有利于延缓血栓进展、改善预后。在临床工作中,要注意血栓的预防以及肝素用量的精确调控及把握,平衡血栓再发及出血风险。

(参加讨论医师:岳慧,周飞虎,宋青)

(岳慧整理)

(收稿日期:2010-09-29;修回日期:2010-10-21)

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β_1 整合素ASODN特异性封闭 β_1 整合素表达可以抑制体外培养的CF的生长和代谢,为下一步研究ASODN对AVP作用下细胞功能的影响奠定了基础。

结果表明,AVP单独作用后,CF的细胞数目、 $^3\text{H-TdR}$ 掺入率均高于未经AVP刺激的细胞。 β_1 整合素ASODN与AVP共同作用后CF的细胞数目、 $^3\text{H-TdR}$ 掺入率均明显降低,而正义序列和AVP共同作用于CF后与AVP单独作用组无甚差别。由此可见, β_1 整合素ASODN抑制了AVP促CF增殖、DNA合成功能的作用,说明针对特异性靶基因片段合成的ASODN可能通过作用于 β_1 整合素遗传信息传递的某个环节,影响 β_1 整合素介导的CF与ECM的黏附,从而产生逆转AVP促CF增殖的作用,拮抗AVP刺激心脏间质重构的形成。进一步提示应用反义药物防治高血压心脏间质重构的可能性。

【参考文献】

- [1] Krishnamurthy P, Subramanian V, Singh M, *et al.* Beta 1 integrins modulate beta-adrenergic receptor-stimulated cardiac myocyte apoptosis and myocardial remodeling[J].

Hypertension, 2007, 49(4): 865-872.

- [2] Malek-Hedayat S, Rome LH. Cloning and sequence of the cDNA encoding the rat oligodendrocyte integrin beta 1 subunit[J]. Gene, 1995, 158(2): 287-290.
- [3] 赵连友,曹世平.高血压患者血浆精氨酸加压素浓度的变化及其与病情的关系[J].中华心血管病杂志, 1993, 21(2): 147-149.
- [4] Hiroyama M, Wang SY, Aoyagi T, *et al.* Vasopressin promotes cardiomyocyte hypertrophy via the vasopressin V1A receptor in neonatal mice[J]. Eur J Pharmacol, 2007, 559(1): 89-97.
- [5] 赵连友,彭育红,陈永清,等.反义寡核苷酸对精氨酸加压素诱导心脏成纤维细胞 β_1 整合素表达的抑制作用[J].中华心血管病杂志, 2003, 31(7): 523-527.
- [6] 彭育红,赵连友,陈永清,等.反义 β_1 整合素寡核苷酸对精氨酸加压素促胶原收缩的抑制作用[J].心脏杂志, 2001, 13(2): 112-114.

(收稿日期:2009-06-27;修回日期:2009-12-23)