

· 临床病理讨论 ·

Clinicopathological Conference

A 75 year old man with renal insufficiency and eosinophilia after coronary angiography

(The 16th case)

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Case presentation

A male patient, 75 years old, received esophageal carcinoma surgery in Oct 2005. On the second day after operation, the symptoms of dyspnea, chest discomfort and sweating took place when he was on bedside ordinary activities. ECG showed that: ST segment was elevated and T wave was depressed in leads V1-6. Biochemical markers of myocardial necrosis were elevated. Diagnosis: acute myocardial infarction of anterior wall. After anticoagulant, antiplatelet and vasodilator therapy, the symptoms relieved in 3 hours. One week before the admission, a visible edema of the left lower extremity occurred. Doppler ultrasound showed: thrombotic occlusion of left superficial femoral vein and popliteal vein. With further anticoagulant and vasodilator therapy, the edema eased off. He was admitted into the hospital for further therapy on Nov 3rd, 2005. Diagnosis on admission: coronary heart disease, acute myocardial infarction of anterior wall, esophageal carcinoma after surgery, thrombosis of left lower extremity vein. Laboratory examination showed that blood, urine and stool routine tests were normal, liver and renal functions were normal too. Doppler ultrasound showed atherosclerosis of both lower extremities, heavily narrowed

inferior part of right superficial femoral artery and unclear image of right posterior tibial artery (occlusion?). UCG showed segmental wall motion abnormalities in distal part of anterior wall of left ventricle and the apex and LVEF (Simpson method) 48%. The coronary angiography performed on Nov 14th showed 100% occlusion of the ostium of LAD. Arteriography of both renal arteries showed normal. The PCI failed. In early December he began to have sour lower extremities with petechia on toes and soles. From Dec 11th serum creatinine was elevated progressively, with the maximum being 403 $\mu\text{mol/L}$, and a gangrene occurred on the right heel. Blood examination showed WBC $> 10\,000/\mu\text{L}$, eosinophil 8% - 15%, ESR 63 - 108 mm/h, IgM 0.36 g/L, other immunoglobulins in the normal levels, complement C3 0.84 g/L and CRP 9.22 mg/L. Skin biopsy showed thrombosis in most small vessels of subcutaneous panniculus adiposus and no cholesterol crystals (Fig1). His renal function recovered gradually and serum creatinine decreased to 166 - 203 $\mu\text{mol/L}$. The gangrene of right heel healed up by changing dressings. The petechia on toes and soles faded away. He recovered well and was discharged.

Clinicopathological discussion

Dr. Shao Geng: In this case, we can find the evidences of atherosclerosis of coronary and peripheral arteries. He had multiple petechia on lower extremities after anticoagulant therapy and CAG with normal

peripheral pulses and normal skin temperature, indicating the embolism at the site of arteriole but not artery. Almost at the same time the occurrence of the renal dysfunction which was manifested by the elevated level of serum creatinine indicated the embolism of the kidneys. In the laboratory examination, acceleration of ESR, elevation of WBC count and especially eosinophilia all reflected the activation of inflammatory reaction.

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When we took all the clinical manifestations into account, the diagnosis of cholesterol crystal embolism was established. Furthermore we should pay attention to that the embolism and inflammatory activation were not merely the effects of cholesterol crystal, other contents in the atheroma also played a role in the progress. Therefore someone suggested that it was suitably called "atheroembolism". There is at present no special treatment for this syndrome. Statins may prevent the recurrence of embolism through stabilization of the cholesterol-rich plaque. This patient was suitable to receive intensive lipid-lowering therapy aiming at lowering the LDL level to 80mg/dl even 60mg/dl. Since the CABG may lead to the recurrence of embolism, the surgery should be considered after the intensive lipid-lowering therapy for a period. Although the patient was in the situation of inflammatory reaction caused by the activated immune system, it was better not to offer the treatment with corticosteroid for following reasons: 1) There was no evidence of improving the prognosis by corticosteroid treatment; 2) The patient had the history of venous thrombosis and heel ulcer.

Dr. Huo Yong: Though the biopsy of the skin lesion found no cholesterol crystals but thrombus, this case should still be diagnosed as cholesterol crystal embolism. The reasons are as follows: First, according to the onset time, the symptoms of thrombotic embolism took place just after the procedures, while the symptoms of cholesterol crystal embolism, which were caused not only by the mechanical embolism, but also by the immune response, often occur about 1 to 4 weeks after the procedures which conforms to the patient's condition. Second, thrombotic embolism usually localized to a site, and is difficult to explain the wide-spread lesions of the skin, kidneys and muscles (he had sour lower extremities) in this patient. The third and the most

important point is that, a thrombotic embolism cannot induce the elevation of WBC count, especially the elevation of acidophils, which is characteristic of cholesterol crystal embolism. On the other hand, the biopsy sampling has its own deficiency, and we should not exclude the possibility of cholesterol crystal embolism just depending on pathological examination. The symptoms of cholesterol crystal embolism are related to inflammatory reaction, and the reaction may have individual variations. This may be why the cholesterol crystal embolism is rarely seen despite of the great deal of intervention therapy.

Dr. Ding Wenhui: As for cholesterol crystal embolism, we have few experience. According to the foreign reports, morbidity varied from 0.08% to 4% in different groups of patient. Persons who have multiple artery atherosclerosis are more likely to suffer from the cholesterol crystal embolism. Most cases are related to anticoagulant, thrombolytic therapy, transluminal intervention or vascular surgery. For these patients embolism occurs in 1-4 weeks after these treatments or operations. However, in some cases embolism results from spontaneous of rupture atheromatous plaques without any causes. Except the lesions of skin, renal failure, the increase in ESR, the elevation of WBC count and eosinophilia presented in this case, clinical manifestations also include symptoms of nervous system and digestive system, anemia, hypertension, hypocomplementemia etc., depending on the organs affected and degree of affection. Biopsies of affected organs including skin, kidney, intestine and muscle can show the needle-shaped clefts left by the dissolved cholesterol crystals in lumina of arteriole. The positive rate of the skin biopsy is about 1/3 to 2/3. The specificity is high, but sensitivity is not 100% yet.

Summary

With the rising number of the cases of atherosclerosis and PCI, the occurrence of cholesterol crystal embolism would be increasing accordingly. Owing to different affected organs, the clinical manifestations are various, so physicians may ignore the diagnosis easily. It calls for

万方数据

physicians to intensify the knowledge about this syndrome. In this case, evidence of atherosclerosis in many sites, embolism in many sites 3 - 4 weeks after anticoagulant therapy and PCI and signs of immunological activation, such as elevation of the counts of WBC and

eosinophils, acceleration of ESR and hypocomplementemia, strongly suggest the diagnosis of cholesterol crystal embolism. The result of skin biopsy can further support the diagnosis but the negative result can not exclude the diagnosis. There is no specific treatment. Symptomatic treatment can be used according to the affected organs.

The indication and effectiveness of corticosteroid and plasmapheresis are still not clear. Statins could prevent further embolism as showed in some reports. However what is more important is to avoid using anticoagulant, thrombolysis, the operation of PCI or vascular surgery. (Translators: LIU Zhaoping, YANG Yang, CHEN Chen)

冠状动脉造影术后肾功能不全及嗜酸性粒细胞增高 1 例

1 病例摘要

患者男性,75岁。2005年10月行食道癌手术,术后第二天于下地活动中出现胸闷、心前区不适、憋气及大汗。心电图示V1-6导联ST段抬高,T波倒置。查心肌酶升高,诊断为急性前壁心肌梗死。予抗凝、抗血小板及扩血管治疗,约3h症状缓解。入院1周前发现左下肢浮肿,血管彩超示左侧股浅静脉及腓静脉闭塞性血栓形成,继续抗凝扩血管治疗,浮肿较前减轻。为进一步诊治于2005年11月3日收入院。入院诊断:冠心病,急性前壁心肌梗死;食道癌术后;左下肢静脉血栓形成。入院后查血尿便常规、肝肾功能均正常。下肢血管彩超示双下肢动脉粥样硬化,右侧股浅动脉下段重度狭窄,右侧胫后动脉显示不满意(闭塞?)。超声心动图示左室前壁远端及心尖部节段运动不良,LVEF(Simpson法)48%。于11月14日行冠状动脉造影示左前降支开口100%闭塞。双肾动脉造影正常。行PCI未成功。12月初出现下肢酸痛、肢端(足趾掌面及脚掌侧)瘀斑,12月11日开始血肌酐进行性升高,最高达403μmol/L,并出现右足跟坏疽。多次查血常规,白细胞>10 000/μl,嗜酸性粒细胞比例8%~15%。血沉63~108mm/h、免疫球蛋白IgM 0.36g/L,余正常范围内,补体C3 0.84 g/L。C反应蛋白9.22mg/L。行皮肤活检示皮下脂膜层多数小血管内血栓,未见胆固醇结晶(图1)。肾功能逐渐恢复,血肌酐166~203μmol/L,换药治疗,右足跟坏疽愈合。足趾及脚掌瘀斑基本消退。病情平稳出院。

2 临床病理讨论

邵耕教授:患者老年男性,除冠状动脉病变外尚有下肢动脉等外周动脉粥样硬化的证据。抗凝和冠状动脉造影后出现肢端多发瘀斑,而大动脉搏动尚可,皮温不低,提示小动脉栓塞而非较大动脉的栓塞。几乎同时出现肾功能受损,表现为血肌酐升高,万方数据

提示肾脏血管床栓塞的存在。实验室检查发现血沉增快、血白细胞计数升高,特别是嗜酸性粒细胞比例升高,反映患者体内存在炎症激活状态,综合患者的

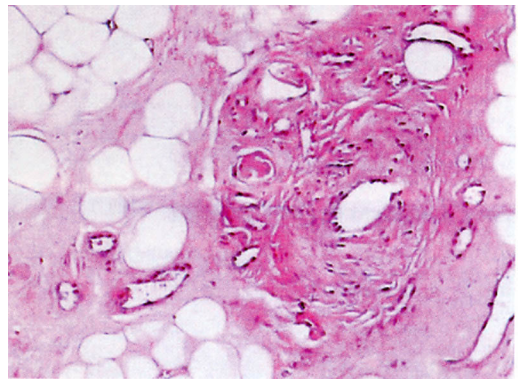


图1 右足趾皮肤活检 (×10)

临床表现,符合胆固醇结晶栓塞的诊断。值得注意的是,其实粥样斑块脱落导致的栓塞和炎症激活并不仅仅是胆固醇结晶的作用,还包括斑块中的其他成分,因此有人提出应称为 atheroembolism。目前对于此情况无特异性治疗。他汀类药物可能通过稳定粥样斑块,避免进一步的栓塞发生。此患者宜强化降脂,将低密度脂蛋白胆固醇水平降至80mg/dl甚至60mg/dl以下。由于心外科的操作可能导致进一步栓塞的发生,所以可考虑在积极降脂治疗稳定斑块一段时间后行冠状动脉旁路移植术。虽然患者存在免疫激活导致的炎症状态,但是目前没有糖皮质激素改善预后的证据,而且此患者曾有静脉血栓,现有足跟溃疡,所以不应用激素治疗。

霍勇教授:虽然皮损部位皮肤活检并未发现有胆固醇结晶,而是血栓,但是此患者仍应考虑诊断胆固醇结晶栓塞,原因有几个方面:首先从发病时间上讲,血栓栓塞临床表现会在术后即刻出现,而由于胆

固醇结晶栓塞的临床表现并不仅仅因为机械栓塞所致,而是与胆固醇结晶导致的炎症反应有关,需要一个过程,所以常常是在诱因后1~4周出现^[1],与此患者的情况符合。另外,血栓栓塞受累部位大多明确而较局限,很难解释此患者皮肤、肾脏和肌肉(发病过程中下肢酸痛)如此广泛的受累。第三,也是最重要的一点,用血栓栓塞无法解释患者白细胞升高,特别是嗜酸性粒细胞比例和计数的升高,而这一点正是胆固醇结晶栓塞的特点。另外考虑到病理取材范围的局限性,所以不应单凭病理排除胆固醇结晶栓塞的诊断,而应综合考虑。由于胆固醇结晶栓塞的临床表现与炎症反应有关,所以患者反应可能存在个体差异。这可能是虽然目前介入操作很多,而胆固醇结晶栓塞并不多见的原因。

丁文惠教授:对于胆固醇结晶栓塞国内经验较少。国外报道,根据观察的人群不同其发生率为0.08%~4%^[2]。多发动脉粥样硬化者易发生,多与抗凝、溶栓、介入诊断或治疗以及血管外科操作有关,也有自发斑块破裂导致栓塞者。如有诱因,多在1~4周后发生。临床表现除此患者表现的皮损、肾衰、血沉增快、白细胞升高及嗜酸性粒细胞增高外,根据受累部位和程度的不同还可表现为神经系统和消化系统受累、贫血、高血压以及低补体血症等,受累部位(包括皮肤、肾脏、肠壁或肌肉)活检可见小动脉内胆固醇结晶被溶解遗留的针状空隙,其中皮肤活检的阳性率为1/3~2/3^[3],因此特异性高,但敏感性并非100%。

3 小结

由于动脉粥样硬化疾病发病率的升高和血管腔内介入操作的增加,胆固醇结晶栓塞的发生也会随之增加。由于主要受累部位不同,患者表现多种多样,因此其诊断常易忽略,需要各科医师提高对此综合征的认识。本例患者有多发动脉粥样硬化,抗凝和介入术后3~4周出现多部位栓塞表现,辅助检查有白细胞升高、嗜酸性粒细胞升高以及血沉增快、补体C3下降等提示免疫激活的征象,临床高度提示胆固醇结晶栓塞的诊断。皮肤活检病理结果可进一步支持此诊断,结果阴性不能排除诊断。可根据受累的脏器进行对症治疗,无特异性治疗,激素、血浆置换的指征和疗效尚不明确。有报道他汀类药物可能避免进一步栓塞,而更重要的是要尽量避免溶栓、抗凝、血管内介入以及血管外科操作。

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(参加讨论医师:邵耕、霍勇、丁文惠,等)
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目前的病因和支持治疗不能降低患者的病死率,新的疗法如拮抗炎症介质治疗、基因治疗和中医药治疗等又未应用于临床^[7-9],所以预防是关键。充分认识MODSE的预后危险因素,采取积极有效的干预措施,可早期预防MODSE的发生,降低其病死率。

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