· 临床病理讨论 ·

**Clinicopathological Conference**

# An 80- year-old patient with continued hypercalcinemia combined with multiple organ failure

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## Case presentation

An 80 years old male was hospitalized on Feb. 9, 2006, because of progressive weakness of limbs. The patient felt weakness of both lower extremities from Feb. 4, 2006 with no obvious cause. The symptom was aggravated in the following days, gradually he could not walk and the weakness slowly spread to both upper extremities.

He was diagnosed as diabetes in 2005 and took acarbose to control blood glucose to a stable level. He had undergone cholecystectomy some years ago and prostatectomy in Dec. 2005, with the pathological diagnosis of hyperplasia of prostate gland.

Physical examination on admission:

Vital signs: T 36.2℃, P 80/min, R 16/min, BP130/90mmHg.

Consciousness state: the patient was drowsy, but he could answer the questions correctly.

Skin: no eruption or unusual pigmentation, no enlargement of lymph nodes, no cyanosis of oral lips.

Neck: no engorgement of jugular vein. Thyroid was palpable, but not enlarged and had no nodule and murmur. Trachea was in the middle.

Chest: normal contour, equal expansion, no abnormal breath sound and no dry or moist rales. Heart rate was 76/min and rhythm was normal.

Abdomen: flat and soft, no tenderness. Liver and spleen were not palpable. Right lower quadrant of abdomen looked full.

Extremities: low muscular tension. Muscular force of both upper extremities was grade 4 and that of both lower extremities was grade 2. Deep and superficial sensation were normal. Tendon jerk of extremities was not elicited. Babinski's sign and Karnig's sign of both sides were negative. No rigidity of neck was found.

Examination on the day of admission:

Blood: WBC $6.0 \times 10^9$/L, N 0.76, RBC $3.89 \times 10^{12}$/L, Hb 106 g/L, PLT $192 \times 10^9$/L, ALT 11 U/L, TP 58.1g/L, Alb 31.1 g/L, Glob 27g/L, A/G 1.2, Glu 8.9mmol/L, BUN 18.5mmol/L, Cr 279μmol/L. $K^+$ 2.9mmol/L. Urine routine: Pro (−), WBC(+). Chest X-ray: normal. ECG: sinus rhythm, incomplete right bundle branch block. UCG: calcification and light narrowing of aortic valve, light regurgitation of mitral valve, reduction of filling rate in early diastolic phase of left ventricle, no abnormality in contraction function of the left ventricle, trace of pericardial effusion.

Treatment: After admission, the patient recieved supplement of potassium and symptomatic treatment. The weakness of extremities was improved; but on the next day, the patient fell into coma. Emergency CT of head showed no obvious abnormality. The blood calcium was 3.78 mmol /L. The coma was considered to be related to hypercalcemia. Intravenous drip of phosphonate and intramuscular injection of calcitonin were given. After these treatment, the patient's consciousness recovered, and the weakness of extremities was improved.

Further examination: Chest X-ray showed

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lung markings thickened. B-ultrasound showed coarse echo of liver, but no definite lesion was identified. No space-occupying lesion was found in thyroid and parathyroid glands. Radioisotopic scan of thyroid did not show positive image of tumor. Bone scan showed multiple lesions, which were highly suspected to be metastatic carcinoma. PET showed widespread bone lesions, the extent was obviously larger than that found in the bone scan. There was abnormal radioactive focus in the right iliac fossa. Pelvis CT: destructive change in right iliac bone, loss of part of the bone and soft tissue mass around it(Fig 1). Marrow smear of right iliac spine did not show abnormal cells. IgA 0.9g/L, IgG 8.3g/L, IgM 0.344 g/L. Protein electrophoresis did not show abnormal M band in blood specimen, and Bence Jones protein in urine was negative. Tumor markers: PSA(−), AFP(−), CEA normal.

The patient's condition worsened progressively and some other symptoms such as low back pain, activity disorder, repeated hypercalcemia occurred. His nutritional state deteriorated progressively, he suffered from anemia (Hb 56g/L) and hypoproteinemia. Multiple organ functions deteriorated, he suffered from acute left heart failure, oliguria, pulmonary infection, pleural effusion, respiratory failure and metabolic acidosis. Alleviating pain, correcting anemia and electrolyte disturbances, nutritional support, anti-infection treatment, hemostasis and other treatments, such as assisted respiration with tracheal intubation and respirator, hemodialysis were given. Finally the patient suffered from pneumonia related to respirator (*Pseudomonas aeruginosa*, *Aerobacter cloacae*). He died after 133 days of hospitalization.

## Clinical Discussion

*Dr. Peng Chaojin*: The clinical characteristics of this case: elderly man of 80 years old, acute onset and fast progression of the disease. Clinical manifestations were progressive weakness of extremities, hypomyotonia and coma. The main clinical clues were hypercalcinemia and hypercalcinemic crisis. Ninety per cent of hypercalcinemia are induced by hyperparathyroidism and malignant tumor. The former secretes excessive parathyroid hormone, causing release of calcium from the bone into blood, and increase in absorption of calcium by kidneys and intestinal tract, and finally hypercalcinemia. The latter can cause hypercalcinemia through malignant tumor's osteolytic metastases and destruction of bone. At the same time, the tumor can secrete stimulating factor for osteoclast, osteolysis factor, prostaglandin E and other cell factors. These factors can increase bone resorption and osteolysis, and finally cause hypercalcinemia. We gave him some examinations guided by this clue. Because of his hypercalcinemia accompanied by multiple osseous lesions, we can exclude the diagnosis of hyperparathyroidism. Results of bone scan showed multiple lesions in bone, and no evidence of diagnosis of lung cancer, liver cancer and carcinoma of prostate. Examination of bone marrow did not show myeloma cell. Serum globulin was normal, Bence Jones protein was not found in urine, immune globulin was normal and protein electrophoresis showed no abnormal M band, these indicated no evidence of multiple myeloma. PET showed obvious lesions in the right iliac fossa and iliac bone. According to these results, we consider that the most possible primary affection was osteogenic sarcoma or soft tissue sarcoma, complicated with multiple bone metastatic carcinoma, which induced hypercalcinemia and hypercalcinemic crisis.

*Dr. Su Qin*: Primary malignant bone tumor mostly occurs in teenagers. The main clinical symptoms are bone ache in primary area, sometimes companied by fever. For people younger than 30 years old, the predilection site is metaphysis of long bone; but for people older than 50 years, the predilection site is in flat bone. The most frequent metastatic site is lung and the next is bone. This patient is an old man, there is little possibility for him to suffer from primary malignant bone tumor. I think there is possibility of extensive multiple osseous metastasis, but the primary tumor is very insidious.

*Dr Yang Qingming*: The diagnosis of multiple malignant bone lesions was definite in this patient,

but the primary lesion was not confirmed. Some examination results suggested that the right iliac fossa and the right ilium were the sites of primary tumor, but there was no identified pathological evidence. The multiple malignant lesions were: ① primary malignant bone tumor; ② osseous metastasis of malignant tumor; ③ multiple myeloma. Prostatic carcinoma is apt to metastasize to bone, but this patient had accepted prostatectomy in Dec. 2005, the pathological report was hyperplasia of prostate gland, PSA was negative and no other evidence supported the diagnosis of solid tumor in prostate gland. Multiple myeloma mostly occurs in middle- and old-age people. Bone marrow is the main site of the tumor. The tumor produces large number of abnormal plasma cells and destroys the bone. The lesions are distributed everywhere in the body. Marrow examination once only can not determine the diagnosis, sometimes many times and many locations of the examination are needed. One of the outstanding characteristics of this disease is appearance of protein M in serum, but 1% of this tumor does not secrete this protein. Diagnosis of this tumor relies on bone marrow puncture smear and pathological examination of bone marrow.

## Pathological results and discussion

*Dr. Lu Jiangyang*: Main characteristics of pathological anatomy: right ilium and surrounding soft tissue tumor. The pathological section was grey-red in color and soft. The tumor extensively eroded the right ilium and infiltrated into the surrounding soft tissue. Under microscope, the tumor cells were arranged in diffuse flakes with poor adhesiveness, the cytoplasm was red in color, the nucleus was dissymmetry, with plasmacyte-like differentiation. Mitotic division was easily seen (Fig 2). Immunohistochemical markers: CD38(++), CD20(−), CD79a(−), Lambda(−), Kappa(−), CD43(−), CD45RO(−), CK(−) and Vim(−). Flakes of focal plasma cell tumor tissue infiltration in medulla of thoracic vertebrae and ribs, pulmonary alveoli by drops and focal bleeding, and local pulmonary bullae formation could be seen. The pulmonary alveolar cavities were filled with many exfoliated epithelial cells, macrophages, chronic inflammatory cells and fibrin granules. Blood vessels in interstitial tissue of lung were highly expanded and congested accompanied by infiltration of chronic inflammatory cells, and there were many microthrombi (Fig 3). Interalveolar septa were widened accompanied by chronic inflammatory cell infiltration. The interstitial tissue of myocardium had dropse. Fibrous tissue hyperplasia was found in the interstitial tissue of pancreas, the pancreatic islets were greatly decreased accompanied by amyloidal degeneration in some parts. Tiny filtration foci of plasma cell tumor located in the hepatic sinus were seen.

Main pathological diagnoses: ① multiple plasma cell myeloma: plasma cell myeloma in right ilium and plasma cell tumor infiltration of thoracic vertebrae, ribs and liver. ② diffuse alveolar damage of both lungs accompanied by bleeding of pulmonary alveoli, blood stagnation in lung interstitial tissue accompanied by microthrombi formation, bilateral pleural effusion. ③ aortic scleratheroma accompanied by intima ulcer. ④ the number of islets of pancreas obviously decreased accompanied by amyloid degeneration of part of islets. Analysis of causes of death: the patient was an elderly of advanced age and had hypertension, diabetes and many other chronic diseases. Four months after finding multiple bone lesions, the tumor grew very fast, diffuse infiltration in the marrow and metastasis outside the marrow occurred, causing metabolic disorder, malnutrition, hypercalcinemia, then he suffered from pulmonary infection and severe diffuse alveolar damage of both lungs. Finally, the patient died of respiratory and circulatory failure.

*Dr Yang Qingming*: Multiple myeloma is a malignant tumor originating from B cells. It is the second common malignant tumor of blood system. I think the ultimate causes of death of this patient were: ① drug resistance induced fast progression of the disease. ② infection. ③ renal failure. The median survival time for patients receiving routine chemotherapy is less than 4 year; for those at ad-

vanced stage, the median survival time is about 2 years. The main clinical characteristics of myeloma have some relation to the following factors: ① malignant plasma cells abnormally accumulate in marrow and other tissues, and destroy the marrow's function of haematopoiesis, resulting in anemia, reduction of platelets and leukocytes. ② these cells can destroy the bone structure through stimulating the osteoclasts. Myeloma cells can synthesize abnormal monoclonal immunoglobulin (protein M), which accumulates in blood and urine, leading to increase in the blood viscosity and renal failure. ③ the normal immunoglobulin synthesis decreases, leading to destruction of the normal immune function and obvious increase in infection. The patient's disease began from hypercalcinemia and progressively developed. Bone ache, anemia, infection, severe bone destruction, and multiple organ failure occurred. These clinical manifestations are consistent with the characteristics of terminal stage of multiple myeloma. However in the lab examinations, there was no common main characteristics of this disease: the bone marrow puncture did not show abnormal plasma cell, and blood biochemical examinations did not show abnormal increase in immune globulin and appearance of protein M. Because about 1% of multiple myeloma belongs to no secretion type, the negative result of bone marrow puncture at one single site and the negative result of protein M can not exclude the diagnosis of multiple myeloma.

(Translator: Fu Xiaoling)

# 80岁持续高钙血症并多脏器衰竭1例

## 1 病例摘要

患者男性，80岁。因四肢进行性乏力5 d于2006年2月9日入院。患者从2006年2月4日始在无明显诱因情况下，出现双下肢乏力，进行性加重，逐渐不能行走，乏力向上漫延至双上肢。

既往史：因胆石症曾胆囊切除。2005年发现糖尿病，口服"阿卡波糖"治疗，血糖控制平稳；2005年12月行前列腺切除术，病理诊断为前列腺增生。

入院查体：体温36.2℃，呼吸16次/min，血压130/90mmHg，嗜睡，能正确回答问题，全身皮肤、黏膜无黄染、皮疹、出血点；浅表淋巴结未触及；口唇无紫绀，颈静脉无怒张，甲状腺未触及肿大、结节，听诊无杂音；双肺未闻及干、湿性啰音；心率76次/min，律齐；腹部平软，无压痛，肝脾肋下未触及，右下腹饱满；胸骨和脊柱无压痛；四肢肌张力低，双上肢肌力4级，双下肢肌力2级，深感觉、浅感觉正常。四肢肌腱反射未引出，双侧Babinski's征阴性。颈部无抵抗，Kernig's征(阴性)。

入院后当日检查：血WBC 6.0×$10^9$/L，N 0.76，RBC 3.89×$10^{12}$/L，Hb 106g/L，PLT 192×$10^9$/L；ALT 11 U/L，TP 58.1g/L，Alb 31.1g/L，Glob 27g/L，A/G 1.2；Glu 8.9mmol/L，BUN 18.5mmol/L，Cr 279μmol/L，血$K^+$ 2.9mmol/L；尿常规：Pro阴性，WBC(+)；X胸片未见明确病变。心电图窦性心律，不完全性右束支传导阻滞。超声心动图示：主动脉瓣钙化，轻度狭窄，二尖瓣少量返流，左室舒张早期充盈速率减低，左心收缩功能未见异常，微量心包积液。

入院后给予补钾及对症治疗，患者乏力好转；次日患者出现昏迷；急诊头颅CT未见明显异常。血钙3.78 mmol/L。考虑意识障碍与高血钙有关，静脉给予磷酸盐，并给予降钙素肌肉注射，患者意识障碍恢复，乏力好转。

进一步检查：胸片示肺纹理增粗，未见明确病变。B超示肝回声粗糙，未见明确病变；甲状腺、甲状旁腺未见占位。甲状腺同位素扫描未见肿瘤阳性显像。骨扫描提示骨多发病变，高度怀疑骨转移癌。PET检查提示广泛骨病变，范围较骨扫描病变明显多，右髂窝异常放射性浓聚灶。骨盆CT平扫：右侧髂骨部分呈破坏性改变，部分骨质缺如，周围可见软组织肿块影(图1)。右髂后上棘骨髓检查未见异常细胞。IgA 0.9g/L，IgG 8.3g/L，IgM 0.344 g/L；蛋白电泳未见异常M带；尿本周氏蛋白阴性。肿瘤标记：前列腺特异性抗原阴性；AFP阴性；CEA正常。

患者病情进行性发展，出现腰痛、活动障碍；反复出现高血钙；营养状况逐渐恶化，出现贫血(HB56G/L)、低蛋白血症；重要脏器功能进行性恶

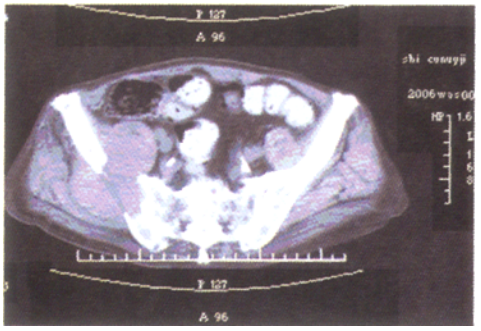

图 1 骨盆 CT 平扫

化，先后出现急性左心衰、少尿、肺部感染、胸腔积液、呼吸衰竭、代谢性酸中毒。给予止痛、纠正贫血、纠正电解质紊乱、营养支持、抗感染、止血等治疗；行气管插管呼吸机辅助呼吸；血液透析等治疗。进一步出现呼吸机相关性肺炎（铜绿假单胞菌、阴沟肠杆菌），住院 133 d，最终抢救无效死亡。

## 2 临床病理讨论

彭朝津医师：本例特点高龄，男性起病急，病程进展快；临床表现为进行性四肢乏力，肌张力减低，昏迷；临床主要线索为高钙血症，高钙危象；高钙血症约 90% 是由于甲状旁腺功能亢进症和恶性肿瘤引起。前者分泌过多的甲状旁腺素导致骨钙释放入血，肾和肠道钙的吸收增加，引起高钙血症；后者由于恶性肿瘤发生溶骨性转移导致骨质破坏引起高钙血症；肿瘤分泌破骨细胞刺激因子、溶骨因子、前列腺素 E 等使骨吸收和溶骨增加，引起高钙血症。根据这一线索，行相关检查，由于高钙血症伴多发骨病变，排除甲状旁腺功能亢进；经骨扫描发现骨多发病变，无肺癌、肝癌、前列腺癌的诊断证据；骨髓检查未见骨髓瘤细胞；血清球蛋白正常，尿本周氏蛋白阴性；免疫球蛋白正常；蛋白电泳未见异常 M 带，无多发性骨髓瘤的证据。PET 检查提示右髂窝、髂骨明显病变，因此考虑原发病变为骨肉瘤或软组织肉瘤可能性大，并发多发性骨转移癌，引起高钙血症、高钙危象。

苏琴医师：原发骨恶性肿瘤多发于青少年，主要症状为原发部位骨痛，常伴发热；30 岁以下好发部位多发生于长骨的干骺端，50 岁以上多发生于扁骨；常见的转移部位为肺，其次为骨。该患者为老年，原发骨恶性肿瘤的可能性较小，有广泛多发骨转移而原发肿瘤非常隐匿的可能。

杨清明医师：患者诊断多发骨恶性病变明确，原发病灶不十分明确，有关检查高度怀疑右髂窝、右髂骨原发病变，但无确诊病理依据。多发骨病变，临床主要见于：(1) 原发骨恶性肿瘤；(2) 恶性肿瘤骨转移；(3) 多发性骨髓瘤等。前列腺癌易发生骨转移，但患者 2005 年 12 月行前列腺切除术，病理报告为前列腺增生，前列腺特异性抗原阴性；相关检查无实体瘤诊断依据。多发性骨髓瘤多见于中老年，病变主要发生在骨髓，肿瘤产生大量的异常浆细胞，并破坏骨质，病变呈灶性分布于全身各处，一次骨髓穿刺检查不能确定诊断，有时需要多次、多部位骨髓检查；血清中出现 M 蛋白是本病的突出特点之一，但不分泌型约占多发性骨髓瘤的 1%，确诊需依据骨髓穿刺涂片和骨髓病理检查。

## 3 病理结果及讨论

陆江阳医师：病理解剖主要特点：右髂骨及周围软组织肿物，切片灰红色，质软。肿瘤广泛侵蚀、破坏右侧髂骨并浸润肿物周围软组织。镜下肿瘤细胞弥漫片状排列，黏附性差，胞浆红染，核偏位，浆样分化，核分裂易见（图 2）。免疫组化标记：CD38（++），CD20（−），CD79a（−），Lambda（−），Kappa（−），CD43（−），CD45RO（−），CK（−），Vim（−）。胸椎与肋骨髓质中见片灶状浆细胞瘤组织浸润。肺泡水肿及灶性出血，局部肺大泡形成；肺泡腔内充满大量脱落退变的上皮细胞、巨噬细胞、慢性炎症细胞及纤维蛋白颗粒等，肺间质血管高度扩张充血伴慢性炎细胞浸润，多见微血栓形成（图 3）。肺泡隔增宽伴慢性炎症细胞浸润。心肌间质水肿。胰腺间质纤维组织增生，胰岛数目明显减少伴部分淀粉样变性。肝脏镜下见肝窦内形成多个浆细胞瘤微小浸润灶。

主要病理诊断：(1) 多发性浆细胞性骨髓瘤：右髂骨浆细胞性骨髓瘤，胸椎、肋骨及肝脏可见浆细胞瘤浸润。(2) 双肺弥漫性肺泡损伤伴肺泡出血，肺间质瘀血伴微血栓形成；双侧胸腔积液。(3) 主动脉粥样硬化伴内膜溃疡。(4) 胰腺胰岛数目明显减少伴部分胰岛淀粉样变性。

死亡原因分析：死者为高龄老人，既往患有高血压、糖尿病等多种慢性疾患。发现多发性骨病变 4 个月，肿瘤生长迅速，髓内弥漫浸润及髓外转移，引起代谢紊乱、营养不良、高钙血症，进而发生肺部感染与严重的双肺弥漫性肺泡损伤，致呼吸衰竭和循环功能衰竭死亡。

杨清明医师：多发性骨髓瘤是 B 淋巴细胞来源的恶性肿瘤，是血液系统第二常见的恶性肿瘤。最终导致患者死亡的原因：(1) 耐药导致疾病进展；

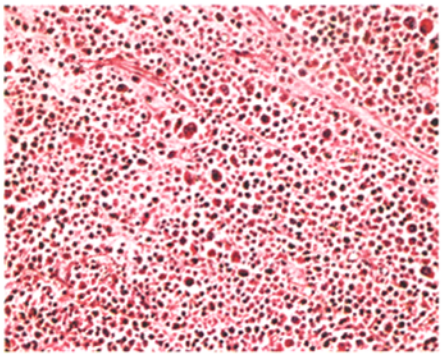

图2 右髂骨肿块病理

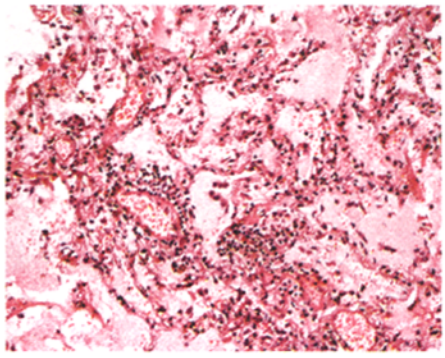

图3 肺组织病理

(2)感染;(3)肾功能衰竭。常规化疗的中位总生存时间不超过4年;对于疾病晚期患者,中位生存时间大约2年。骨髓瘤的主要临床特点与以下因素有关:恶性浆细胞在骨髓和其他组织中的异常累积,破坏骨髓的造血功能,导致贫血、白细胞和血小板减少;对破骨细胞的局部刺激导致骨结构破坏;骨髓瘤细胞合成异常的单克隆免疫球蛋白(M蛋白),在血液和尿中累积,导致血液粘稠度增加、肾功能衰竭;正常免疫球蛋白合成减少,导致正常免疫功能受到破坏,感染机会明显增加。该患者以高钙血症发病,病情进行性发展,出现骨痛、贫血、感染、严重的骨破坏、多器官功能损坏,临床表现符合多发性骨髓瘤的终末期特点;但本例在实验室检查中,缺少常见多发性骨髓瘤的主要特征,如骨髓穿刺检查未能查到异常浆细胞,血液生化检查未发现免疫球蛋白异常升高或出现M蛋白,不分泌型约占多发性骨髓瘤的1%,因此单一部位的骨穿阴性结果和M蛋白阴性,尚不能排除多发性骨髓瘤的诊断。

(参加讨论医师:彭朝津、苏琴、杨清明、陆江阳)

(彭朝津 整理)

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(3)早期出现过度炎症反应征象,如寒战、高热,血像增高大于$2.0\times10^9$/L。SAP是胰腺自身消化启动的严重全身反应性疾病,炎症细胞被过度激活并大量释放细胞因子,以及由此产生的细胞因子级链反应是SAP病情加重的重要环节。文献报告进行床边血液净化是SAP早期行之有效的治疗,可以明显降低SAP的病死率[2]。(4)早期虽采用逆行胰胆管造影,乳头括约肌切开术微创介入技术,但未收到好的效果。分析其原因,可能有胆管内支架术引起胆道逆行感染的因素,从而加重了胰腺炎。文献报告鼻胆管引流能够预防逆行胰胆管造影术后胰腺炎,起到有效引流胆汁,减少胰液反流作用[3]。(5)合并较大胰腺脓肿,直接影响了预后。SAP死亡病例中80%以上与感染有关,胰腺脓肿是其中的一个严重并发症,是多器官功能衰竭的始动原因。有报道认为胰腺脓肿一经确立应立即手术,否则可导致多器官功能衰竭而死亡[4]。近年文献报告有关经皮胰腺脓肿穿刺引流能取得较好的疗效,但该方法是否能替代脓肿切开引流术,是值得探讨的一个问题。较大的脓肿,单纯依靠脓肿穿刺引流达不到彻底清创的目的。(6)低氧血症在SAP患者早期并发MOF中起了重要作用。尽早、及时和可靠地纠正低氧血症,如合适的无创通气或有创机械通气,同时预防肺部感染,可能会避免SAP恶化。

由此可见,高龄SAP患者的病情变化因素较多,不但需要及时采取综合治疗措施,而且要注意个体化治疗,并在治疗过程中不断调整治疗方案,这样才有可能挽救高龄SAP早期并发MOF患者的生命。

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