· 临床病例讨论 ·

Clinicopathological Conference

An elderly patient with chronic myeloid leukemia presented with massive gastrointestinal bleeding

(the 34th case)

Department of Gastroenterology, Chinese PLA General Hospital

Case presentation

A male patient, 86 years old, was admitted to our department on Dec 13, 2008 because of melena, fatigue and loss of appetite for 3 days.

Present history: Three days ago, the patient's food intake decreased significantly with no obvious incentives, and his complaints were left upper abdominal discomfort and sour regurgitation after meal, with a little melena once on that day, but without fever, bone pain, nausea and vomiting, hemoptysis, mucosanguineous feces, and tenesmus, so he did not care. The next day, the patient defecated about 500g melena again, with fatigue and hyperhidrosis. He couldn't stand by himself. The night before hospitalization, the patient defecated about 100g melena again, with fatigue aggravated, but without syncope, and no medication was performed then. The next day, he was carried to the emergency department, the blood routine showed: haematoglobin(HB)58g/L, white blood cell(WBC)82.04×10^9/L, and neutrophil was 91.6%, which was considered as leukemoid reaction by hematologist. The blood biochemical test indicated high urea nitrogen level. The patient was admitted to our department with the diagnosis of gastrointestinal bleeding. Since this episode, the urinary volume was about 500-1000 ml per day, and his body weight decreased significantly in recent half years.

Past history: The patient had gastroduodenal ulcer, chronic bronchitis, old tuberculosis, old left basal ganglia hemorrhage, senile tremor, benign prostatic hyperplasia, post operation of left femoral neck fracture fixation. He was hypersensitive to erythromycin, isoniazid and streptomycin.

Physical examination: The patient was thin, his face was pale. No jaundice, rash and hemorrhage were seen on the skin, but the skin temperature was low, and the peripheral circulation of limbs was poor. No superficial lymph nodes could be palpated, and no sternum tenderness was found. The conjunctivae were pale, the breathing sound of both lungs was clear and no obvious rale could be heard. His cardiac rhythm was regular at 105 per minute, and no obvious pathological murmur could be heard on the valve auscultation areas. He had scaphoid abdomen without visible intestinal peristalsis; the abdominal aortic pulsatility could be seen on the abdominal wall. The abdomen was soft with no tenderness and rebound tenderness, no mass could be touched. The liver and spleen could not be palpated below the costal margin, Murphy's sign was negative. The abdominal percussion sounded like drum, the shifting dullness was negative, and the bowel tones couldn't be heard. There was no edema on the legs. The appearance of genitalia and anus was normal.

Blood test: The blood routine showed: HB 58g/L, WBC 82.04×10^9/L, neutrophil 91.6%

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and red blood cell (RBC) 1.44×10^{12}/L. The biochemical test showed: blood urea nitrogen (BUN) 29.4 mmol/L, uric acid 465.6 μmol/L and lactic dehydrogenase (LDH) 560.9 U/L. Arterial blood gas analysis: pH 7.419, PO_2 86.7 mmHg, PCO_2 28.5 mmHg, SpO_2 96.4%, HCO_3 18.1 mmol/L, BE -5.5 mmol/L.

The primary diagnosis: (1) anemia of unknown origin; (2) chronic bronchitis; (3) old tuberculosis; (4) old left basal ganglia hemorrhage; (5) senile tremor; (6) post operation of left femoral neck fracture fixation; (7) prostate hyperplasia.

After admission, enteroclysis was performed for three times, plenty of black loose stools were tested with positive occult blood. We treated the patient with fasting, anti-infection, antiacid, fluid replacement, hemostasis, blood transfusion (total of 800 ml of erythrocyte suspension and 400 ml of plasma) and supporting therapy, and his vital signs stabilized, his heart rate was not more than 90 per minute, his blood pressure was kept at 120-140/35-50 mmHg. The black stools turned into yellow mushy, the appetite improved, the urinary volume was 1300-1600 ml per day. Blood biochemical test indicated that his liver function, renal function and electrolyte were normal, plasma levels of BUN and uric acid were reverted to normal range, plasma LDH level declined significantly. The blood routine showed: HB 72 g/L, WBC 12.91 $\times10^9$/L, and neutrophil 79%. The patient experienced repetitive slight fever, with the highest body temperature 37.5℃ which could declined to normal without treatment. The patient coughed and expectorated moderate white and watery sputum, with the blood tubercular antibody positive, but no acid-fast bacillus was seen in the sputum. Peripheral blood smear indicated that most of the neutrophils were myelocytes and metagranulocytes. The neutrophil alkaline phosphatase (NAP) score was elevated. Bone marrow smear and biopsy showed proliferative response of bone marrow, the flow cytometry showed doubtful myelodysplastic syndrome, the chromosome detecton showed positive Ph' chromosome: t(9;22) (Fig 1) and positive BCR/ABL b3a2 fusion gene was indicated by gene detection (Fig 2), which was considered as chronic myelogenous leukemia (CML) by hematologist. The patient was transferred to the Department of Hematology, where the detection showed the positive rate of BCR/ABL fusion gene was 78%, and imatinib mesylate (Gleevec) treatment was performed. One month later, the positive rate of BCR/ABL fusion gene declined to 48.4%. The blood routine showed: HB 86g/L, WBC 4.82×10^9/L, neutrophil 55% and RBC 2.83×10^{12}/L. The biochemical test showed: BUN 10.24 mmol/L, uric acid 412.1 μmol/L and LDH 243.2 U/L.

Discussion

Dr. CHEN Siwen: The patient was admitted to the Department of Gastroenterology because of melena with positive stool occult blood and elevated plasma BUN level, so the diagnosis of gastrointestinal bleeding was confirmed. Considering the patient's past history of peptic ulcer, we deduced that the patient experienced upper gastrointestinal bleeding induced by the recurrent peptic ulcer. The blood routine after admission indicated severe anemia with HB 58 g/L and RBC 1.44×10^{12}/L. To review the past history of the patient, the WBC and neutrophil remained elevated for more than one year with the ranges $11.87-27.86\times10^9$/L and 0.714－0.920 respectively, since his last hospitalization on Oct 2007 because of cerebral hemorrhage, which was considered as leukemoid reaction then, and no special treatment was performed. The last blood routine test before admission to our department (Sept 10 2008) showed: RBC 3.58×10^{12}/L and HB 129 g/L. Three months later, HB was declined from 129 g/L to 58 g/L with severe anemia, while the patient only defecated melena 3 times, accompanied with fatigue and hyperhidrosis. Furthermore, the vital signs of the patient after admission was stable, without hypovolemic shock. The clinical manifestation of the patient was conflicting to the laboratory examination. Moreover, considering the high

level of WBC, we thought that the diagnosis of leukemia couldn't be excluded. So the peripheral blood smear, NAP score, bone marrow aspiration and biopsy were performed, which showed positive BCR/ABL fusion gene and positive Ph' chromosome, the diagnosis of CML was confirmed. I think this case is an atypical CML.

Dr. WU Daohong: The patient was admitted to our department with the diagnosis of "anemia of unknown origin", which may be due to the gastrointestinal bleeding. But according to the patient's clinical manifestations, we deduced that the blood loss was less than 10 percent of his total blood, which could not result in the severe anemia. We also noticed the high levels of WBC, neutrophil, uric acid and LDH(the later two could be released from the damaged leukocyte), which reminded us the diagnosis of leukemia, but the spleen was not large in physical examination and ultrasound examination, no sternum tenderness was found in the physical examination. Fortunately, bone marrow aspiration and biopsy showed positive BCR/ABL fusion gene and positive Ph' chromosome, which confirmed the diagnosis of CML. To retrospect the diagnostic procedure of the patient, his clinical manifestations included light fever, weight loss, anemia, and melena, but didn't include bone pain, hepatosplenomegaly, elevated blood WBC more than 100×10^9/L, and hemorrhage under the skin and mucosa, which were the typical clinical manifestations of leukemia; moreover, he also experienced chronic bronchitis and respiratory infection, which resulted in the misdiagnosis and missed diagnosis. To review the published medical literatures, CML without splenomegaly was not infrequent. All in all, to elderly patients with elevated hemogram and anemia which couldn't be explained by their symptoms, we should not only search for the possible occult source of infection and bleeding actively, but also think of the diagnosis of leukemia, even in the absence of lymphadenectasis, hepatosplenomegaly and sternum tenderness, the typical symptoms of leukemia. Bone marrow aspiration and biopsy examination could help us clarify the diagnosis.

Dr. WU Benyan: This is an elderly case of CML who was diagnosed because of gastrointestinal bleeding. To review the patient's medical history, he had been in hospital for cerebral hemorrhage and respiratory infection for several times. Even though his WBC had elevated for more than one year, he still was misdiagnosed as leukemoid reaction. Leukemoid reaction is a stress response to severe infection, poisoning, hemolysis, malignant tumors, blood loss, etc. The clinical manifestations of leukemoid reaction include elevated WBC and appearance of naive cells in peripheral blood, which are similar to leukemia. But in leukemoid reaction, all of the above can be quickly restored once the cause removed, and the Ph' chromosome is negative, which is different from CML. The reason of being misdiagnosed in this case included: (1) the non-specific clinical manifestations, such as the absence of lymphadenectasis, hepatosplenomegaly, hemorrhage under the skin and mucosa and sternum tenderness, which are the typical clinical manifestations of leukemia; (2) the complications, including respiratory infection, could also result in the elevated WBC. The patient was diagnosed as CML for his melena, which could not explain the severe anemia. The diagnosis was confirmed by bone marrow aspiration and biopsy finally. The patient experienced elevated WBC as 82.04×10^9/L after admission, and the highest WBC was 97.7×10^9/L during the hospitalization, which declined significantly to 12.91×10^9/L, the percentage of neutrophil also declined to 79% after anti-infection therapy, and the NAP score elevated, so we deduced that the acute infection contributed to the elevated WBC partly. Simultaneously, as a case of gastrointestinal bleeding, we couldn't exclude that the elevated WBC were induced by pachyemia partly. In addition, the patient had experienced elevated WBC during the last hospitalization for cerebral hemorrhage, we could not exclude that the cerebral hemorrhage was one of the clinical manifestations of CML. Fortunately, the patient was still in

the chronic phase of CML, his condition improved significantly after imatinib treatment, the positive rate of BCR/ABL fusion gene declined significantly, the neutrophil percentage, WBC and RBC count returned to their normal ranges. It is a pity that the patient was senile and asthenia, so he couldn't accept the endoscopic examination, and the cause of gastrointestinal bleeding had not been clarified finally. To review the published internal medical literatures, elderly patients diagnosed as CML with its primary symptom as gastrointestinal bleeding was not rare. Of course, we were not sure that if gastrointestinal bleeding was the clinical manifestation of CML in this case, maybe the CML of this case was so insidious that it was only diagnosed when the active gastrointestinal bleeding occurred. As the life-span of human prolonged, the incidence of elderly patients' leukemia was also elevated, but the occult and non-specific symptoms in the early stage, and the multi-organ, multi-system diseases associated with elderly patients, such as chronic obstructive pulmonary disease, diabetes, hypertension, coronary heart disease and cerebral infarction always interfer our diagnosis and easily lead to misdiagnosis and missed diagnosis. In summary, to the elderly patients with anemia of unknown origin, the gastroenterologist shoud consider not only the diagnosis of gastrointestinal bleeding, but also the diagnosis of leukemia. When the gastroenterologist found that gastrointestinal bleeding could not explain the anemia, it is necessary to perform bone marrow aspiration and biopsy to make the correct diagnosis.

(Translator: CHEN Siwen)

因消化道出血而确诊的老年慢性粒细胞白血病1例

1 病历摘要

患者男性，86岁，主因“黑便、乏力、纳差3d”于2008年12月13日急诊收住院。患者入院3d前无明显诱因出现进食量减少，进食后左上腹不适，伴返酸，当天解黑便1次，量少，无发热、骨关节疼痛、恶心呕吐和咯血，无黏液血便及里急后重，当时未在意。次日再解黑便1次，量约500g以上，伴乏力、全身大汗，无法站立，需家人搀扶。入院前1d晚间又解1次黑便，量少，约100g，伴乏力症状加重，无晕厥，未用任何药物治疗。遂至解放军总医院急诊就诊，查血常规提示血红蛋白58g/L，白细胞总数82.04×10^9/L，中性粒细胞百分比0.916，血生化提示尿素氮偏高。请血液科会诊，考虑白细胞升高为类白血病反应可能性大。遂由急诊收住南楼消化内科。患者发病以来神志清，精神差，进食量少，每日尿量为500～1000ml，近半年来体重下降明显。

既往史：既往有胃十二指肠溃疡、慢性支气管炎、陈旧性肺结核、左侧基底节区陈旧性出血、老年性震颤、前列腺增生症、左股骨颈骨折内固定术后等病史。对红霉素、异烟肼及链霉素过敏。

查体：消瘦貌，面色苍白，全身皮肤黏膜无黄染、皮疹及出血点，四肢末梢循环差、皮温低。浅表淋巴结未触及肿大，胸骨无压痛。结膜苍白，双肺呼吸音清，未闻及明显干湿性啰音。心率105次/min，律齐，各瓣膜听诊区未闻及明显病理性杂音。舟状腹，未见肠型及蠕动波，可见腹主动脉搏动，全腹触诊软，无压痛及反跳痛，未触及包块，肝脾肋下未触及，墨菲征阴性，腹部叩诊鼓音，移动性浊音阴性，肠鸣音消失。双下肢不肿，肛门外生殖器外观正常。

辅助检查：血常规：血红蛋白58g/L、血小板231×10^9/L、白细胞82.04×10^9/L、中性粒细胞0.916。血生化：尿素29.4 mmol/L、尿酸465.6μmol/L、乳酸脱氢酶560.9 U/L。血气分析：pH 7.419、PO_2 86.7 mmHg、PCO_2 28.5 mmHg、SpO_2 96.4%、HCO_3 18.1 mmol/L、BE -5.5 mmol/L。

入院诊断：(1)贫血原因待查；(2)慢性支气管炎；(3)陈旧性肺结核；(4)左侧基底节区陈旧性出血；(5)老年性震颤；(6)左股骨颈骨折内固定术后；(7)前列腺增生症。

诊疗经过：入院后先后灌肠3次，排出黑色稀便，查便潜血阳性，予禁食、抗感染、补液、抑酸、止血、输血(共输4U红细胞悬液和2U血浆)及对症支

持治疗后，生命体征趋于平稳，心率78～85次/min，血压维持在120～140/35～50mmHg，大便由初入院时的黑色稀便转为黄色糊状便，饮食睡眠可，尿量1200～1600ml/d，复查肝肾功能、电解质正常，血尿酸水平降至正常，乳酸脱氢酶水平也较前明显下降，但血清白蛋白和前白蛋白水平偏低。复查血常规提示白细胞总数降至12.91×10⁹/L，中性粒细胞降至0.79，血红蛋白升至72g/L。但患者存在间断低热，体温最高37.5℃，未予特殊处理能自行降至正常，有咳嗽咯痰，但痰不多，不黏，血生化提示C反应蛋白升高，为25mg/L，血结核抗体阳性，但痰中未查见抗酸杆菌。行外周血涂片检查提示中性粒细胞以中幼粒和晚幼粒为主，中性粒细胞碱性磷酸酶(neutrophil alkaline phosphatase，NAP)积分升高。骨穿结果提示反应增生性骨髓象。骨穿标本流式细胞检测显示可疑骨髓增生异常综合征。染色体检查提示Ph'染色体阳性：t(9;22)，见图1。融合基因检测表明BCR/ABL b3a2融合基因阳性(图2)。血液科会诊认为可以确诊慢性粒细胞白血病，遂转血液科。基因检测表明BCR/ABL融合基因阳性率为78%，

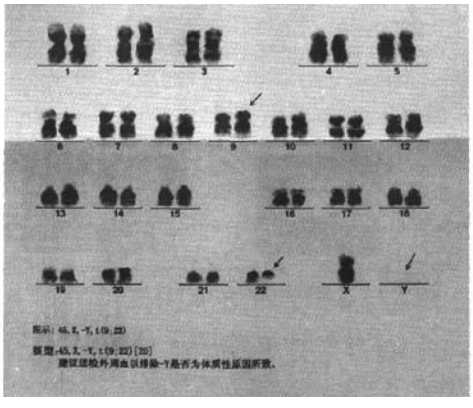

图1 染色体检查提示Ph'染色体阳性：t(9;22)

图2 融合基因检测表明BCR/ABL b3a2融合基因阳性

给予甲磺酸伊马替尼(格列卫)治疗1个月后复查BCR/ABL融合基因阳性率降为48.4%。复查血常规示：红细胞2.83×10¹²/L、白细胞4.82×10⁹/L、中性粒细胞0.55，血红蛋白86 g/L。复查血生化示：尿素10.24 mmol/L、尿酸412.1μmol/L、乳酸脱氢酶243.2 U/L。

2 临床病理讨论

陈思文：患者本次因黑便入院，查便潜血阳性，血尿素升高，消化道出血诊断明确，结合患者有消化性溃疡病史，初步考虑为消化性溃疡复发所致上消化道出血。入院后查血常规提示患者重度贫血，红细胞仅1.44×10¹²/L，血红蛋白仅58g/L。复习患者既往病史，患者自2007年10月因脑出血在神经内科住院期间发现血白细胞总数较高，当时考虑为类白血病反应，未予特殊处理。此后血白细胞水平波动于11.87×10⁹/L～27.86×10⁹/L，中性粒细胞百分比波动于0.714～0.92，血小板、红细胞和血红蛋白一直处于正常范围。入院前最后一次查血常规(2008-9-10)示红细胞3.58×10¹²/L，血红蛋白129g/L，从9月至12月仅3个月时间，血红蛋白由129g/L降至58g/L，为重度贫血，但患者病程中仅有3次解黑便病史，其中一次量大，伴全身大汗、不能站立，且患者入院后生命体征较平稳，尿量也不少，临床表现和化验结果不相符。结合患者白细胞总数较高，考虑白血病诊断不能排除，进一步检查提示BCR/ABL融合基因阳性。染色体检查提示Ph'染色体易位，确诊慢性粒细胞白血病。该病例为不典型的慢性粒细胞白血病。

吴道宏：患者因贫血原因待查收住我科，贫血原因首先考虑为消化道出血。但是根据患者临床表现判断患者失血量小于全身血量的10%，不致于引起重度贫血，结合患者白细胞总数和中性粒细胞百分比较高，血尿酸和乳酸脱氢酶水平较高(尿酸和乳酸脱氢酶为白细胞破坏释放入血)，考虑白血病诊断不能除外。但是患者查体和B超检查均未提示肝脾肿大，胸骨也没有压痛，最终骨髓穿刺活检发现BCR/ABL融合基因阳性和Ph'染色体易位才确诊为慢性粒细胞白血病。回顾该患者的诊疗过程，其临床主要表现为低热、体重下降、贫血、黑便，而无骨髓疼痛、肝脾肿大、皮肤黏膜出血等白血病的典型临床表现，外周血白细胞总数升高，但未超过100×10⁹/L，且合并慢性支气管炎、呼吸道感染，容易造成误诊和漏诊。复习文献，无脾脏肿大的慢性粒细

胞白血病病例并不少见。因此，对于老年患者，出现血白细胞总数升高及用已有症状不能解释的贫血，除了积极寻找可能的隐匿感染灶和出血灶外，即使没有淋巴结肿大、肝脾肿大和胸骨压痛等典型的白血病症状和体征，亦不能轻易排除白血病的可能，可行骨髓穿刺活检以明确。

吴本俨：这是一例因消化道出血而被诊断为慢性粒细胞白血病的老年病例。回顾其病史，因呼吸道感染和脑出血多次住院治疗，尽管当时已有血白细胞总数的升高，但一直被误诊为类白血病反应。类白血病反应是机体受严重感染、中毒、溶血、恶性肿瘤、失血等刺激后的一种应答反应，表现为外周血白细胞数明显增高，并出现幼稚细胞，类似白血病。但是病因去除后，血白细胞总数可迅速恢复，遗传学检查也无Ph'染色体。该患者被误诊为类白血病反应，乃是因其临床表现没有特异性，无淋巴结肿大、肝脾肿大和胸骨压痛等典型的白血病症状和体征，且合并有感染、出血等可以导致血白细胞总数升高的疾病。本次因黑便、贫血入院，发现用黑便不能解释其重度贫血，行骨髓穿刺活检才最终确诊的。该患者住院时白细胞总数82.04×10⁹/L，住院期间白细胞总数最高达到97.7×10⁹/L，且NAP积分升高，经抗感染治疗后白细胞降至12.91×10⁹/L，中性粒细胞百分比降至0.79，故考虑患者还是合并有急性感染所致的白细胞总数升高，当然作为消化道出血病例，亦不能排除有血液浓缩的因素参与其中。另外，患者2007年10月因脑出血住院治疗，血白细胞总数已经升高，不能排除脑出血即为慢性粒细胞白血病的临床表现之一。所幸患者慢性粒细胞白血病尚处于慢性期，经伊马替尼治疗后病情明显好转，BCR/ABL融合基因阳性率明显降低，血白细胞总数、中性粒细胞百分比恢复正常，贫血改善。可惜的是因患者高龄，体质较弱，不能耐受胃肠镜检查，其消化道出血的最终原因未能得到明确。复习国内文献报道，高龄患者因消化道出血被诊断为慢性粒细胞白血病的尚不多见。当然，本例病例的消化道出血不一定为慢性粒细胞白血病的临床表现，可能仅仅是患者隐匿起病的慢性粒细胞白血病，因消化道活动性出血而被查出。随着人类寿命的延长，老年性白血病的发病率有上升趋势，但因为白血病早期症状隐匿，无特异性，且老年患者常合并有慢性阻塞性肺疾病、糖尿病、高血压、冠心病、脑梗等多器官、多系统疾病，对白血病诊断造成干扰，容易引起误诊和漏诊。总结经验，对于消化科医师来说，遇到贫血原因待查的老年患者，除考虑消化道出血的可能性外，还应想到白血病的可能，当发现用消化道出血不能解释其贫血时有必要行骨髓穿刺活检以协助诊断。

（参加讨论医师：陈思文、吴道宏、吴本俨）

（陈思文 整理）

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马礼坤等[8]研究相似。减少卧床时间，提早下床活动，也是现在提倡的治疗方式之一，有利于患者恢复，同样减少住院时间，节约经费。心肌梗死往往需要强力抗凝，双重抗血小板及抗凝治疗易造成术后出血风险。通过桡动脉途径可减少这些风险的发生，笔者的研究已表明了出血并发症的减少。两者手术成功率及植入支架的情况基本相似，通过桡动脉路径手术治疗成功率可以同经典路径媲美。

本研究大多数为高龄患者，其血管病变复杂，病情危重，并发症多，时间紧迫，对技术要求高，遇到穿刺不成功，血管痉挛，或导管支撑欠佳等问题时需花费时间，同时增加了手术风险，及时改为股动脉入路可减少风险的发生。

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