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SMALL BOWEL BLEEDING WITH CHRONIC MYELOMONOCYTIC LEUKEMIA: A RARE CASE REPORT

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ABSTRACT

Background: To investigate the diagnosis and treatment of patients with small intestinal telangiectasia complicated with chronic myelomonocytic leukemia and to improve the diagnosis and treatment level. **Methods:** We have collected the clinical data of one patient with small intestinal telangiectasia complicated with chronic myelomonocytic leukemia were summarized and analyzed and reviewed the relevant literature by summarizing the diagnosis and treatment process of this case, the clinical manifestations combined with laboratory results in the diagnosis of such diseases, and the reasons for the rapid progression of the disease after surgery. **Results**: In this case, due to the poor conservative treatment effect of small intestinal telangiectasia, after surgical removal of the diseased intestine, the perioperative white blood cells continued to maintain a high level, the anemia was difficult to correct, and the blood in the stool was repeated after surgery. Finally, bone marrow aspiration was performed to confirm the diagnosis of chronic monocytic leukemia (CMML), and the patient died due to leukemia exacerbation and lung infection. **Conclusion:** The small bowel bleeding with CMML rate is low, but mortality is high. If we encounter hematoma or anemia that is difficult to control clinically, physicians need to expand the thought process of diagnosis and treatment, find the root cause, and pay attention to distinguish small bowel bleeding from other hematological diseases to avoid being confused with other diseases that are often overlooked and misdiagnosed clinically.

KEYWORDS: Small intestinal bleeding, chronic myelomonocytic leukemia, bone marrow aspiration.

CASE PRESENTATION

We report the case of a 73-year-old male who got intermittent melena for 15 days, which was exacerbated for 2 days". The patient first emerged 15 days ago without any evident causes; a black color formed once a day. colonoscopy revealed multiple polyps in the rectum, patient had a polypectomy and during the postoperative recovery patient complained about black stool for 2 days, consecutively the number of times has increased compared with before, 5 times a day, followed by dizziness, fatigue, palpitation, and discomfort, again we ordered colonoscopy examination which showed upper gastrointestinal bleeding then suddenly we decided to give blood transfusion, hemostasis, and other treatments, continuously blood in the stool symptoms were not relieved, so we ordered complete blood routine which showed WBC: 9.89x109/L, Hemoglobin 89x109g/L, platelets: 110x109/L, at the same time we had taken the BP: 105/56mmHg, HR: 95 times/min, after ordering a colonoscopy revealed no obvious abnormalities, and capsule endoscopic which showed multiple ulcers in the small intestine, multiple mucosal bulges in the small intestine so we decide to do intraoperative surgical exploration and found that fine capillaries that we saw in many places in the ileal intestinal wall, and then we consult with the gastroenterology department which assisted us with the intraoperative colonoscopy exploration: which showed multiple ulcers of the ileal mucosa, and some ulcers which were bleeding, Therefore, partial ileal resection were performed. the patient's white WBC began to rise to 37x109/L, hemoglobin increased insignificantly to 82x109g/L, and platelets began to decrease to 99x109/L, then we consulted with the hematology department and recommended bone marrow

aspiration and the patient refused, and there was no more blood in the stool, the re-examination of hemoglobin showed stable, and the condition improved and discharged. [Fig 1ab]

One month after being discharged from the hospital, blood appeared again in the stool, which was a dark red tar stool, he had 10 times more blood in the stool than before, and he was readmitted to the hospital. His blood routine showed: WBC: 20.76 x 109/L, HGB: 60.00 x 109 g/L, PLT: 206 x 109/L and his vitals showed a pulse rate of 79/min and a blood pressure of 100/65 mmHg. We ordered a colonoscopy, the result of which showed telangiectasia at the end of the ileum (5cm ileal valve). After that, the patient underwent a blood transfusion, fluid replacement, acid suppression, hemostasis, and other symptomatic treatments. Unfortunately, there was still occasional blood in the stool, HB dropped to 47 g/l, and the variability of white blood cells was always high at 32x109/l, as a result, we performed a bone marrow aspiration, and the results of bone marrow peripheral blood showed the presence of naive granulocytes, a significant increase in the proportion of monocytes, and abnormal hematopoiesis in bone marrow granulocytes and erythroid. The patient was diagnosed with chronic myelomonocytic leukemia and further analysis of genetic mutation in myeloid blood disease revealed that a frameshift mutation was detected in the ASXL gene (mutation frequency:41%), false sense mutation was detected in the EP300(43.8%), PTPN11 (32.3%), the SRSF2gene (42.8%) and mutations were detected in the TET2 gene (82.6%), all of which ar considered pathogenic changes associated with myelopathy. All were confirmed as mutations obtained in this sample. Among them, ASXL gene mutations suggest a poor prognosis in CMML patients. The patient refused to be referred to a hematologist for further treatment. Therefore, after treatment with iron polysaccharide and thalidomide, there was no blood in the stool, stable hemoglobin (HB:89x109g/L), white blood cells decreased significantly (WBC:9.63x109/L), platelets were not decreased (PLT:202x109/L), and his condition improved, and he was discharged. After discharge, the patient had no blood in the stool for 10 months, received chemotherapy twice in an outpatient hospital, and died one year after surgery due to a severe lung infection and leukemia. [Table1ab]

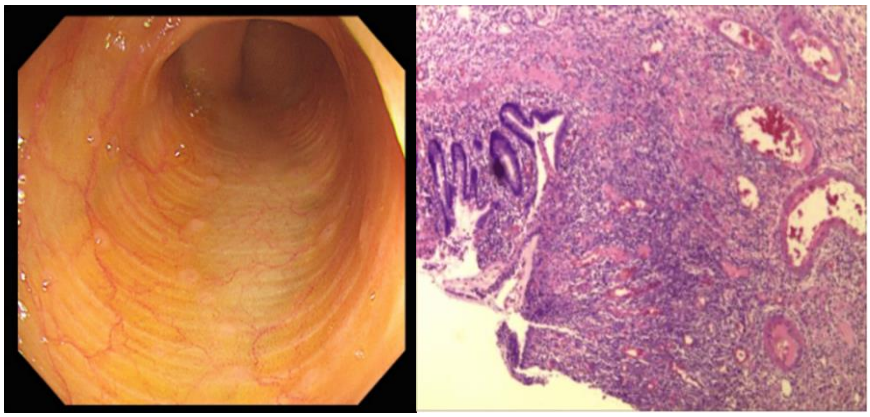

Fig. 1ab: (a) shows intraoperative colonoscopy (b)shows Postoperative pathological examination (internal Documentation).

Table 1a: Analysis of gene mutations in myeloid blood disease.

Class I Variation site: mutation site with clear clinical significance				
Gene	**Chromosome coordinates**	**Mutation site**	**Variation frequency**	**Source of Variation**
ASXL1 NM_015338.6	Chr20:31022441	C.1934dup P.Gly646trpfster12	41% Sequencing depth:5355X	Somatic Cell mutation
• ASXL1 gene mutations indicate poor prognosis in AML, MDS, CMML, PMF, and PV patients. NCCN-AMLNCCN-MDS, PMID: 24695057,NCCN-MPN>				
PTPN11 NM_002834.4	Chr12:112888210	c.226G>A p. Glu76lys	32.3% Sequencing depth:5682X	Somatic Cell mutation
• Mutations in the PTPN11 gene are associated with shorter overall survival rates in MDS patients PMID:30504321>. • PTPN11 mutation is associated with poor prognosis in adult AML patients<PMID: 32561839>.				
SRSF2 NM_001195427.2	Chr17: 74732959	c.284C>A p. Pro95His	42.8% Sequencing depth: 4156X	Somatic Cell mutation
• Mutations in the SRSF2 gene indicate poor prognosis in MDS, AML, PMF, and PV patients.>NCCN-MDS, NCCN-MPN. Diagnostic and Treatment Guidelines for Adult Acute Leukemia (2018 Edition)				

TET2 NM_001127208.2	Chr4:106164061	c.3571C>T p.GIn1191Ter	82.6% Sequencing depth: 2393X	Somatic Cell mutation
• Mutations in the TET2 gene are associated with poor prognosis in AML patients<PMID: 24994606, PMID: 28070990> • Mutations in the TET2 gene indicate poor overall survival in MPN patients and are associated with leukemia transformation<PMID: 24478400> • Mutations in the TET2 gene increase treatment response to 5-azacytidine and decitabine in MDS patients<NCCN MDS>				
Class II Variantion sites with potential clinical significance				
EP300 NM_001429.4	Chr22:41536160	c.1777C>T P.pRP593Ser	43.8 Sequencing depth:1343X	Somatic Cell mutation

Table 1b: Analysis of gene mutations in myeloid blood disease.

Class III Variation Site: variant site with unknown clinical significance				
Gene	**Chromosome coordinates**	**Mutation site**	**Variation frequency**	**Source of Variation**
ATM NM_000051.3	chr1l:108175463	c.5558A>T p.Asp1853Val	54.7% Sequencing depth:1768X	Germline variation
• This mutation has been reported in both B-CLL and AML patients<PMID: 10397742PMID: 27534895. CO5M21628>, and M083593>is included in the HGMD database. Its clinical significance is currently unclear.				
CSMD1 NM_033225.6	chr8:3474296	c.1033G>C p.Val345Leu	64.7% Sequencing depth:6892X	Germline variation
The mutation has not been reported to be related to myeloid hematological diseases, and its clinical significance is currently unclear.				
EP300 NM_001429.4	chr22:41545159	c.2359G>A p.Gly787Ser	48.1% Sequencing depth:2037X	Germline variation
• The mutation has been reported in patients with PMD: CCM4380244, and its Clinical Significance is currently unclear .				
TET2 NM_001127208.2	Chr4:106164061	c.3571C>T p.GIn1191Ter	82.6% Sequencing depth: 2393X	Germline variation
• this mutation has been reported in children with ALL, PMD:2652232, and no reports reto myeloid hematological diseases have been found yet. The clinical significance is current unclear.				
ROBO2 NM_001128929.3	chr3:77612488	c.1730+8A>G	50.3% Sequencing depth:4127X	Germline variation
Class IV mutation sites: Benign or potentially benign mutation sites				
There are 38 single nucleotide polymorphisms (SNPs), which are currently believed to have no pathogenic significance related to myeloid hematological diseases; There is one synonymous variation that does not cause changes in amino acids and has no clinical significance; There are 20 mutation sites, which are identified as benign mutations based on database retrieval; There are 2 mutation sites, which were retrieved from the database as possible benign mutations.				
Detection Results: A frameshift mutation c.1934dup (p.Gly646TrpfsTer12) was detected in the ASXL1 gene of this sample (heterozygous, mutation frequency 41%), EP30 (missense mutation c.1777C>T (p.Pro593Ser) (heterozygous, mutation frequency 43.8%), PTPN11 gene missense mutation c.226G>A (p.Glu76Lys) (heterozygous, mutation frequency 32.3%), and SRSF2 gene missense mutation c 284C>A (p.Pro95His) (heterozygous, mutation frequency 42.8%), and nonsense mutations c.3571C>T (p.Gln1191Ter) (heterozygous, mutation frequency 82.6%) were detected in the TET2 gene. All of the above mutations are considered pathogenic changes related to myeloid hematological diseases and have been confirmed to be somatic acquired mutations in this sample. Among them, ASXL1 gene mutations suggest poor prognosis in CMML patients.				

DISCUSSION

Telangiectasia, also known as Spider Veins, is a disorder characterized by abnormal dilation of capillary diameters, increased fragility of microvascular walls, and increased permeability and blood drainage.[1] Telangiectasia has a low incidence but a higher case fatality rate. In recent years, the reports of small bowel bleeding due to capillary dilation have increased gradually; the incidence is 0.5%-1.0%, the major bleeding volume is 100–400 ml, and the condition is threatening. and the case fatality rate is also high, like 30%~80%. The relationship between small bowel bleeding and capillary dilation was mainly

confirmed by pathological changes and endoscopic findings. The clinical signs and symptoms of small bowel bleeding are atypical and lack specificity. Because the small intestine is adjacent to nearby organs such as the stomach, duodenum, and colon, small bowel bleeding can be distinguished from other digestive disorders. Clinically, the treatment methods for small bowel bleeding include endoscopic hemostasis, endoscopic anticoagulation, and surgical treatment, in which endoscopic hemostasis is the main treatment method at present. With the development of diagnostic and therapeutic techniques, the diagnosis and treatment of small bowel bleeding have improved significantly, but a proportion of patients remain undetected due to the absence of typical clinical symptoms.

In this case, we used capsule endoscopy to determine the bleeding site, supported intraoperative colonoscopy to clarify the cause and location of bleeding, and performed a partial ileostomy. The patient's symptoms of blood in the stools were in remission, and the hemoglobin was significantly higher than before. But after surgery, the white blood cells started to increase. Considering this could be related to the emergency response after surgery, we found that not only did white blood cells continue to increase, but monocytes also began to increase and platelets began to decrease, which caught our attention. Although the diseased bowel was surgically removed, the possibility of hematological diseases was not excluded, after discussing this with the patient, the patient refused to have a bone marrow aspiration and was discharged. After one month of surgery, the patient was re-admitted to the hospital because of blood in the stool. No abnormalities were found after the endoscopy was completed, and the diagnosis was confirmed by bone marrow aspiration and genetic testing (CMML).

Chronic mononucleosis (CMML) is a rare and highly variable disease that is an overlap of myelodysplastic syndromes and myeloproliferative neoplasms, associated with leukemic dysplasia, pathologic hematopoiesis, and marked proliferation of monocytes. Mainly elderly patients, because there is currently no effective treatment, so the prognosis is poor, and the average survival time is only 12 to 18 months. CMML can present in different ways in different patients, usually manifesting as leukocytosis, monocytosis, and thrombocytosis. Some patients may also develop anemia, thrombocytopenia, and splenomegaly. A wide range of gene mutations have been detected in CMML patients, and approximately 90% of CMML patients have molecular mutations in TET2, SRSF2, and ASXL1, which have important diagnostic and prognostic value, including association with SRSF2. and TET2 is highly specific in CMML.[2] In a gene mutation analysis based on 629 patients with CMML, TET2 mutations were found to be significantly different between CMML-0 and CMML-1. ASXL1, RAS (including NRAS and KRAS), TP53, and RUNX1 mutations occur at similar rates in type 3.[3] Furthermore, in elderly patients with extremely high leukocytes and extremely low PLT, ASXL1 frameshift mutations or nonsense mutations are independent risk factors for poor prognosis.[4] and even the ability to convert to acute myeloid leukemia.[5]

The clinical manifestations of CMML are so insidious at onset and the laboratory features are so ambiguous that they are easily missed and misdiagnosed. Bleeding from the small intestine is very rare clinically. When combined with preoperative capsule endoscopy, intraoperative colonoscopy resulted in surgical treatment, although the symptoms of blood in the stool were reduced and the postoperative anemia symptoms did not improve significantly. In this patient's admission to the hospital, leukocytes and platelets showed no obvious abnormalities; we only noticed a decrease in hemoglobin, an abnormal increase in the leukocyte counts after surgery, an anemia that was difficult to correct, and finally a clear diagnosis with CMML. The reason for the delay in diagnosis in this patient may be our misinterpretation that the leukocytosis is due to the compensatory capacity of the bone marrow more than hypersplenism in gastrointestinal bleeding, or it may be masked. by the temporary narrowing of the spleen in gastrointestinal bleeding. After surgical stimulation, the body falls into a state of high stress, the hematopoietic process of the bone marrow after surgery becomes more active, and leukemia also progresses strongly. In addition, the mucosal injury of this patient's small intestine may cause small bowel bleeding due to white blood cell infiltration into the vascular wall, resulting in decreased elasticity and increased fragility of the vascular wall. The lumen is filled with white blood cells, the permeability of the vascular wall is increased, and ischemia and necrosis of the small intestine mucosa are complicated by small bowel bleeding.

CONCLUSION

The small bowel bleeding rate is low, the clinical symptoms are insidious and lack specificity, the anatomical features of small bowel bleeding also have blind spots in diagnosis, and the misdiagnosis rate is high. Bleeding is a common clinical manifestation and cause of death in CMML, and clinical reports of patients presenting with early GI bleeding are rare, such as blood in the stool or anemia that is difficult to correct. Doctors should expand the thought process of diagnosis and treatment, find the root cause, and combine it with the actual situation of the patient to examine and treat. At the same time, there is an urgent need to improve diagnostic techniques so that these important cases can be fully understood and recognized.

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Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the record, the patient has consented for his images and other clinical information to be reported in the journal.

Conflicts of interest
There are no conflicts of interest.

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