COLCHICINE-INDUCED BONE MARROW APLASIA IN AN ELDERLY FEMALE WITH RENAL INSUFFICIENCY

Chen-Sen Huang*, Jen-Pi Tsai**, Horng-Rong Chang***

Colchicine has long been employed to treat and prevent acute attacks of gout and also applied to a variety of conditions such as familial Mediterranean fever, Behcet’s disease, and amyloidosis. Severe pancytopenia induced by therapeutic oral colchicines has been reported though rarely. However, there is currently no recommended treatment.

We described a 78-year-old female with pancytopenia and bone marrow aplasia induced by oral colchicines and treated with granulocyte colony-stimulating factor (G-CSF) and erythropoietin (EPO). Pancytopenia and bone marrow aplasia eventually recovered after treatment.

Severe side effects of colchicine are rare, but may be more frequent among elderly patients with renal insufficiency and hepatic dysfunction. Treating colchicine-induced pancytopenia with combination of G-CSF and EPO may be effective. (Acta Nephrologica 2010; 24: 53-56)

Key words: colchicine, pancytopenia, EPO, G-CSF

INTRODUCTION

Colchicine has long been employed to treat and prevent acute attacks of gout and also applied to a variety of conditions such as familial Mediterranean fever, Behcet’s disease, and amyloidosis. Under therapeutic oral dose, the most common side effects of oral colchicine are gastrointestinal symptoms including diarrhea, nausea, vomiting and abdominal pain. However, severe side effects such as pancytopenia or bone marrow aplasia, especially in the elderly are reported. There is currently no recommended treatment for pancytopenia caused by colchicine. We described a case with pancytopenia and bone marrow aplasia induced by oral colchicines. Diagnosis was made by bone marrow biopsy and the patient recovered gradually under treatment with granulocyte colony-stimulating factor (G-CSF) and erythropoietin (EPO).

CASE REPORT

A 78-year-old female resident at a nursing home was admitted to our hospital in August 2007 because of general weakness for two days. She had the history of old cerebrovascular accident (CVA), hypertension and chronic gouty arthritis under medical treatment. Three days prior to admission, the patient was brought to the emergency room (ER) because of watery diarrhea and fresh bloody stool for five times. She also had nausea and vomiting, but denied abdominal pain or fever. Other residents of the nursing home had no similar symptoms. The patient denied taking any medication except those from the out-patient department. Her daily medications for gouty arthritis were prednisolone 5 mg, colchicine 0.5 mg, allopurinol 100 mg, and celebrex 200 mg from June 26 to August 13, 2006. One week before admission, her daily medications were adjusted because of increased episodes of gouty arthritis. (prednisolone 20 mg, colchicine 1.5 mg, allopurinol 100 mg, diclofenac 50 mg and cimetidine 600 mg). Acute gastroenteritis and hemorrhagic bleeding were considered in the ER and she was brought home after treatment. Medications for gouty arthritis were discontinued since then.
The patient was brought to the ER again two days later due to progressive general weakness. Her blood pressure was 164/117 mmHg, body temperature was 36°C, pulse rate was 105 beats/min, and respiratory rate was 14 times/min. Physical examination revealed clear consciousness, pale conjunctivae and tophi over the right hand. Complete blood cell count showed white blood cell (WBC) count 2410/mm$^3$ with 75% neutrophils, hemoglobin 10.7 g/dL and platelet 50 × 10$^3$/ul at admission (Table 1). Blood urea nitrogen was 59 mg/dl and creatinine 2.9 mg/dl (estimated glomerular filtration rate (eGFR) calculated by Modification of Diet in Renal Disease formula was 16.68 ml/min). Urinalysis revealed pyuria with bacteriuria. Abdominal echo revealed bilateral contracted kidney with degenerative cystic lesions and no hepato-biliary problems. Brain CT images revealed hypodense lesion over the right parietal lobe, which was compatible with diagnosis of previous CVA.

After admission, cefazolin 1 g was administered intravenously every 12 hours under the suspicion of urinary tract infection. Hematological data at Day 4 revealed WBC 1.63 × 10$^3$/ul, RBC 3.21 × 10$^6$/ul and platelet 53 × 10$^3$/ul. Bone marrow biopsy was performed for the evaluation of pancytopenia and revealed aplastic bone marrow (Fig. 1 and 2). Because of infectious disease and pancytopenia, GCS-F 250 µg administered subcutaneously was prescribed for her at Days 5, 8 and 12 after hospitalization. EPO 2000 IU administered subcutaneously was also prescribed for her sequentially for three days since Day 6 after hospitalization. She was discharged at Day 13 with hematological data revealing WBC 6.78 × 10$^3$/ul, hemoglobin 9.2 g/dl, and platelet 137 × 10$^3$/ul.

**DISCUSSION**

Colchicine is a neutral and liposoluble alkaloid that interferes with microtubule growth and mitosis. It is absorbed mainly in the ileum, partially metabolized in the liver with its metabolites excreted through the biliary tract. Kidneys excreted about 20% of unchanged colchicine. Patient with hepatic or renal impairment may have prolonged elimination.$^1$

Colchicine toxicity and death is usually a consequence of oral colchicine overdosage exceeding 0.5 mg/kg, the lowest fatal overdose reported being 7.5 mg. Bismuth and colleagues reported minor toxicity with 100% survival after ingestion of less than 0.5 mg/kg, major toxicity (myelosuppression) with 10% mortality after ingestion of 0.5 to 0.8 mg/kg, and 100% mortality (cardiogenic shock and death) after ingestions of doses exceeding 0.8 mg/kg.$^6$ The risk factors for colchicine toxicity include (a) intravenous use, (b) use of loading dose, (c) use in elderly patients, (d) renal insufficiency, (e) hepatic dysfunction, and (f) drug interaction (cimetidine, erythromycin, tolbutamide).$^7$

The course of colchicine toxicity can be divided into three sequential and usually overlapping stages. The first stage occurs during the first 24 hours after ingestion and is dominated by gastrointestinal symptoms, including diarrhea, nausea and vomiting, leading volume depletion and leukocytosis. The second stage develops from 24 to 72 hours after ingestion and is dominated by gastrointestinal symptoms, including diarrhea, nausea and vomiting, leading volume depletion and leukocytosis. The second stage develops from 24 to 72 hours after ingestion and is dominated by gastrointestinal symptoms, including diarrhea, nausea and vomiting, leading volume depletion and leukocytosis. The third stage is recovery of bone marrow with rebound leukocytosis, resolution of organ system derangement, and development of alopecia.$^8$

Colchicine causes bone marrow depression, particu-

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**Table 1. Hematological data**

<table>
<thead>
<tr>
<th>Date</th>
<th>ER</th>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 6</th>
<th>Day 10</th>
<th>Day 12</th>
<th>Day 19</th>
<th>Day 26</th>
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<tbody>
<tr>
<td>WBC (10$^3$/ul)</td>
<td>2.8</td>
<td>2.41</td>
<td>1.63</td>
<td>1.35</td>
<td>2.41</td>
<td>1.39</td>
<td>3.73</td>
<td>6.78</td>
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<td>N (%)</td>
<td>87.2</td>
<td>75</td>
<td>74</td>
<td>63</td>
<td>92.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L (%)</td>
<td>6.4</td>
<td>14</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>B (%)</td>
<td>0</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>Mono. (%)</td>
<td>6.4</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>31</td>
<td>18</td>
<td>2.8</td>
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<tr>
<td>Eosin. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.3</td>
<td>10.7</td>
<td>9.1</td>
<td>7.9</td>
<td>9.2</td>
<td>9.2</td>
<td>10</td>
<td>9.2</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>32.6</td>
<td>27.2</td>
<td>24.2</td>
<td>29.2</td>
<td>29.6</td>
<td>31.6</td>
<td>28.1</td>
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<td>RBC (10$^6$/ul)</td>
<td>3.21</td>
<td>2.80</td>
<td>3.23</td>
<td>3.25</td>
<td>3.49</td>
<td>3.23</td>
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<tr>
<td>RDW (%)</td>
<td>16.1</td>
<td>15.9</td>
<td>16.5</td>
<td>18.3</td>
<td>18.2</td>
<td>18.9</td>
<td>18.1</td>
<td></td>
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<td>PL (10$^3$/ul)</td>
<td>84</td>
<td>50</td>
<td>53</td>
<td>50</td>
<td>69</td>
<td>82</td>
<td>107</td>
<td>137</td>
</tr>
</tbody>
</table>
Fig. 1. Bone marrow containing less than 10% cellularity (Bone marrow, PAS stain, 40 X)

Fig. 2. Precursors of hematopoietic series were markedly decreased with inappropriate ratio of erythrocytes and granulocytes. (Black arrow represents erythrocyte precursor; red arrow, granulocyte precursor) (Bone marrow, PAS stain, 400 X)
larly when associated with acute intoxication and has also been reported after intravenous and oral administration of therapeutic doses. Most patients had gastrointestinal and neurological toxicities before or at onset of severe hematopoietic suppression. A typical arrest of marrow function includes leukopenia, reticulocytopenia, thrombocytopenia and hypocellular bone marrow. Although pancytopenia induced by oral administration of therapeutic dose of colchicines had been reported, the majority of cases had received colchicine intravenously, and oral administration seemed safer. Characteristically, leukopenia lasts for 2-5 days after colchicine is given; while leukocytosis appears at the 7th or 8th day and may persist for two weeks.

In this study, the patient received therapeutic dose of colchicine and recovered from pancytopenia, which lasted more than two weeks. The possible causes of intoxication under therapeutic dose include age, decrease in excretion due to renal insufficiency (eGFR 16.68 to 38.65 ml/min) and combined use with cimetidine. Although allopurinol is another possible cause of leukocytopenia and aplastic anemia, allopurinol dose was not titrated and the patient’s clinical course was compatible to intoxication of colchicine.

The management of severe colchicine poisoning is mainly supportive. Because of colchicine’s rapid tissue distribution and high binding affinity at the intercellular site, hemodialysis, charcoal hemoperfusion and plasma exchange are not effective. A colchicines-specific Fab fragment has been employed to treat a life-threatening intoxication of colchicine.

In conclusion, clinical use of colchicine is safe and severe side effects of colchicine are rare, but probably more frequent in elderly patients with renal insufficiency and hepatic dysfunction. To treat colchicine-induced pancytopenia with combination of GCSF and EPO may be effective, but definitive dose and duration for treatment still need further investigation.

REFERENCES