CASE REPORT
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A Case of Therapy-related Myelodysplastic Syndrome after FOLFOX4 Chemotherapy in Advanced Gastric Cancer

Kwang Il Seo, Sung Eun Kim, Moo In Park, Seun Ja Park, Won Moon, You Jin Han

Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Oxaliplatin is a third-generation platinum compound widely used to treat gastrointestinal malignancy. One of the major side effects of oxaliplatin is thrombocytopenia, the development of which can limit appropriate treatment. We report a 38-year-old man with advanced gastric cancer who developed severe thrombocytopenia after FOLFOX4 (oxaliplatin, leucovorin, and fluorouracil) chemotherapy. The thrombocytopenia was associated with therapy-related myelodysplastic syndrome after cytotoxic chemotherapy and was confirmed by bone marrow biopsy and genetic study. Therefore, physicians should be aware of therapy-related hematologic complications, especially with an oxaliplatin-based chemoregimen, and might consider the bone marrow study in those patients.

Key Words: Gastric cancer, Oxaliplatin, Myelodysplastic syndrome, Side effect

INTRODUCTION

Therapy-related myeloid neoplasm (t-MN), previously described as therapy-related myelodysplastic syndrome (t-MDS), sometimes occurs as a complication of cytotoxic therapy.[1] Recently, stomach cancer has been shown to respond well to oxaliplatin-based chemotherapy.[2] However, a major side effect of oxaliplatin is thrombocytopenia, the development of which can limit the appropriate treatment dose and schedule likely due to direct myelosuppression, splenic sequestration, or an immune-mediated mechanism.[3] This report describes a case of myelodysplastic syndrome (MDS) presenting as severe thrombocytopenia in a patient with advanced gastric cancer after repeated FOLFOX4 administration consisting of oxaliplatin, 5-flourouracil, and leucovorin.

CASE REPORT

A 38-year-old man was transferred from a local hospital for evaluation of abdominal pain and postprandial abdominal bloating. Any other specific past medical history was not found. He had not heard about the Helicobacter pylori infection. And there was no family history related to malignancy. When we per formed esophagogastroduodenoscopy (EGD), a huge Borrmann type IV advanced gastric cancer tumor was noted through the side of lesser curvature, from the upper body to the distal antrum. In addition, food retention was observed with pyloric ring obstruction, probably due to tumor infiltration (Fig. 1). An upper gastrointestinal series showed abnormal luminal narrowing with mucosal irregularity in the antrum and pyloric area of the stomach. Therefore, a pyloric stent was inserted into the stenotic portion. In the abdominal computerized tomography (CT) scan, irregular wall thickening at the gastric antrum with perigastric adenopathy and ascites were noted. Finally, stomach cancer with cancer peritonei was confirmed by pathologic diagnosis using laparoscopic peritoneal biopsy.

Thus, we started systemic chemotherapy with the FOLFOX4 regimen. After the second cycle of chemotherapy, moderate leukopenia (common terminology criteria for adverse effects [CTCAE]: grade 2) was observed. Therefore, the dose of che-

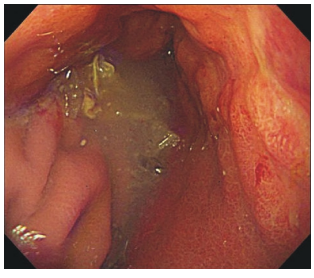

Fig. 1. Initial Endoscopic Fin ding. Poorly circumscribed, infiltrating masses with ulceration and the base infiltrated with cancer was noted from whole antrum to the AW-LC-PW side of the body.

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Corresponding Author: **Sung Eun Kim**, MD, PhD
Department of Internal Medicine, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-5205, Fax: +82-51-990-5055
E-mail: solefide@hanmail.net

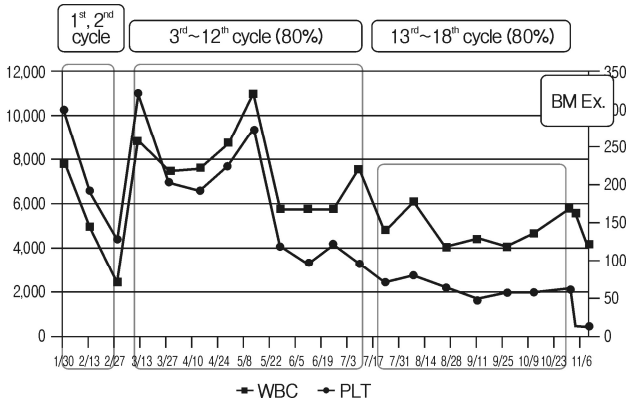

Fig. 2. Flow Chart. After the 18th cycle of chemotherapy, severe thrombocytopenia was sustained (common terminology criteria for adverse effects [CTCAE]; grade 4), and it did not recover to the previous level.

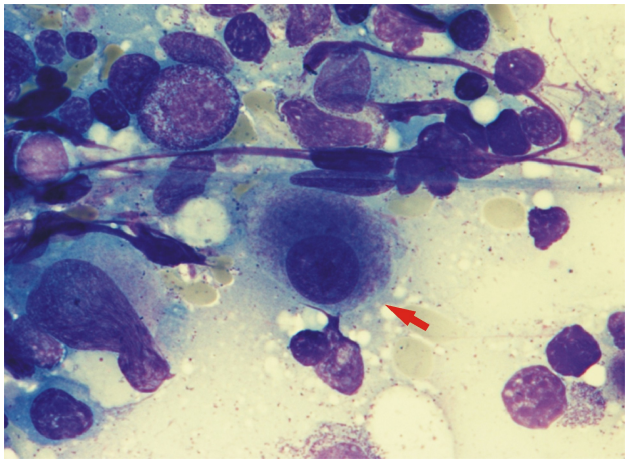

Fig. 3. Bone Marrow biopsy. Megakaryocytes increased in number, and several showed hypolobulation or multinucleation.

motherapy was reduced to 80% of the normal dosage in subsequent chemotherapy. After the 13th cycle of chemotherapy, moderate thrombocytopenia (CTCAE: grade 2) was again observed. Gradual worsening of the thrombocytopenia was subsequently observed after sequential chemotherapy. After the 18th cycle of chemotherapy, severe thrombocytopenia (CTCAE: grade 4) was sustained, and it did not recover to the previous level. Unfortunately, we could not continue the chemotherapy (Fig. 2).

Bone marrow biopsy was recommended by the hematologist. On the pathologic report of bone marrow biopsy, most of the marrow space was acellular or hypocellular. In addition, approximately 10% of the erythroblasts showed nuclear irregularities, such as nuclear budding or binuclearity. Megakaryocytes were increased in number, several showed hypolobation (Fig. 3), and some ring sideroblasts were noted (Fig. 4).

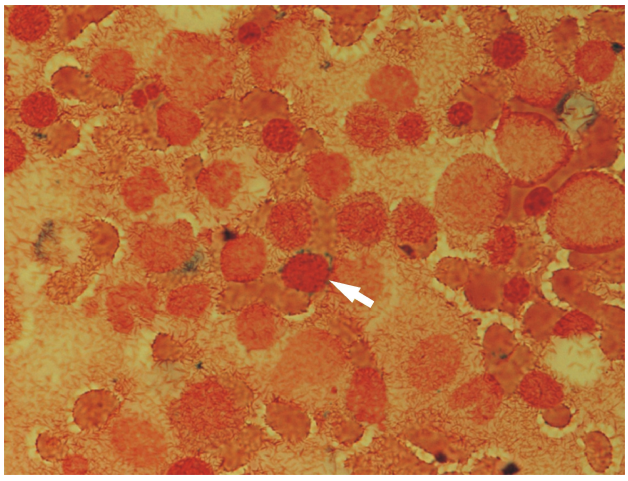

Fig. 4. Iron Stain. Stainable iron (arrow) was seen on the slide examined, and some ring sideroblasts were present.

Chromosomal study showed that, despite poor chromosome quality, about 80% of cells were -3, del(3p), der(3)t(3) (q10), -5 or -7. These were considered a marrow dysplastic condition after cytotoxic chemotherapy. Finally, we diagnosed the patient with t-MDS.

Several therapeutic options were considered to manage the t-MDS and gastric cancer. However, the patient refused further evaluation or management of his disease, and he was discharged and transferred to the hospital for supportive care.

DISCUSSION

Thrombocytopenia and hematologic toxicities are frequent side effects of cytotoxic chemotherapy. One well-known cytotoxic drug that has thrombocytopenic effects is oxaliplatin, which is a third-generation platinum compound widely used for gastrointestinal malignancy. The FOLFOX4 regimen, a combination of 5-flourouracil, leucovorin, and oxaliplatin, is a very well-recognized therapy for colorectal cancer therapy, and it is now being used in advanced gastric cancer.[2]

Despite good results with the FOLFOX4 regimen, many patients experience side effects, such as peripheral neuropathy, diarrhea, thrombocytopenia, and rarely, pulmonary fibrosis.[4] Mild to severe thrombocytopenia can be caused by oxaliplatin. The thrombocytopenia is usually not serious, such as grade 3-4, but the severe thrombocytopenia can delay the chemotherapy schedule or require reduced dosage of the regimen. Thus, many clinicians have concerns about the development of thrombocytopenia. Several mechanisms have been suggested to explain the occurrence of thrombocytopenia: (1) bone marrow suppression, (2) an immune-mediated mechanism, and (3)

splenic sequestration.[3] Transient bone marrow suppression revealed by thrombocytopenia can be managed by modulating the chemotherapy schedule or adjusting the dose. However, persistent bone marrow suppression can limit the scheduled therapy and have life-threatening results.

The incidence of t-MN is increasing due to the increased number of people who survive cytotoxic chemotherapy and experience underlying malignant or non-malignant conditions.[5] In general, t-MN can be subdivided into t-MDS and therapy-related acute myeloid leukemia (t-AML). Although distinct clinical and genetic characters are recognized, these disorders are regarded as a single disease spectrum, t-MNs.[5] A higher genetic susceptibility was reported to be a strong cause of the association between some patient- and therapy-related myeloid neoplasms.[6] In a recent review of 277 t-MN patients in Italy, 64% of patients had cytogenetic abnor- malities. The karyotype was unfavorable in 39% of patients and involved chromosome 5 or 7 deletions in most cases.[7]

In our case, repeated cytotoxic chemotherapy led to recurrent thrombocytopenia and, eventually, an irreversible thrombocytopenic state. The thrombocytopenia occurred in well-controlled underlying primary malignancy, without prior underlying hematologic abnormality. And when we performed the bone marrow aspiration, most of the bone marrow was hypocellular or acellular, and chromosomal study confirmed deletion of both the 5 and 7 chromosomes, a common cytogenic abnormality of t-MNs.[8] Although various side effects of oxaliplatin-based chemotherapy have been observed, few reports have confirmed MDS through biopsy and chromosomal study. In this report, we confirmed syndrome-MDS through biopsy in an advanced gastric cancer patient after the oxaliplatin-based FOLFOX4 regimen.

In conclusion, the incidence of t-MDS has been increasing as a result of increasing numbers of cancer survivors. FOLFOX4 chemotherapy has been shown to be an outstanding chemoregimen in advanced gastric cancer. We can expect an increase in t-MDS among advanced gastric cancer patients who are undergoing systemic chemotherapy, such as the FOLFOX4 regimen. Therefore, it is important for clinicians to be aware of therapy-related hematologic complications, especially in oxaliplatin-based chemoregimens. In addition, bone marrow study could be considered in patients who underwent chemotherapy with the hematologic abnormality.

Core tip: Oxaliplatin widely used to treat gastrointestinal malignancy and it can cause side effects such as thrombocytopenia. This case report shows the importance for clinicians to recognize therapy-related hematologic complications during oxaliplatin-based chemoregimens and the necessity of bone marrow study in patients who underwent chemotherapy with the hematologic abnormality.

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