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Slowly Progressive Bone Marrow Metastasis of Gastric Cancer Followed-up Without Treatment

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Abstract. *Background/Aim: Bone marrow metastasis (BMM) of gastric cancer (GC) is complicated by disseminated intravascular coagulation syndrome (DIC), which is more prominent in poorly differentiated carcinoma. This is one of the first case reports of a slowly progressing BMM of GC after approximately 1 year of follow-up without treatment. Case Report: A 72-year-old woman underwent total gastrectomy and splenectomy for GC in February 2012. The pathological diagnosis was that of a moderately differentiated adenocarcinoma. Five years later in December 2017, she developed anemia; however, its cause remained unknown. Due to worsening of the anemia, the patient visited the Kakogawa Central City Hospital in October 2018. Bone marrow biopsy revealed an infiltration of caudal type homeobox 2-positive cancer cells, and our diagnosis was BMM of GC. There was no DIC. The incidence of BMM is high in well- or moderately differentiated breast cancer but rarely causes DIC. Conclusion: As with breast cancer, in moderately differentiated cancer cells, BMM of GC may progress slowly after the appearance of symptoms without causing DIC.*

When solid cancer invades the bone marrow, it is termed bone marrow metastasis (BMM) or bone marrow carcinomatosis. BMM is associated with disseminated intravascular coagulation (DIC) and severe microangiopathic hemolytic anemia, and has a poor prognosis (1, 2). Gastric cancer (GC) is the most common cause of BMM among solid tumor types, with poor prognosis despite treatment (3-5).

To our knowledge, this study is one of the first reported cases of a slowly progressing BMM of GC that was untreated and not followed-up for 11 months, and discusses reasons for the slow progression of the disease. Written informed consent was obtained from the patient for the publication of this report.

Case Report

A 72-year-old woman underwent total gastrectomy and splenectomy for GC in February 2012. The histopathological diagnosis was tubular 2, moderately differentiated (Union for International Cancer Control classification, seventh edition) (6), ERB-B2 receptor tyrosine kinase 2-negative, tubular, moderately differentiated (WHO classification 2019) (7), and the pathological stage was pT2N0M0, stage IB (Union for International Cancer Control classification, seventh edition) (6). She was followed-up without adjuvant chemotherapy. Five years later, in December 2017, she visited a local physician for mild shortness of breath on exertion. The local physician noted the presence of anemia (hemoglobin level=9.5 g/dl) and elevated serum alkaline phosphatase (ALP) levels (1,202 IU/l). However, the cause of the anemia remained undiagnosed and the local doctors continued to observe the patient. At the next visit (September 2018), her local physician referred her to the Kakogawa Central City Hospital (October 2018) for worsening anemia (hemoglobin level=8.9 g/dl) and elevated serum ALP level (1,843 IU/l), compared to the levels at her previous checkup. She had not been tested for *Helicobacter pylori* infection and had no history of cancer except GC. She also had no family history of suspected hereditary tumors. The physical examination at the initial visit to our Department revealed a body temperature of 36.4˚C, a heart rate of 89 beats/min, blood pressure of 132/65 mmHg, a respiratory rate of 16 breaths/minute, eyelid conjunctiva pallor, no heart murmur,

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flat soft non-tender abdomen, no edema, and no palpable superficial lymph nodes. The blood tests revealed normocytic anemia (hemoglobin level=8.5 g/dl, mean corpuscular volume=93.0 fl) and high serum levels of ALP (4,197 IU/l) and carbohydrate antigen 19-9 (CA19-9=303.8 IU/ml), without evidence of any iron or vitamin B12 deficiency, elevated levels of liver enzymes or serum creatinine, or DIC (Table I). A computed tomography scan did not identify any causes of anemia (Figure 1). Bone marrow biopsy revealed solute carrier family 4 member 1/member 3 (AE1/AE3)-positive, caudal type homeobox 2-positive cancer cells, which with a history of gastric cancer surgery led to the diagnosis of BMM of GC (Figure 2). S-1 plus oxaliplatin therapy for BMM of GC was initiated in November 2018. The serum ALP and CA19-9 levels returned to normal, although the hemoglobin remained around 7 g/dl (Figure 3). The bone marrow biopsies in January 2019 showed no cancerous infiltration, although they were hypoplastic. In addition, the bone marrow biopsy in December 2019 showed that the blood cells of each lineage showed a differentiation trend and no cancer cells. After the start of chemotherapy, computed tomography every 3 months did not detect any metastasis of GC, and the disease remained stable for more than 2 years.

Table I. *Patient's laboratory results at her initial visit to our Department.*

Blood components	Patient	Normal range
Complete blood count		
White blood cells, /μl	4760	3,300-8,600
Red blood cells, $\times10^4$/μl	270	386-492
Hemoglobin, g/dl	8.5	11.6-14.8
Hematocrit, %	25.1	35.1-44.4
Mean corpuscular volume, fl	93.0	83.6-98.2
Platelets, $\times10^4$/μl	24.3	158-348
Neutrophils, %	49.0	40.0-70.0
Lymphocytes, %	41.0	20.0-50.0
Monocytes, %	7.0	0.0-10.0
Eosinophils, %	3.0	1.0-5.0
Basophils, %	0.0	0.0-1.0
Reticulocytes, %	1.9	0.2-2.0
Immature platelet fraction, %	1.9	1.0-4.8
Coagulation test		
Activated partial thromboplastin time, s	26.0	26.0-38.0
Prothrombin time, %	101.6	70.0-130.0
Fibrinogen, mg/dl	303	200-400
Fibrin/fibrinogen degradation products, μg/ml	20.9	0.0-5.0
D-Dimer, μg/ml	24.4	0.0-1.0
Biochemistry		
Total protein, g/dl	7.1	6.6-8.1
Albumin, g/dl	4.1	4.1-5.1
C-Reactive protein, mg/dl	0.02	0.00-0.14
Aspartate aminotransferase, IU/l	23	13-30
Alanine aminotransferase, IU/l	12	7-23
Alkaline phosphatase, IU/l	4197	106-322
Total bilirubin, mg/dl	0.4	0.4-1.5
Lactate dehydrogenase, IU/l	269	124-222
Blood urea nitrogen, mg/dl	23.2	8.0-20.0
Creatinine, mg/dl	0.60	0.46-0.79
Na, mEq/l	139	138-145
K, mEq/l	4.6	3.6-4.8
Cl, mEq/l	103	101-108
Creatine kinase, IU/l	128	41-153
Amylase, IU/l	124	44-132
Glucose, mg/dl	99	73-109
CEA, ng/ml	3.3	0.0-5.0
CA19-9, IU/ml	303.8	0.0-37.0
IgG, mg/dl	996	861-1,747
IgA, mg/dl	260	93-393
IgM, mg/dl	51	50-269
Fe, μg/dl	101	40-188
Ferritin, ng/ml	8	5-152
Total iron-binding capacity, μg/dl	472	246-410
Unsaturated iron-binding capacity, μg/dl	371	108-325
Cu, μg/dl	159	70-132
Thyroid-stimulating hormone, μIU/ml	6.28	0.34-4.22
Free thyroxine, ng/dl	0.76	0.77-1.59
Erythropoietin, mIU/ml	246.0	4.2-23.7
Vitamin B12, pg/ml	185	233-914
Folic acid, ng/ml	11.8	3.6-12.9
Direct Coombs test	Negative	

Discussion

We present a case of GC with BMM which had been followed-up without treatment for approximately 11 months after worsening anemia.

GC with BMM is rare, with no established treatment (1, 8). BMM is associated with hematological disorders, such as anemia and DIC, and the prognosis of GC in patients with DIC is unfavorable (1, 9-11). A small series of retrospective studies reported methotrexate and 5-fluorouracil therapy was effective for GC with DIC (9, 12). However, the most common histological types of GC with DIC are those with poor prognoses and resistance to chemotherapy, such as poorly differentiated carcinoma and signet-ring cell carcinoma (1, 10). Therefore, with chemotherapy, the prognosis for GC with DIC is short (median of 2-5 months) and without chemotherapy, median survival is approximately 2 weeks (9-12).

In contrast, the rate of BMM in breast cancer is approximately 30% in the early stages; however, reports of DIC are minimal (13, 14), which may be related to the high proportion of hormone-positive subtypes (46-68%) among BMM cases (13, 14). Well-differentiated hormone-positive breast cancer shows slow growth in the bone marrow and is associated with delayed recurrence (15, 16).

As with breast cancer, the higher the degree of differentiation in GC, the slower the progression of BMM might be. The present patient survived without treatment for more than 11 months after the severity of anemia increased.

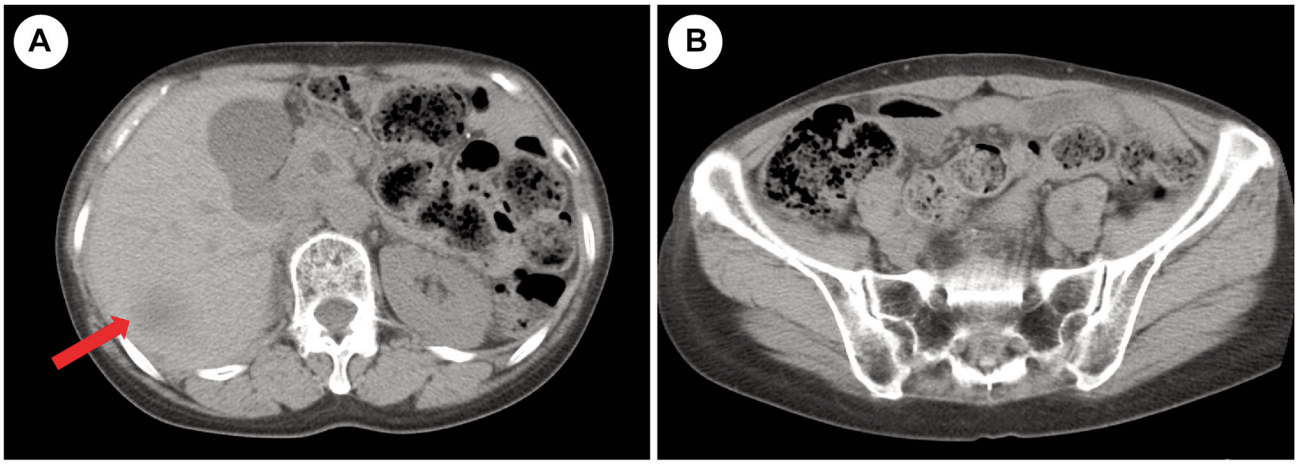

Figure 1. *Plain computed tomography findings of the abdomen and pelvis at the initial visit: A: Hepatic cyst (red arrow). B: No recurrent lesions in the pelvis after total gastrectomy.*

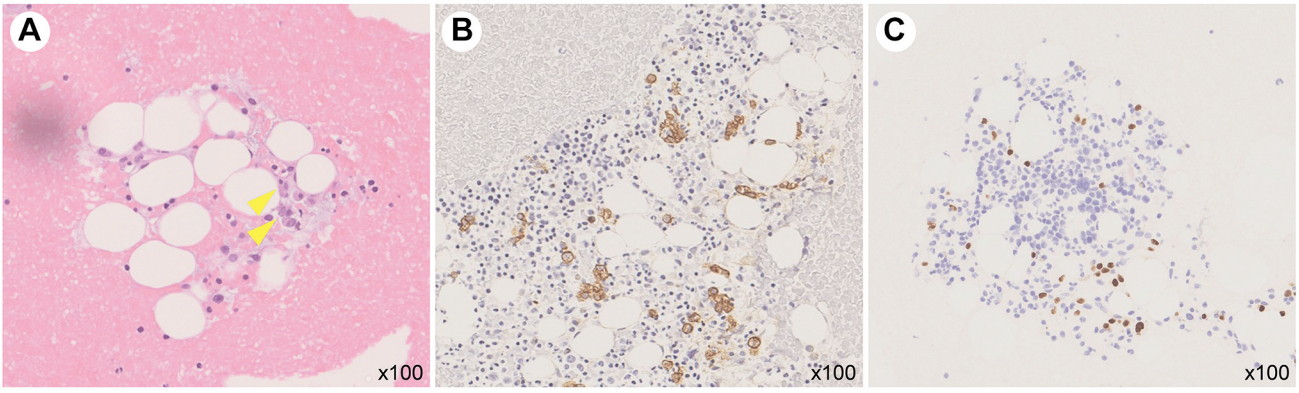

Figure 2. *Histopathological examination of the bone marrow. A: Carcinoma cells (yellow arrowheads) (hematoxylin and eosin staining, ×100). B: Expression of solute carrier family 4 member 1/member 3 (AE1/AE3) (immunohistochemical staining, ×100). C: Expression of caudal type homeobox 2 (CDX2) (immunohistochemical staining, ×100).*

Although iron-deficiency anemia and megaloblastic anemia after gastrectomy are differential diagnoses for worsening anemia, this patient's laboratory results showed no iron or vitamin B12 deficiency when the anemia was developing, and there was no evidence of bleeding, hemolysis, chronic renal failure or hepatic cirrhosis. Therefore, we concluded that the worsening anemia was due to myelosuppression caused by BMM of GC.

We determined the onset of BMM was when the abnormal serum ALP level appeared, as it occurred with worsening anemia before the initiation of systemic chemotherapy.

There is little literature on the approximate period between surgery for GC and the onset of symptomatic BMM. However, there are a few reports of symptoms occurring more than 10 years after surgery (17-19), and the disease progresses rapidly after becoming symptomatic. The latent period might not be proportional to survival time after the appearance of symptoms.

In conclusion, in cases of BMM of GC, well-differentiated cancer cells may progress slowly after the appearance of symptoms and not cause DIC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

Conceptualization, H.S., and A.O.; methodology, H.S., and A.O.; investigation, H.S., Y.I., and A.O.; data curation, H.S., Y.I., and A.O.; writing–original draft preparation, H.S.; writing–review and editing, H.S., Y.I., A.O., and A.O. All Authors have read and agreed to the published version of the article.

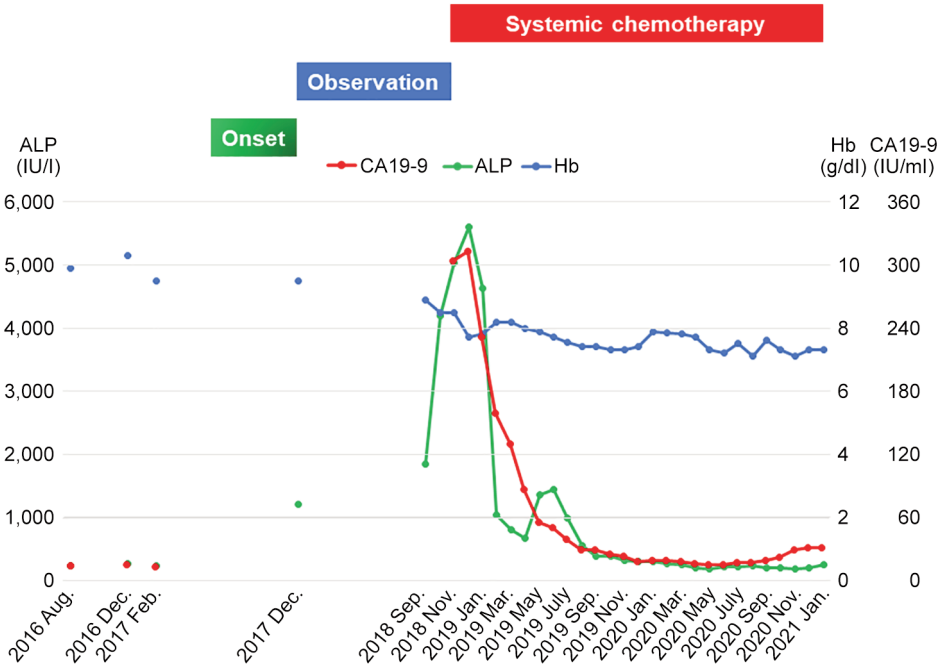

Figure 3. *Time course of changes in hemoglobin (Hb), alkaline phosphatase (ALP), and carbohydrate antigen 19-9 (CA19-9).*

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