Aplastic Anemia Associated with Stomach Cancer
— A Case Report —

Jee Sook Hahn,1 Doe Young Kim,1 Dong Ki Nam,1 Young Sik Lee,1 Sun Ju Lee,1 Yun Woong Ko1
and Chang Hwan Cho2

Herein is presented a case of aplastic anemia associated with adenocarcinoma of the stomach which seemed to be coincidental. A 52 year-old man was admitted with a 3 year history of dyspnea. Three years previously, he was diagnosed as bone marrow hypoplasia and had been treated with oxymetholone for 1 year. After confirmation of aplastic anemia during the first admission, he was followed up with fluoxymesterone and steroids. One year later, he was readmitted with melena. Fibergastroscopy and an UCI study revealed a fungating mass on the antrum suggestive of stomach cancer. Following perioperative platelet transfusions and intensive supportive care, a subtotal gastrectomy was performed and there were no postoperative complications. Pathologic examinations disclosed a moderately well differentiated adenocarcinoma. This is the first report in Korea of adenocarcinoma of the stomach occurring in a patient with aplastic anemia. He survived 17.5 months after the surgery and 5.4 years after the onset of aplastic anemia. Gastrointestinal bleeding in aplastic anemia may be incorrectly ascribed to steroid use and overlooked, thus the need to fully investigate gastric pathology by endoscopy as well as radiology is stressed. In a patient with pancytopenia, the major surgical procedures are frequently evaded by both surgeons and internists due to the possibility of morbidity from bleeding and infection. In this case, intensive perioperative supportive care and surgery were combined to prolong the patient's survival time.

Key Words: Aplastic anemia, stomach cancer, surgery

Both aplastic anemia and malignancy are not uncommon in Korea, and occasionally more than one type of malignancy occurs in one patient. Delamore and Geary (1971) described four patients with idiopathic aplastic anemia whose disease transformed to acute leukemia, while Hirota (1981) and Oda et al. (1983) reviewed cases of hepatocellular carcinoma and other hormone related cancers in patients with aplastic anemia after long term use of androgens, the most common treatment for aplastic anemia. The association between Fanconi's anemia and squamous cell carcinoma is well known. However adenocarcinoma of the stomach in idiopathic aplastic anemia so far as ascertained, has not previously been reported. The authors present herein a case of aplastic anemia associated with stomach cancer.

CAST REPORT

A 52 year-old man presented at Severance Hospital complaining of dyspnea of 3 year duration on April 4, 1984. Three years prior to admission, he was diagnosed elsewhere as bone marrow hypoplasia and was treated with oxymetholone. Two years ago, he discontinued oxymetholone therapy and used herb medicines for the following 6 months. One month before admission, the dyspnea became more aggravated. He had no history of pulmonary tuberculosis and was taking no other medications. During the first admission, the patient appeared to be chronically ill, pale, dyspneic and alert. Blood pressure was 120/80 mmHg, pulse rate 82/min, and temperature 36.8°C. Conjunctivae were very pale. Lungs were clear and
a grade III/VI functional systolic heart murmur was heard at the apex of heart. There was no organomegaly and extremities were normal.

Routine laboratory tests included the following: blood urea nitrogen 8.0 mg/dl, creatinine 0.7 mg/dl, glucose 125 mg/dl, calcium 7.5 mg/dl, phosphorous 4.3 mg/dl and total protein 6.2 gm/dl (albumin 3.6 gm/dl, globulin 2.6 gm/dl). SGOT was 15 IU/L, SGPT 48 IU/L, alkaline phosphatase 35 IU/L, and LDH 236 IU/L. Serum iron was 176 ug/dl and UIBC 58 ug/dl. Urinalysis was

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**Fig. 1.** Bone marrow aspirate showing slight to moderate hypocellular marrow with decreased megakaryocytes. (Wright-Giemsa stain ×100)

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**Fig. 2.** Bone marrow biopsy specimen showing moderate hypoplasia. (H&E stain, ×100)
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normal and Ham test was negative. CBC results were hemoglobin 4.5 g/dl, WBC 3,100/mm³ with 6% neutrophils and 94% lymphocytes and platelet count 14,000/mm³. Corrected reticulocyte count was 1.5%.

A peripheral blood smear showed normocytic and slightly hypochromic RBC's, moderate anisocytosis and slight polychromasia, a markedly decreased number of platelets and segmented neutrophils. A bone marrow aspiration revealed normocellular to slightly hypocellular marrow (Fig. 1). Megakaryocytes were markedly decreased. No tumor or storage cells were found. The iron stain showed grade 3 positivity. The myeloid and erythroid ratio was 1:2 with erythroid hyperplasia. The maturation was megaloblastoid. Bone marrow biopsy showed moderate hypoplasia (Fig. 2).

During hospitalization, the patient was transfused with 6 units of fresh packed RBC, 6 units of platelet rich plasma and one unit of platelets, apheresis. Daily 30mg doses of fluoxymesterone and 5 mg of dexamethasone were given. On the 23rd day of medication, dexamethasone was changed to 20 mg of prednisolone and gradually tapered in dosage. He was discharged in an improved condition on May 28, 1984.

He was readmitted to the hospital because of a tarry stool of 6 days duration on March 14, 1985. Since the previous admission, he had been treated at the out-patient clinic with 10mg of prednisolone and 30mg of fluoxymesterone. On second admission, the patient looked markedly pale. Blood pressure was 155/70mmHg, pulse rate 70/min and temperature 36.4°.

C. There were multiple petechiae on both extremities. A grade III/VI functional systolic heart murmur was heard at the apex. The abdomen was soft and there was no palpable mass, organomegaly or tenderness. There was grade 1 pitting edema on both extremities. Hemoglobin was 5.7gm/dl, and WBC count 2,900/mm³ with 22% neutrophils, 71% lymphocytes, 6% eosinophils and 1% monocytes. The platelet count was 15,000/mm³. Blood chemistries were normal with the exception of a slightly decreased calcium level, 7.8mg/dl and a slightly increased SGOT level, 67IU/L. HBsAg, antiHBs and antiHbc were all negative. Stool examination for occult blood was positive.

On the second hospital day, fibergastroscopy showed a large polypoid mass on the anterior wall near the lesser curvature side of the antrum (Fig. 3). A biopsy was not performed due to the bleeding tendency. An UGI study revealed an irregular shaped polypoid mass with small ulcerations (Fig. 4).

He was transfused with 4 units of packed red cells and of platelet rich plasma. Following transfusion of three units of platelet concentrate by apheresis, a radical subtotal gastrectomy and gastrojejunostomy were performed on the 23rd hospital day. The tumor was a well defined polypoid mass measuring 3×3.5cm in diameter and was located on the anterior wall of the lesser curvature side of the antrum. The serosa was grossly involved. The postoperative course was uneventful and he was discharged on the 37th hospital day, April 18, 1985 in an improved condition (Fig. 5). The pathologic findings of the resected specimen revealed a moderately well differentiated fungating adenocarcinoma infiltrating the outer muscular layer.

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![Fig. 3. Fibergastroscopic findings in the patient. Note a polypoid mass on the anterior wall of the antrum.](image1)

![Fig. 4. Upper GI findings in the patient. Note an irregular shaped polypoid mass with surface ulcerations.](image2)
Fig. 5. Schematic presentation of hemograms during second admission.

Fig. 6. Photomicrograph of adenocarcinoma showing infiltration of neoplastic glands in the submucosa and muscular layer of stomach. (H&E stain, ×40)
of the stomach walls (Fig. 6 & 7). Regional lymph node metastases were present in zones I & II (6 of 10), indicating stage III (T2N1M0) stomach cancer.

Since his last discharge, he had been treated approximately once a month with red cell transfusions and medication (folic acid 100mg and fluoxymesterone 30mg/day). Sixteen months postoperatively, he returned to the hospital on July 22, 1986 complaining of diffuse abdominal pain and melena. On the third admission, he was markedly pale, and the abdomen was soft, flat and diffusely tender. Hemoglobin was 3.4gm/dl, and WBC count 1,700/mm$^3$ with 47% neutrophils, 50% lymphocytes and 3% band forms. The platelet count was 12,000/mm$^3$. Fibergastroscopy disclosed mild inflammation of the remnant stomach with no evidence of intraluminal recurrence. An ultrasonography and abdominal CT scan revealed extensive metastasis to the abdominal organs, especially the liver and pancreas.

During hospitalization, his condition was complicated by salmonellosis and shigellosis which were controlled with the appropriate antibiotics. Chemotherapy for the extensive metastasis could not be considered due to the patient’s pancytopenia and poor general condition. After receiving supportive care including pain control, he was discharged on September 16, 1986, and expired at home several days later.

**DISCUSSION**

Aplastic anemia is defined as the condition in which an acellular or markedly hypocellular bone marrow results in pancytopenia with no evidence of myelofibrosis or infiltration of malignant cells. Several modalities including androgens, steroids, antithymocyte globulin, immunosuppressive agents and bone marrow transplantation are utilized in the treatment of aplastic anemia. A review of the literature through 1983 cites more than 60 cases of aplastic anemia which were transformed into acute leukemia, a relatively low incidence (Lynch and Jackson 1983).

Delamore and Geary (1971) described four cases of acute myeloblastic leukemia which developed after treatment of aplastic anemia with androgens, and suggested that though no definite causal relationship between oxymetholone therapy and the onset of leukemia had been established, the number of cases was greater than might have been expected by chance. Androgens which were also used in this case prior to the occurrence of stomach cancer improved both the remission rate and survival rate in aplastic anemia, but long term use can cause peliosis hepatitis, acne, hypertrichosis and in rare cases, hepatoma. Hirota (1981) reported that when oxymetholone was
used for 1 to 2 years or longer than 5 years with a total quantity in excess of 30,000 mg of androgen, 6 cases of cancer including 3 hepatomas developed among 319 patients. Oda et al. (1983) reviewed long term anabolic steroid therapy associated with hepatocellular carcinoma in two cases of aplastic anemia. They observed that the possibility of malignancy whether disease or drug associated must not be overlooked in the long term use of androgens. There is no previous report of the development of stomach cancer after long term use of anabolic steroids in aplastic anemia, and as the dose of androgens in this case was much less than that in Hirota and Oda's case, the possibility of androgens causing stomach cancer seemed unlikely.

Fanconi's anemia, a congenital type of aplastic anemia is an inherited disorder characterized by chromosomal abnormalities. Leukemia (Obeid et al. 1980), hepatoma (Abbondanzo et al. 1986), and orogenital and esophageal squamous carcinoma (Kozarek and Sanowski 1981; Kennedy and Hart 1982; Reed et al. 1983; Kaplan et al. 1985) have been found to occur more commonly with Fanconi's anemia whether or not treated with androgenic anabolic steroids. The underlying mechanism of why patients with Fanconi's anemia are more susceptible to malignancy is unclear except that it is known that they are immunodeficient (Torando et al. 1966; Kaplan et al. 1985).

Although immune deficiency has been suggested as a possible pathogenesis of idiopathic acquired aplastic anemia (Champlin et al. 1983; Gluckman et al. 1984), there is no explanation for the association of malignancy with this disease. Accordingly, this case could be considered a fortuitous occurrence.

Hill et al. (1981) described the first case of adenocarcinoma of the stomach occurring in Fanconi's anemia. Surgery on a 21-year-old male with Fanconi's anemia and recurrent gastrointestinal bleeding revealed an ulcerative carcinoma. Microscopic findings showed the tumor to be a poorly differentiated adenocarcinoma of the stomach. As most cases of Fanconi's anemia are treated with prednisolone and androgenic steroids which may exacerbate gastrointestinal bleeding, a patient presenting with gastrointestinal blood loss might be considered as having a steroid related blood loss. It would appear that a thorough endoscopic and barium study of the upper gastrointestinal tract is indicated in patients with signs or symptoms of acute or chronic blood loss or where there is sudden deterioration in an otherwise stable patient.

In the past, surgery had been frequently avoided in patients with granulocytopenia or thrombocytopenia including aplastic anemia and leukemia. But the recent development of component transfusion and intensive postoperative supportive care has resulted in increased survival rates and decreased postoperative complication rates (Lehman and Armitage 1980). Major surgery was possible in this case due to perioperative platelet transfusions and intensive care.

Our patient survived 17.5 months after the diagnosis of stomach cancer, which's from the standpoint of stage III stomach cancer survival rates (5 year survival 17%, Remine et al. 1964), was a moderate length of time. Also, in view of the median survival time for aplastic anemia in Korea (Kim et al. 1979; Suh et al. 1987), the survival duration of this case seemed to be prolonged (5.4 years after the onset of aplastic anemia). Also without surgery, the continuous bleeding would have led to death. Compared with Hill's case (ulcerative and poorly differentiated type), the more favorable gross and pathologic type (polypoid and moderately well differentiated) could have contributed to the prolonged survival in this case.

One and half years after surgery, the patient experienced an extensive metastasis, and chemotherapy was not considered due to the patient's pancytopenia and poor general condition. There are no reports of chemotherapy in aplastic anemia in the literature.

Whether the association of stomach cancer in aplastic anemia is coincidental or a de novo development as a part of its natural course is a correlation which is difficult to establish. However, since one case of stomach cancer has occurred during the course of aplastic anemia, it is possible that similar cases may occur in the future in Korea where these two diseases are not uncommon. As Hill et al. (1981) suggested, gastrointestinal bleeding in aplastic anemia which may be ascribed only to steroid use should not be overlooked. Thorough endoscopic and barium examinations should be performed to determine the cause of gastrointestinal bleeding. An elective surgical approach with both intensive preoperative and postoperative care might improve patients survival time. Also, improved therapeutic strategies are needed for complicated cases.

REFERENCES

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