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A Case of Vitamin B12 Deficiency Megaloblastic Anemia Following Total Gastrectomy

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Megaloblastic anemia following gastrectomy is due to the total absence or inadequate secretion of intrinsic factor and is manifested by megalobastic changes in bone marrow, blood cells, and other proliferative cells. In Korea, detailed description and precise analyses of the cases of megaloblastic anemia following gastrectomy are relatively rare in contrast to the potential of its incidence from gastrectomy due to many causes or to the importance of its clinical significance. Here, we present the case of a 51-year old man who had undergone a total gastrectomy with esophagojejunostomy and incidental splenectomy due to early gastric cancer and developed megalobastic anemia 7 years after surgery. After gradual improvement of clinical and hematologic features with treatment of parenteral vitamin B_{12}, he was followed-up with vitamin B_{12} maintenance therapy.

Key Words: Megaloblastic anemia, total gastrectomy, neuropathy, intrinsic factor, vitamin B_{12} deficiency

The major clinical manifestations of megalobastic anemia are anemia, pancytopenia and megalobastic changes in the hematopoietic system with various abnormalities of the digestive system involving oral and gastrointestinal tract mucosa resulting from defects in DNA sysnthesis. More than 90% of the cause of the disease is a deficiency of vitamin B_{12} or folic acid (Chararin 1969; Ko *et al.* 1978; Martin 1981). Vitamin B_{12} deficiency megaloblastic anemia can occur in various conditions, i.e., inadequate intake of vitamin B_{12}, absorption abnormalities, increased demand, and increased utilization of vitamin B_{12}. Vitamin B_{12} binds the intrinsic factor secreted from the parietal cells and is absorbed in the distal ileum. Megaloblastic anemia following pernicious anemia and gastrectomy is caused by total absence or deficiency of the intrinsic factor (Chararin 1969; Herbert 1959: William 1970; Harvey 1956; MacLean 1958; Khalid *et al.* 1973). There have been a few reports on megaloblastic anemia in Korea (Ko *et al.* 1978; Hahn *et al.* 1977; Hahn *et al.* 1977; Kim and Lee 1979; Kim 1962), but the number of cases of megaloblastic anemia following gastrectomy were much rarer probably due to the difficulties of follow-up. Therefore we present a case of megaloblastic anemia in a 51 year old male patient with diverse clinical manifestations 7 years after total gastrectomy due to early gastric cancer.

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CASE REPORT

A 51 year old man was admitted to the hospital because of general weakness, sore tongue and paresthesia of both upper and lower extremities.

He had had a total gastrectomy with esophagojejunostomy and incidental splenectomy due to early gastric cancer 7 years previously.

He had been subject to be easily anxious and agitated with aggressive behaviors since last 2 years, and he noted paresthesia (numbness, tingling and burning) in both lower extremities and sore throat with tongue ache. He also complained of loss of taste to meat. Two to three months prior to admission, weight loss, general weakness, and visual impairment (he said "Buildings look tilted!") developed. Therefore he was admitted to this hospital due to the above sym-

toms which didn't improve in spite of therapy.

He appeared very pale and chronically ill but presented good development and fair nutrition. The tongue was not enlarged, but was reddish and flattened with papillary atrophy (Fig. 1). Premature depigmentation of the scalp hair couldn't be observed due to hair-dye. Heart sounds were regular without murmur and lung examination revealed no significant findings. There were no specific neurological dysfunctions on examination except for slightly decreased DTR's. Mental symptom fluctuated, including paranoid ideation and marked anxiety, sufficiently severe to mimic paranoid schizophrenia or senility which might suggest megaloblastic madness.

Urine and stool examinations were normal.

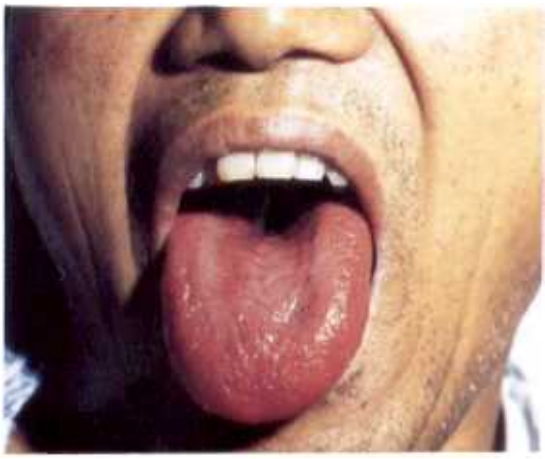

Fig. 1. Photograph of tongue showing beefy red, smooth appearence and papillar atrophy.

Table 1. Laboratory findings

Blood counts	
White blood cell	7,800/mm³
(seg 34%/lympho 47%/eosino 17%)	
Hemoglobin/Hematocrit	7.7g/dl/23.2%
Platelet	75,000/mm³
Reticulocytes	0.8% (uncorrected)
Blood chemistry	
Calcium	8.0mg/dl
Inorganic phosphate	3.6mg/dl
BUN/Creatinine	12/1.0mg/dl
Uric acid	4.3mg/dl
Total bilirubin	1.4mg/dl
Lactic dehydrogenase	224IU/L
Total protein/Albumin	5.9/3.7g/dl
SGOT/SGPT	26/24IU/L
Serum electrolytes	
Sodium	136mM/L
Potassium	3.6mM/L
Chloride	102mM/L
Carbon dioxide (CO2)	27mM/L
Other Laboratories	
Prothrombin time	12.2sec (100%)
Serum Iron/UIBC	162/36μg/dl
Haptoglobulin	114mg/dl
Vitamin B_{12}	10pg/ml (200-1,000 pg/ml)
Folate	5.1ng/ml (5-15ng/ml)
Lysozyme	
Serum	11.25μg/ml
Urine	0.8μg/ml
T3	79.06ng/dl (80-210ng/ml)
T4	5.8ng/dl (5-15ng/dl)
Free T4	0.83ng/ml (0.68-1.80ng/ml)

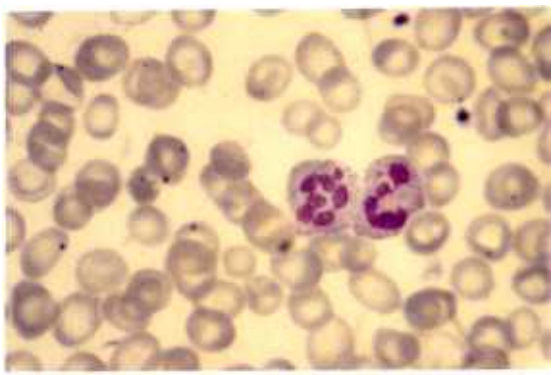

Fig. 2. Peripheral blood smear showing hypersegmented neutrophils and macrocytic red blood cells. Howell –Jolly bodies and target cells are also seen. (×1,000)

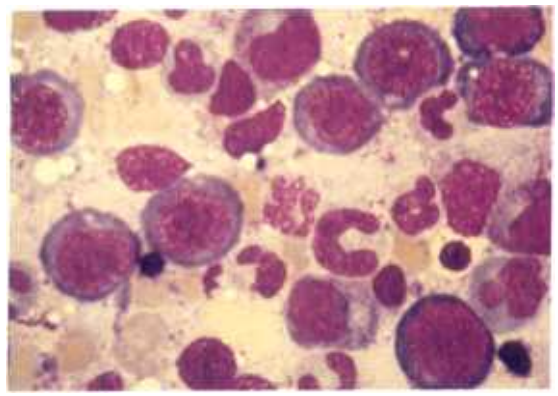

Fig. 3. Bone marrow aspiration smear showing erythroid hyperplasia with megaloblastic changes and giant metamyelocytes. (× 1,000)

Hemoglobin and hematocrit were 7.7g/dl and 23.3 percent respectively, MCV 142.3fl/dl, MCH 46.2pg/dl and MCHC 32.9g/dl; white-cell count was 7,800/mm³ with a differential count of 34 percent neutrophils, 47 percent lymphocytes, 17 percent eosinophils, 1 percent monocytes, and 1 percent basophils. The platelet count was 75,000/mm³, and the reticulocyte count (uncorrected) was 0.8 percent. Lactic dehydrogenase (LDH) was 224IU/L, with each isoenzyme as LD1 123, LD2 70, LD3 17, LD4 8, and LD5 6 IU/L showing an inversed LD1/LD2 pattern. Serum iron was 162μg/dl, UIBC 36μg/dl, serum vitamin B_{12} 10pg/ml, serum folic acid 5.1 ng/ml, and serum haptoglobin 114 mg/dl (Table 1). The peripheral blood smear (Fig. 2) showed hypersegmented polymorphonuclear leukocytes with a lobe count average 3.3±0.25 with 1% polys with 1 lobe, 22% with 2 lobes, 36% with 3 lobes, 31% with 4 lobes, 8% with 5 lobes and 2% with 6 lobes. Macroovalocytosis with Howell-Jolly body, basophilic stippling and target cells were also noted. Bone marrow aspiration and biopsy (Fig. 3) revealed normal cellularity with an M:E ratio of 2:1 with erythroid hyperplasia, and showed megaloblastic changes with giant metamyelocytes having U shaped nuclei. Iron staining of the bone marrow specimen showed a positivity of 2 to 3. The other diagnostic tests, including chest X-ray, liver scan, abdominal ultrasonography, abdominal computerized tomography, and ECG and nerve conduction velocity were all unremarkable.

He was given a parenteral vitamin B_{12} analogue, Calomide-S (Cobamamide; 5,6-Dimethylbenzimidazolyl-cobamide-5-deoxyadenosine), 1,000ug daily from the 4th to 17th hospital day (Fig. 4). With the medication, he showed gradual improvement in subjective symptoms, such as visual impairment, sym-

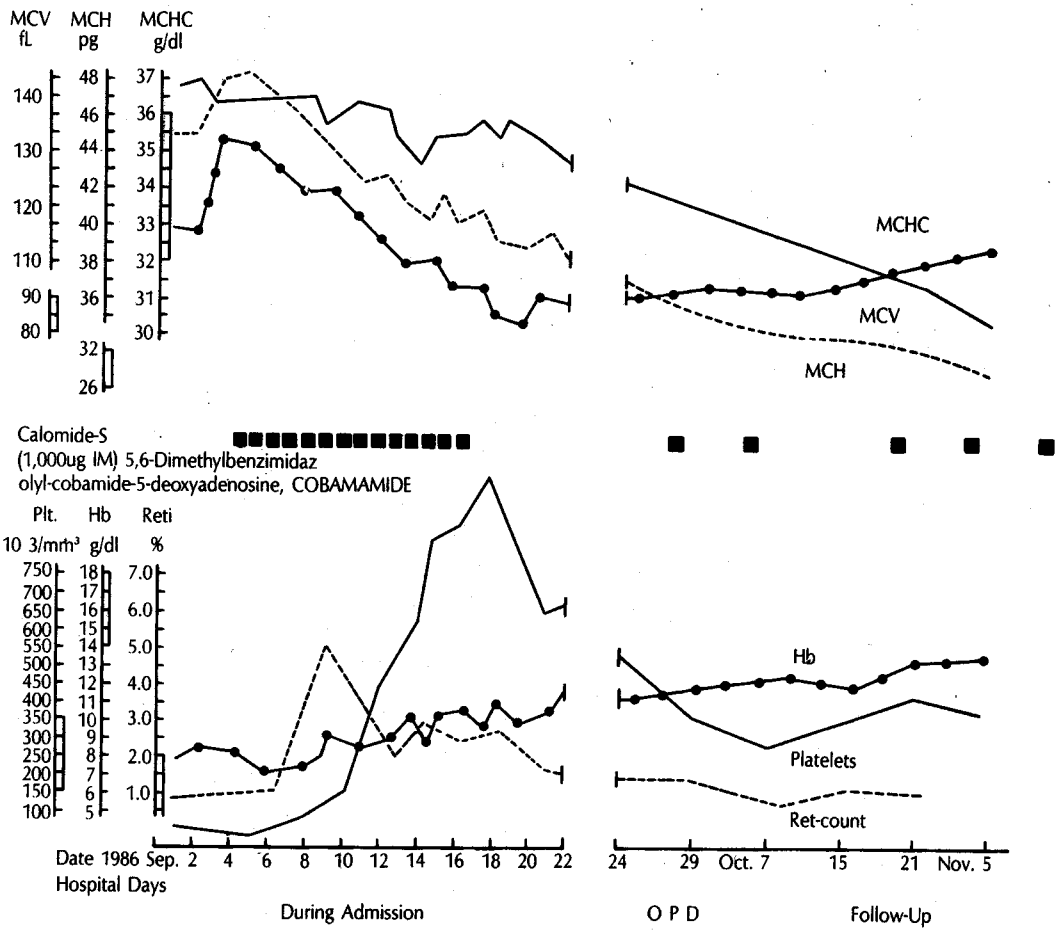

Fig. 4. Treatment and hematologic changes in this patient.

metrical paresthesia in the feet, and other psychiatric unstability. Also the sore throat with tongue ache which were marked on admission diminished a few days after vitamin B_{12} therapy.

The reticulocyte count peaked at 5.4% on the 8th day with parenteral vitamin B_{12} therapy and the platelet count also showed a peak level on the 15th day up to 954,000/mm³, but decreased to 604,000/mm³ at the time of discharge. On the day of discharge, hemoglobin and hematocrit were 12.1g/dl and 35% respectively, and MCV 125.2fl, MCH 36.5pg, and MCHC 31.4g/dl, indicating marked improvement in megaloblastic features as compared to the results on admission; hemoglobin 7.7g/dl, hematocrit 23.2%, MCV 142.3fl, MCH 46.2pg, and MCHC 32.9g/dl (Fig. 4). Serum iron and UIBC of 90μg/dl and 298μg/dl respectively were also comparable to those on admission, 162μg/dl and 36μg/dl indicating the effective consumption of absorbed iron in the hematopoietic system. Lactic dehydrogenasase (LDH), on the 15th day after treatment was 143IU/L (LD1 60, LD2 50, LD3 20, LD4 5, LD5 8IU/L), and on discharge 105IU/L (LD1 29, LD2 42, LD3 24, LD4 9, LD5 1IU/L), showing a normal LDH level and a normal pattern of isoenzyme fractions (Fig. 5). After discharge, he was maintained on a therapy of vitamin B_{12} supplementation.

DISCUSSION

Nutritional anemia is traditionally divided into the following groups; 1) Iron deficiency anemia (IDA), 2) megaloblastic anemia, 3) protein deficiency anemia, and 4) pyridoxine deficiency anemia. Most authors (Ko *et al.* 1978; Kim 1962; Prager 1972) report that IDA is the most common type of anemia, and Ko *et al.* (1978) described its frequency as up to 96.1% and megaloblastic anemia 3.4%, protein deficiency anemia 0.4%, and pyridoxine deficiency anemia 0.2% in Korea. Kim (1962) reported the incidence of microcytic, hypochromic anemia as up to 62%, macrocytic anemia 17.6%, and Prager (1972) reported the incidence of IDA as 61%, hemolytic anemia as 15%, the second most common and megaloblastic anemia as 5%, the fifth most common type of anemia. Other authors in Korea (Lee and Kim 1976; Sun 1977) noted the importance of nutritional deficiency anemia, of these, megaloblastic anemia, both vitamin B_{12} deficiency and folic acid deficiency anemia, have been subject to extensive research (Hahn *et al.* 1977; Hahn *et al.* 1977; Kim and Lee 1978).

The first report of megaloblastic anemia following total gastrectomy was described by Moynihan (1911) in a patient 44 months after total gastrectomy due to stomach cancer who showed no evidence of cancer recurrence. Thereafter, Denig (1929) noted the improvement of megaloblastic anemia following gastrectomy with liver extracts, and Conway and Conway (1951) treated it with vitamin B_{12} and folic acid. Rainer and Zollner (1985) emphasized the importance of vitamin B_{12} in preventing the development of megaloblastic anemia following gastectomy.

Reports of megaloblastic anemia following gastrectomy are relatively rare in Korea, Kim and Lee (1979) reported 16 cases of megaloblastic anemia but only one case in which the cause was malabsorption syndrome following total gastrectomy, but diagnosis was

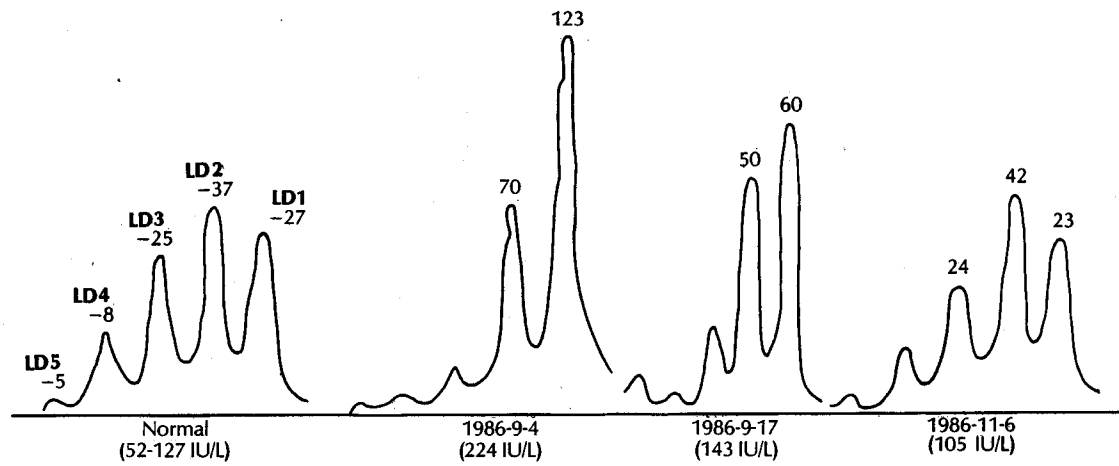

Fig. 5. Changes of LDH and its isoenzymes before and after treatment of vitamin B12.

solely based on peripheral blood features and bone marrow study without direct measurement of the vitamin B_{12} or folic acid levels. Ko *et al.* (1979) reported 45 cases of megaloblastic anemia with deficiency anemia based on clinical and hematologic features and response to treatment. In 12 cases the cause of anemia was vitamin B_{12} deficiency, and one case had had a gastrectomy. Chung and Song (1984) reviewed 326 cases of previous stomach surgery, and described delayed complications. Anemia was found in 37.1% (121 cases), most frequently following radical subtotal gastrectomy (Billorth type II). However the incidence of anemia in each operative method was not specified.

Impairment or total loss of intrinsic factor (IF) secretion is the major pathogenetic mechanism of megaloblastic anemia following gastrectomy, and with time both hematologic and neurologic alterations eventually ensue (Table 2) (Herbert 1985). In the case of total gastrectomy, total loss of IF secretion, and in the case of partial gastrectomy, impairement of IF secretion is the cause of anemia. Vitamin B_{12} deficiency megaloblastic anemia following partial gastrectomy may be explained by the following mechanisms; 1) The severity of anemia depends on the degree of atrophy of the residual gastric mucosa after surgery; Jokes and Blackwell (1959) stated that most patients with severe gastric mucosal atrophy developed megaloblastic anemia and others commented on postoperative gastritis which in most cases improves spontaneously, but in some may progress to atrophic gastritis resulting in impairment of vitamin B_{12} absorption (Jones *et al.* 1962). 2) Since the majority of parietal cells secreting IF are distributed in the gastric body and fundal mucosa, the more these area are resected, the more the impairment of vitamin B_{12} absorption. 3) The rapid transit of food following partial gastrectomy (Dumping syndrome) could also cause a vitamin B_{12} absorption defect (Jones *et al.* 1962). 4) Iron deficiency anemia following gastrectomy may interfere with the absorption of vitamin B_{12}, and iron therapy could normalize its absorption (Chararin *et al.* 1965; Biggs *et al.* 1962). 5) Blind loop syndrome, bacterial overgrowth in the afferent loop after partial gastrectomy may interfere with vitamin B_{12} absorption competitively and antibiotic therapy is usually effective in this phenomenon (Chanarin 1969; Barret and Holt 1966). 6) Achlorhydria following gastrectomy may cause impairment of the genesis of a free form of vitamin B_{12} from protein bound vitamin B_{12} resulting in a relative absoption defect of vitamin B_{12} (Herbert, 1985).

Table 2. Probable sequence of events in developing vitamin B_{12} deficiency due to inadequate absorption

Time	Event
1 day	Inadequate absorption of food B_{12} and reabsorption of bile B_{12}
	Serum B_{12}-binding capacity 40±10% saturated
	Serum B_{12} (normal: >250pg/ml)
1∼2 yr	Serum B_{12}<200pg/ml
	B_{12} in reproducing cells approximately one-half normal
	Early bone marrow and peripheral blood changes
	Hypersegmentation
	Mean corpuscular volume elevated
	Methylmalonic aciduria
	High urine formimimoglutamate
	dU suppression test abnormal in bone marrow
1.5∼2 yr	Early damage to myelin
2∼3 yr	Serum B_{12}<150 pg/ml
	Serum B_{12} binding capacity<10% saturated
	B_{12} in reproducing cells approximately 10% of normal
	Bone marrow unequivocally megaloblastic
	Low red cell folate
	dU suppression test abnormal in peripheral blood lymphocytes
	Serum folate normal or elevated
2.5∼3yr	Severe damage to myelin

Taken from Herbert, 1985

Hematologic alterations following gastrectomy show different types of anemia, depending on either a partial or total gastrectomy, but most of them belong to IDA, up to 15-33%, following partial gastrecotmy (Chararin 1969; Hines *et al.* 1967). Paulson and Harvey (1954) noted that almost all patients following total gastrectomy suffered from iron deficiency anemia 2 to 3 months after surgery. Vitamin B_{12} deficiency megaloblastic anemia develops in almost all patients following total gastrectomy but some have different features with respect to the time of development of anemia (McLean 1958; Moynihan 1911; Conway and Conway 1951; Paulson and Harvey 1954; McLean and Dorothy 1956), megaloblastic anemia develops in 5-10% of the patients following partial gastrectomy (Khalid *et al.* 1973; Hines *et al.* 1967; Deller 1962; Birnbaum *et al.* 1956; MacLean 1957; Deller and Witts 1962; Deller *et al.* 1968; Water 1968); and Chanarin (1969) reported 128 (1.1%) cases of megaloblastic anemia in 11,229 patients with partial gastrectomy until 1969; Hines *et al.* (1967) reported 12 (4%) cases of vitamin B_{12} deficiency anemia and 6 (2%) cases of folic acid deficiency anemia in 18 cases of megaloblastic anemia from 292 patients with partial gastrectomy and observed a

lower incidence of folic acid deficiency than vitmain B_{12} deficiency anemia.

Preoperative diagnosis also affects the severity and incidence of megaloblastic anemia; Jones *et al.* (1962) stated that gastric ulcer rather than duodenal ulcer surgery is more prone to develop megaloblastic anemia; but Deller *et al.* (1968) found no significant difference between them and the exact difference between them is still not certain.

Operative methods also affect the incidence of deficiency anemia. Almost all patients following proximal partial gastrectomy including the gastric body and fundus suffer from vitamin B_{12} deficiency megaloblastic anemia, however it is rare in patients with a distal partial gastrectomy, and there is a variation in its incidence with respect to the degree of gastric mucosal atrophy at the time of surgery (Chanarin 1969; Water 1968). Billroth type II operation used to result in vitamin B_{12} deficiency megaloblastic anemia more frequently than Billroth type I operation due to bacterial overgrowth in the afferent loop and rapid gastric emptying (Harkins and Nyhus 1956; Crowley and Olson 1983).

There is a great deal of debate concerning the time required for megaloblastic anemia to develop after gastrectomy. Deller and Witts (1962) reported that serum vitamin B_{12} is decreased, in 10% of cases about 5 years after partial gastrectomy and in 20% after 10 years. Chanarin (1969) noted that the incidence of megaloblastic anemia gradually increase 3 years after total gastrectomy and peaks after 5 years and also noted that it develops in almost all patients 8 years after surgery. In our case, various clinical features including those of megaloblastic anemia developed 7 years after surgery and neurologic and gastrointestinal alterations other than hematologic features were overtly encountered.

The major pathology of neurologic manifestations of megaloblastic anemia is traditionally divided into two basic features; 1) myelopathy and 2) peripheral neuropathy. Biochemical defects of neuronal damage in megaloblastic anemia are based on the impairment of methionine systhesis from homocysteine due to a deficiency of methylcobalamine, and on the accumulation of methymalonyl CoA and propyl CoA due to an adenosylcobalamin deficiency resulting in impaired neuronal lipid synthesis (Chanarin 1969; Herbert 1985; John 1983). The first manifestation of these impaired neuronal lipid syntheses is a myelopathy with myelin swelling of the posterolateral column of the spinal cord in which myelin distributes most plentifully and thereafter clinical manifestations of subacute combined degeneration will eventually ensue (Jones *et al.* 1986; Weir and Gatenby 1963). Subacute combined degeneration following gastrectomy was once reported by Denig in 1929 in a patient who received gastrectomy 9 years previously showing bizzare neurologic signs as paresthesia, ataxia and decreased deep tendon reflexes with megaloblastic anemia. Loss of deep tendon reflexes with muscle weakness is a characteristic feature in vitamin B_{12} deficiency peripheral neuropathy, and paresthesia mimicking that of vitamin B_{12} deficiency myelopathy may develop due to peripheral nerve demyelinization with dying-back type of axonal degeneration also (Macleod *et al.* 1969). Clinical manifestations from these degenerative processes of the nervous system include paresthesia, impaired tactile, vibratory or positional senses which symmetrically involve the toes and fingers, and it may progress to spastic ataxia. Other neurologic symptoms in megaloblastic anemia include impairment of vision, taste, smell and optic atrophy.

Eventually megalobastic madness characterized by irritability or somnolence from abnormalities in brain metabolism can occur. In our case, the patient showed typical clinical features of megaloblastic madness such as paranoid ideation, with severe irritability on admission like the case of Smith and Oliver (1967); and visual and taste disturbances were also presented.

Patients suffering from megaloblastic anemia following gastric surgery require parenteral vitamin B_{12} supplementation, and complete hematologic recovery soon ensues. Neurologic damage with no evidence of its improvement after 12 to 18 months of therapy was regarded as irreversible (Chanarin 1969), but in this case, the bizzare neurologic and psychiatric manifestations improved to nearly normal one week after parenteral vitamin B_{12} supplementation. Hematologic features also improved gradaully (Fig. 4).

The fact that almost all patients after total gastrectomy will eventually develop megaloblastic anemia must be stressed, and even after partial gastrectomy or, in a state of nearly normal IF secretion from residual stomach mucosa, in the majority of patients, serum vitamin B_{12} levels may remain in the normal range up to 20 years after surgery, but then will progressively decrease depending upon the type of surgery and the degree of pre or postoperative gastric mucosal atrophy. Therefore, in postoperative patients, annual blood sampling for CBC, serum iron, vitamin B_{12} and folic acid should be done, and if any deficits are found, a bone marrow study should be performed to evaluate storage iron and megaloblastic features, and the vitamin B_{12} or folic acid absorption test will

be helpful in the detection of megaloblastic anemia as early as possible.

As a preventive measure, vitamin B_{12} supplements should be given within 3 years of surgery (MacLean and Dorothy 1956), and Maclean (1958) stressed the importance of monthly parenteral supplement of vitamin B_{12}, 50μg, in patients with previous total or proximal partial gastrectomy who had survived more than 2 years, and in patients showing atrophic changes in the gastric mucosa who had had a distal partial gastrectomy, to prevent the development of megaloblastic anemia.

CONCLUSION

We presented a case of megaloblastic amemia which developed in a 51 year old man 7 years after total gastrectomy due to early gastric cancer. Diffuse neuropsychiatric manifestations and a beefy reddish tongue with papillary atrophy were observed concommitantly. He presented dramatic improvement in the clinical and hematologic pictures with vitamin B_{12} therapy.

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