Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3695-19
Intern Med 59: 859-861, 2020
http://internmed.jp

【 CASE REPORT 】

Vitamin B12 Deficiency Anemia and Polyneuropathy Due to Chronic Radiation Enteritis

Hiroyuki Fukuda[1], Munetaka Takekuma[2] and Yasuyuki Hirashima[2]

Abstract:
A 62-year-old Japanese woman developed numbness of the extremities and megaloblastic anemia. She had undergone total abdominal hysterectomy, whole-pelvis radiation therapy and chemotherapy for gynecological cancer 10 years before. Chronic abdominal pain, diarrhea and intermittent small-bowel obstruction had afflicted her for a long time. We diagnosed her with vitamin B12 deficiency anemia and polyneuropathy due to chronic radiation enteritis causing malabsorption. Vitamin B12 injections improved her numbness and anemia. The early diagnosis and treatment of deficiency of vitamin B12 are important. Physicians should regularly measure vitamin B12 levels and supplement vitamin B12 as needed in patients with chronic radiation enteritis.

Key words: gynecological cancer, megaloblastic anemia, polyneuropathy, radiation enteritis, vitamin B12 deficiency

(Intern Med 59: 859-861, 2020)
(DOI: 10.2169/internalmedicine.3695-19)

Introduction

Radiation enteritis is an injury of the small intestine and colon secondary to radiotherapy and divided into acute and chronic forms. The acute type has been recognized to cause diarrhea, and the chronic type has been reported to cause perforation, ileus, chronic diarrhea and nutritional deficiency (1). Malfunction of the terminal ileum due to the chronic form can cause vitamin B12 deficiency, as vitamin B12 is absorbed in the form of a conjugate with the intrinsic factor in the terminal ileum.

We herein report a case of vitamin B12 deficiency anemia and polyneuropathy due to chronic radiation enteritis.

Case Report

A 62-year-old Japanese woman who had a history of tuberculosis was admitted because of numbness of the extremities and anemia. She had undergone total abdominal hysterectomy, whole-pelvis radiation therapy (50.4 Gy, 1.80 Gy ×25 fractions of extended field and anterior/posterior opposed fields with low dose in multiple fractions) and chemotherapy (5- fluorouracil and cisplatin) for cervical cancer (stage IIb, pT2N1M0) 10 years before. Her body mass index (BMI) was 17.0. Chronic abdominal pain and diarrhea had afflicted her for a long time after chemoradiotherapy. She also had often developed intermittent small-bowel obstruction (Fig. 1) despite medical treatments and been clinically diagnosed with chronic radiation enteritis. She had noticed numbness in both hands and legs six months before the admission but did not report any difficulty in using her hands or walking. She also had developed anemia, but her general condition had been good.

A physical examination on admission revealed a normal mental function and normal cranial nerves. The motor and sensory functions, including superficial and deep sensations, were normal. There was no ataxia or gait disturbance. The tendon reflexes except for the Achilles tendons were depressed. Laboratory data revealed pancytopenia (megaloblastic anemia), hypoproteinemia and hypocalcemia: WBC 3,700 μL, RBC 157×10^4 μL, Hb 6.8 g/dL, Ht 19.8%, mean corpuscular volume (MCV) 126.1 fL, mean corpuscular hemoglobin (MCH) 43.3 pg, mean corpuscular hemoglobin concentration (MCHC) 34.3%, platelet 9.2×10^4 μL, total protein 5.5 g/dL, albumin 3.3 g/dL, glutamic oxaloacetic

[1]Division of Neurology, Shizuoka Cancer Center, Japan and [2]Division of Gynecology, Shizuoka Cancer Center, Japan
Received: July 22, 2019; Accepted: October 3, 2019; Advance Publication by J-STAGE: November 18, 2019
Correspondence to Dr. Hiroyuki Fukuda, h.fukuda@scchr.jp

transaminase (GOT) 33 U/L, glutamic pyruvate transaminase (GPT) 17 U/L, lactate dehydrogenase (LDH) 106 IU/L, γ-GTP 130 U/L, blood urea nitrogen (BUN) 15.7 mg/dL, creatinine (Cr) 0.4 mg/dL, Ca 6.6 mg/dL, Fe 117 μg/dL, TIBC 203 μg/dL, glucose 90 mg/dL, F-T3 2.36 pg/mL, F-T4 1.30 ng/mL, thyroid-stimulating hormone (TSH) 2.18 IU/L. vitamin B1 24 ng/mL, vitamin B12<50 pg/mL, folic acid 13.6 ng/mL and negative anti-gastric parietal cell antibody. Gastroscopy and colonoscopy revealed no abnormalities. Capsule endoscopy was deemed dangerous due to the history of repeated bowel obstructions and so was not performed. A nerve conduction study demonstrated no response of the sural nerve and slightly slow conduction of the other sensory nerves (Table, Fig. 2). These results indicated that she had vitamin B12 deficiency anemia and polyneuropathy. The neurological findings of the normal motor and sensory functions appeared to indicate that there was no subacute combined degeneration of the spinal cord. She was given multiple vitamin B12 injections (hydroxocobalamin 1,000 μg three times a week), and her numbness and anemia had improved (Hb 12.7 g/dL) by 2 months later. A nerve conduction study 16 months after the initiation of vitamin B12 treatment showed a marked improvement (Table, Fig. 2).

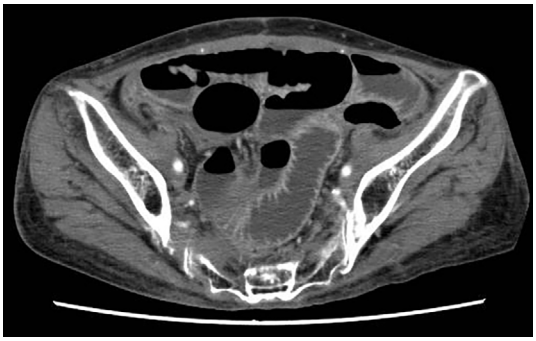

Figure 1. Computed tomography scan showing dilation and fluid retention of the small intestine.

Discussion

We encountered a patient with megaloblastic anemia and polyneuropathy due to vitamin B12 deficiency during the course of chronic enteritis.

Chronic radiation enteritis develops months to years after exposure to radiotherapy and usually presents with diarrhea and malabsorption (1). Factors on the patient side that increase the risk of developing radiation enteritis have been reported to be a history of intestinal surgery, low BMI, hypertension, diabetes mellitus, inflammatory bowel disease and smoking. The volume of the small bowel in the radiotherapy field, radiotherapy dose and fractionation, radiotherapy technique and concomitant chemotherapy use have been presented as factors related to treatment (2). The present patient had no history of hypertension, diabetes mellitus, inflammatory bowel disease or a smoking habit. However, she had undergone surgery and chemotherapy associated with radiation, and her BMI had been low at that time. The total radiation therapy dose received was 50.40 Gy, and the incidence of serious injury is reported to increase when the dose exceeds 50 Gy (3). The amount of radiation received and the fields of her radiation therapy were suggested to be strong factors that increased her risk of radiation enteritis. We suspected that the radiation therapy had been the main factor causing her chronic enteritis, with her history of chemotherapy and low BMI also influencing the occurrence to some extent.

Causes of malabsorption of vitamin B12 can be divided into gastric and ileal disorders, as the key components of the normal pathway for vitamin B12 absorption require a functioning stomach for the production of the protein intrinsic factor and an intact cubilin receptor in the terminal ileum. We considered that the main cause of vitamin B12 deficiency in our case was malabsorption in the terminal ileum, which had been damaged by radiation therapy, as the find-

Table. The Results of Nerve Conduction Studies before Vitamin B12 Treatment (white Frames) and 16 Months after the Initiation of the Treatment (gray Frames).

	MCV (m/s) DL (ms)		CMAP (mV)		SCV (m/s) DL (ms)		SNAP (μV)	
right median nerve	56.7 3.1	58.7 2.5	14.2	15.3	48.0 2.5	65.1 1.9	19.9	17.5
right ulnar nerve	56.7 2.7	67.9 2.5	14.3	17.2	41.7 2.4	61.8 1.7	8.4	18.5
right tibial nerve	45.2 3.5	52.8 3.4	23.8	35.9				
right sural nerve					NR	46.6 3.2	NR	1.8

The right sural nerve showed no response before the treatment but a normal conduction velocity with a small amplitude after the treatment. The conduction velocities became faster, distal latencies were shortened, and the amplitudes grew larger in other nerves after the treatment, except for the SNAP of the right median nerve. MCV: motor nerve conduction velocity, DL: distal latency, CMAP: compound muscle action potential, SCV: sensory nerve conduction velocity, SNAP: sensory nerve action potential, NR: no response

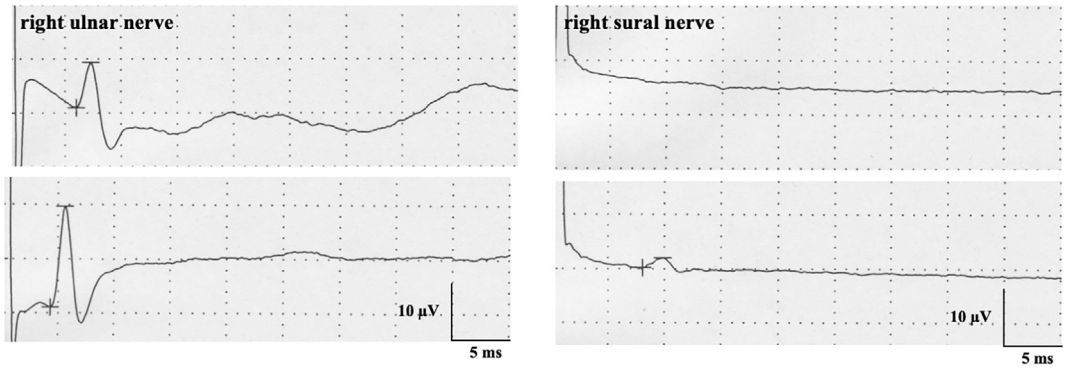

Figure 2. **The wave forms of orthodromic sensory nerve conduction studies of the right ulnar and sural nerves before (top traces) and 16 months after the initiation of vitamin B12 treatment (bottom traces).**

ings on gastroscopy were normal and she was negative for anti-gastric parietal cell antibody. Her development of vitamin B12 deficiency may also have been influenced by the fact that she had reduced her daily food intake in order to avoid constipation and diarrhea.

Previous studies have reported cases of vitamin B12 deficiency due to malabsorption after radiotherapy in gynecologic cancer patients (4-10). A significant vitamin B12 deficiency was reported in 20% of 55 patients at 6-12 years after pelvic radiation (11). Various causes of vitamin B12 deficiency have been recognized, but disease or resection of the ileum as the cause of absorption disturbance has been described in recent reviews (12-14). To our knowledge, no other reports have described a case of vitamin B12 deficiency associated with chronic radiation enteritis in Japan, and chronic radiation enteritis does not seem to be well recognized as a potential cause of vitamin B12 deficiency. Keeping in mind that vitamin B12 deficiency is likely to occur in patients with chronic radiation enteritis, physicians should regularly measure the vitamin B12 levels and supplement vitamin B12 as needed in such patients.

Peripheral nerves affected by vitamin B12 deficiency are reported to show myelin sheath fragmentation and axon degeneration (15). The relatively early and good recovery of the neuropathy in our case suggest that myelin sheath fragmentation was the main factor in her neuropathy.

In conclusion, we encountered the first case of vitamin B12 deficiency anemia and polyneuropathy due to chronic radiation enteritis in Japan. The serum levels of vitamin B12 should be regularly measured in patients with chronic radiation enteritis.

The authors state that they have no Conflict of Interest (COI).

References

1. Webb GJ, Brooke R, De Silva AN. Chronic radiation enteritis and malnutrition. J Dig Dis **14**: 350-357, 2013.
2. Theis VS, Sripadam R, Ramani V, Lal S. Chronic radiation enteritis. Clin Oncol **22**: 70-83, 2010.
3. Bismar MM, Sinicrope FA. Radiation enteritis. Curr Gastroenterol Rep **4**: 361-365, 2002.
4. Greenberger NJ, Isselbacher KJ. Malabsorption following radiation injury to the gastrointestinal tract. Am J Med **36**: 450-456, 1964.
5. Duncan W, Leonard JC. The malabsorption syndrome following radiotherapy. Q J Med **34**: 319-329, 1965.
6. Tankel HI, Clark DH, Lee FD. Radiation enteritis with malabsorption. Gut **6**: 560-569, 1965.
7. Wellwood JM, Jackson BT. The intestinal complications of radiotherapy. Br J Surg **60**: 814-818, 1973.
8. Anderson CG, Walton KR, Chanarin I. Megaloblastic anaemia after pelvic radiotherapy for carcinoma of the cervix. J Clin Pathol **34**: 151-152, 1981.
9. Bandy LC, Clarke-Pearson DL, Creasman WT. Vitamin-B12 deficiency following therapy in gynecologic oncology. Gynecol Oncol **17**: 370-374, 1984.
10. Snijders-Keilholz A, Griffioen G, Davelaar J, et al. Vitamin B12 malabsorption after irradiation for gynaecological tumours. Anticancer Res **13**: 1877-1881, 1993.
11. Vistad I, Kristensen GB, Fosså SD, Dahl AA, Mørkrid L. Intestinal malabsorption in long-term survivors of cervical cancer treated with radiotherapy. Int J Radiat Oncol Biol Phys **73**: 1141-1147, 2009.
12. Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med **368**: 149-160, 2013.
13. Green R. Vitamin B_{12} deficiency from the perspective of a practicing hematologist. Blood **129**: 2603-2611, 2017.
14. Wolffenbuttel BHR, Wouters HJCM, Heiner-Fokkema MR, et al. The many faces of cobalamin (Vitamin B_{12}) deficiency. Mayo Clin Proc Innov Qual Outcomes **3**: 200-214, 2019.
15. Kosik KS, Mullins TF, Bradley WG, Tempelis LD, Cretella AJ. Coma and axonal degeneration in vitamin B12 deficiency. Arch Neurol **37**: 590-592, 1980.