Case report

Seventy-Three-Year-Old Man with Pernicious Anemia Complicated by Subacute Combined Spinal Cord Degeneration and Cognitive Impairment

Kei SASAKI[1], Yasuhiro ENDO[1,2], Koharu HARADA[1], Manami TERAMOTO[1], Makoto SASAKI[1], Shinji YAMAMOTO[3] and Katsunori IKEWAKI[1]

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Abstract: Pernicious anemia (PA) is a type of megaloblastic anemia caused by autoimmune gastritis. We report the case of a 73-year-old man with PA complicated by subacute combined spinal cord degeneration and cognitive impairment. After diagnosis, the patient was treated with vitamin B12, which markedly improved pancytopenia and neurological symptoms including cognitive impairment.

In the present case, elevated mean corpuscular volume (MCV) had preceded the pancytopenia and neurological symptoms. Elevated MCV may therefore be a useful early marker for diagnosing PA.

Key words: pernicious anemia ／ autoimmune gastritis ／ cognitive impairment ／ vitamin B12 deficiency

Background

Pernicious anemia (PA) is a type of megaloblastic anemia caused by autoimmune gastritis (AIG) with a prevalence of around 0.49% in Japan[1)]. Characteristic clinical and laboratory features of PA are macrocytosis with neutrophilic hypersegmentation, high mean corpuscular volume (MCV), neurological symptoms resulting from peripheral neuropathy or subacute combined degeneration (SCD) of the spinal cord, and neuropsychiatric symptoms. PA is also known to be associated with cognitive impairment[2)]. Here, we report the educational case of a 73-year-old man with PA associated with SCD of the spinal cord and cognitive impairment.

Case presentation

A 73-year-old Japanese man with chronic atrial fibrillation and hypertension was admitted to our department with dysesthesia of bilateral upper and lower extremities, gait disturbance, and pancytopenia. He had noticed dysgraphia and difficulty in walking three months before admission, and these symptoms had progressively worsened. A blood test performed by the attending physician revealed pancytopenia with macrocytic anemia. He was then referred to our department for a detailed investigation. The clinical course is summarized in Figure 1.

On admission, he complained of shortness of breath and gait disturbance. He was taking anticoagulants and beta-blockers for chronic

[1]Division of Anti-aging and vascular medicine, Department of Internal Medicine, National Defense Medical College, Tokorozawa, Saitama 359-8513, Japan
[2]Division of Environmental Medicine, National Defense Medical College Research Institute, Tokorozawa, Saitama 359-8513, Japan
[3]Yasuragi Clinic, Iruma, Saitama 358-0011, Japan

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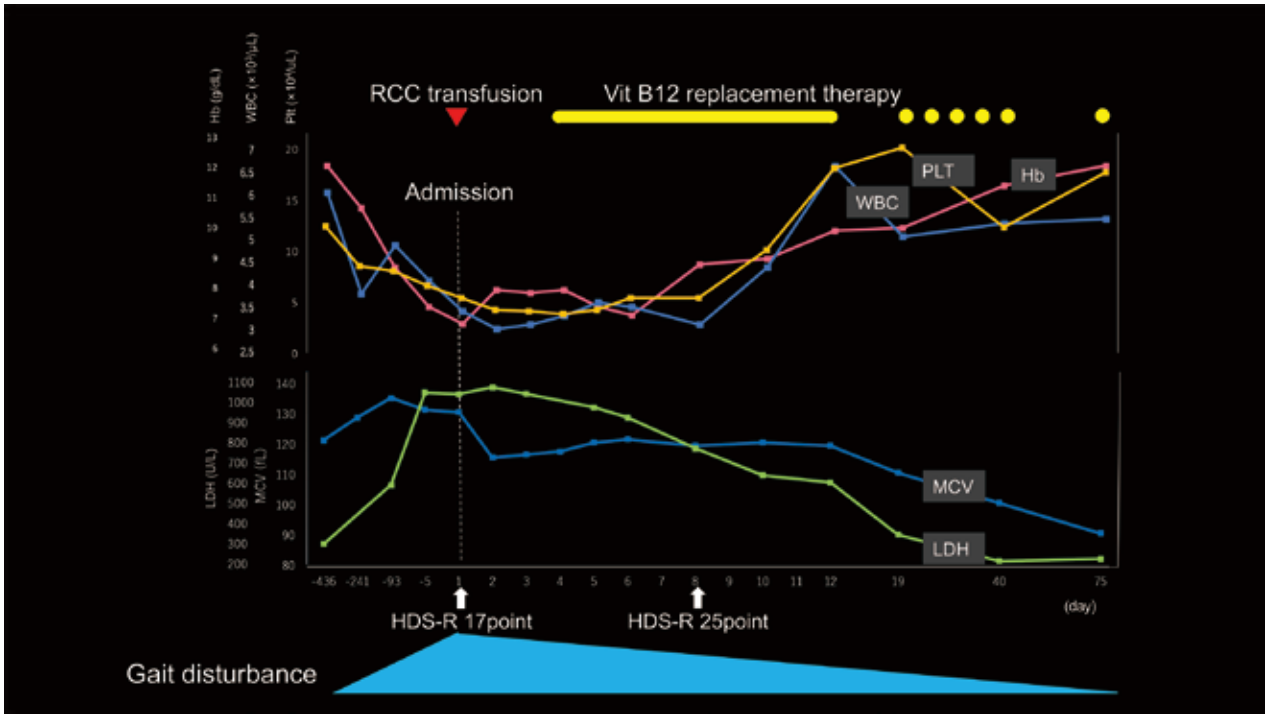


Figure 1. Clinical course
One year before admission, the patient's thrombocytopenia worsened and neurological symptoms appeared. After transfusion of red cell concentrates on the first day of admission, his numbness tended to improve. On the 4th day, Vit B12 replacement therapy was started, and LDH decreased, followed by improvement of pancytopenia. Cognitive function also improved gradually. He was discharged from hospital on the 12th day. (Illustration was created by Koharu Harada)

atrial fibrillation and hypertension, respectively, had no history of surgery or gastric cancer, and was not taking a proton pump inhibitor. He had never been diagnosed with cognitive impairment. He had no allergy to foods or drugs. On physical examination, he had pitting edema in the lower extremities and dysesthesia of bilateral upper and lower extremities. As for neurological findings, he had muscle weakness in the distal lower and upper extremities with truncal ataxia, Achilles tendon reflex was absent, and vibration sensation was reduced. He also had cognitive impairment as indicated by a score of 17/30 on the Hasegawa Dementia Scale-Revised (HDS-R) scale.

As shown in Table 1, a laboratory evaluation revealed macrocytic anemia with thrombocytopenia and leukopenia (WBC 3.3×10^3/μL, Hb 6.8g/dL, MCV131fL, platelets 5.5×10^4/μL) and elevated lactate dehydrogenase (LDH: 1054 U/L). As shown in Figure 2, a blood smear examination revealed neutrophilic hyper-segmentation and variations in the size of red blood cells. In addition, serum vitamin B12 (Vit B12) concentration was low (88 μg/dL, reference range 230 - 920), while folic acid levels were normal (11.4 ng/mL, reference range 3.6 - 12.9). We therefore made a diagnosis of megaloblastic anemia and started Vit B12 replacement therapy (cobalamin 500 μg/day by intramuscular injection).

As shown in Figure 3A on day 8 of admission, contrast-enhanced magnetic resonance imaging (MRI) revealed T2 high-signal-intensity lesions of bilateral lateral funiculus and posterior funiculus in C3-Th3, consistent with SCD of the spinal cord. Additionally, high-signal areas were observed in the cerebral white matter on T2WI/FLAIR, indicative of chronic ischemic changes, while no intracranial space-occupying lesions were found in Figure 3B.

In the nerve conduction test, a reduction in sensory nerve action potential (SNAP) was observed in the ulnar nerve suggested the

Table 1. Laboratorydata on admission

Total bilirubin	1.41	mg/dL	White blood cell count	3.3×10^3	/μL	Thyroid-stimulating hormone	3.06 μIU/L
Direct bilirubin	0.89	mg/dL	Red blood cell count	1.49	$\times10^6$/μL	Free triiodothyronine	3.21 pg/mL
Aspartate aminotransferase	40	U/L	Hemoglobin	6.8	g/dL	Free thyroxine	2.82 pg/mL
Alanine aminotransferase	26	U/L	Hemotocrit	19.5	%	Anti-nuclear antibody	40 ×
Lactate dehydrogenase	1054	U/L	Mean corpuscular volume	131	fL	IL-2 receptor	549 U/mL
Choline esterase	85	U/L	Mean Corpuscular Hemoglobin	45.6	pg	CH50	29.7 /mL
Total protein	6.1	g/dL	Mean Corpuscular Hemoglobin Concentration	34.9	%	C3	56 mg/dL
Albumin	4	g/dL	RBC volume distribution width	74	fL	C4	21 mg/dL
Total cholesterol	90	mg/dL	Platelet count	5.5×10^4	/μL	Intrinsic factor antibody	negative
Glucose	90	mg/dL	Reticulocyte	16.9	‰	Anti-parietal cell antibody	positive
Urea nitrogen	17	mg/dL	Vitamin B12	88	μg/dL	Anti-Hepatitis B Surface Antigen	positive
Creatinine	0.8	mg/dL	Folic acid	11.4	ng/mL	Hepatitis Be antigen	negative
Sodium	144	mEq/L				Anti-Hepatitis Be antigen	positive
Potassium	4.5	mEq/L				Anti-Hepatitis B antibody	negative
Ferritin	282.8	ng/mL					

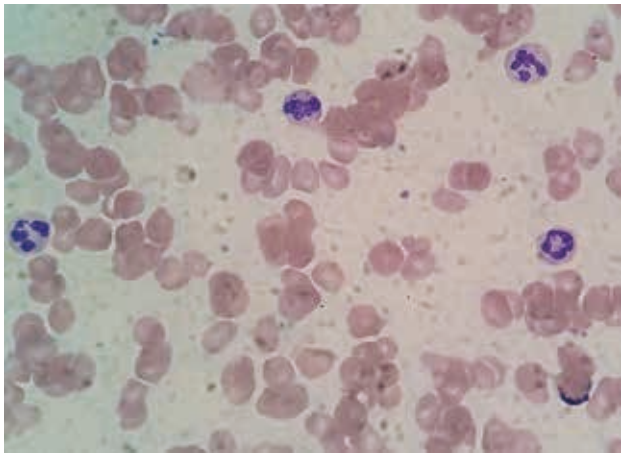
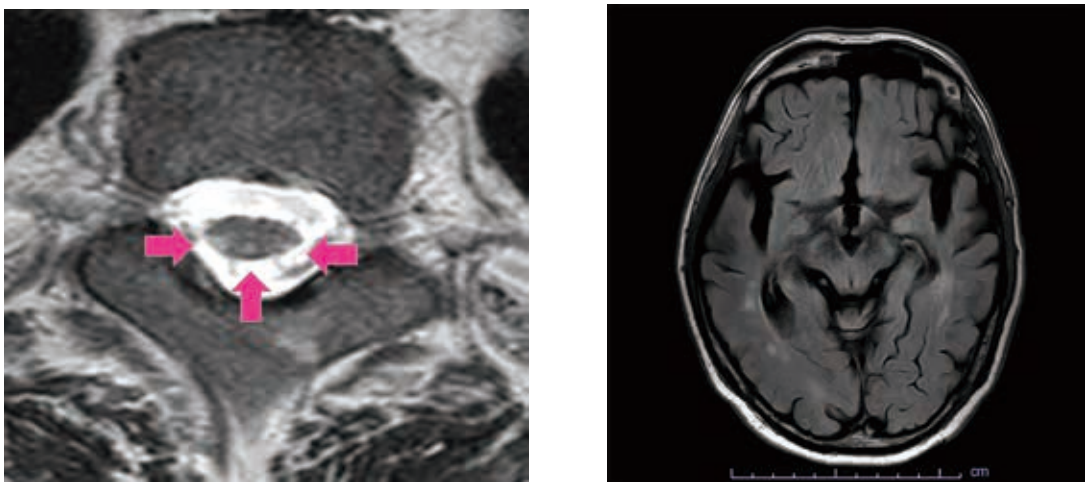


Figure 2. Blood smear images
Neutrophilic hyper-segmentation and variations in the size of red blood cells were observed in the blood smear test.



A B

Figure 3. Magnetic resonance imaging
A) Contrast-enhanced MRI on 8th day of admission. High-signal-intensity T2WI areas are evident in the bilateral lateral and posterior funiculus from the cervical to the thoracic spinal cord.
B) MRI on 3rd day of admission
High-signal areas were observed in the cerebral white matter on T2WI/FLAIR, indicative of chronic ischemic changes, while no intracranial space-occupying lesions were found

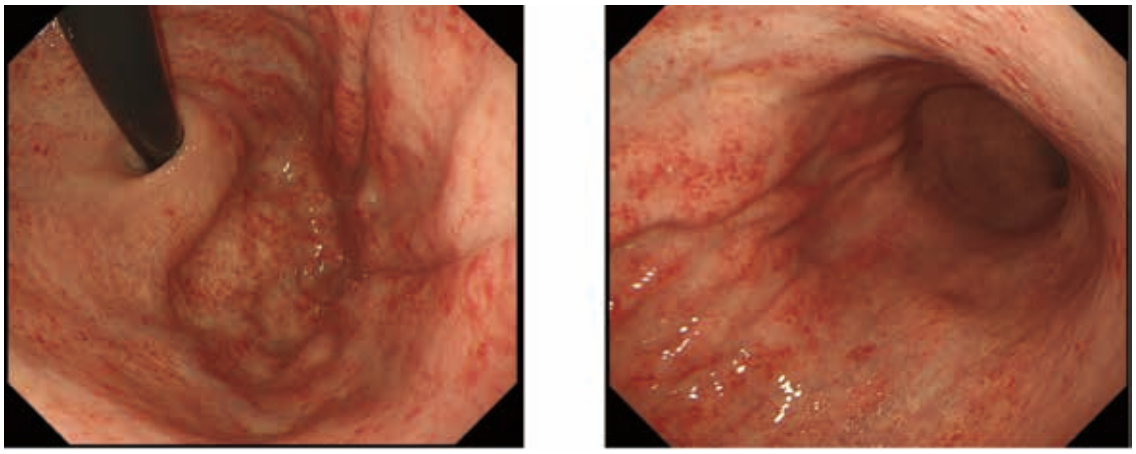


Figure 4. Endoscopic images on day10 of admission
Mucosal atrophy was observed in the gastric body by EGD

coexistence of peripheral neuropathy. However, typical findings of sensory-dominant axonal damage characteristic of Vit B12 deficiency neuropathy were not prominent. As shown in Figure 4, esophagogastroduodenoscopy (EGD) revealed atrophic gastritis in the gastric body without evidence of malignancy. Anti-parietal cell antibodies (APCA) were positive, but anti-intrinsic factor antibodies (IFA) were negative. We made a diagnosis of autoimmune gastritis (AIG).

Vit B12 therapy rapidly reduced LDH levels and improved pancytopenia. The symptoms of truncal ataxia and dysesthesia improved. There was a recovery in HDS-R score from 17 to 25 points in 8 days. The patient was discharged on day 12 of hospitalization.

Discussion

In this case report, we describe a case of PA complicated by SCD of the spinal cord with hematological and neurological abnormalities, including peripheral neuropathy and cognitive impairment, that were rapidly alleviated by Vit B12 replacement therapy.

PA is a type of megaloblastic anemia caused by impaired absorption of Vit B12. Vit B12 acts as a cofactor in the reaction that produces methionine from homocysteine, which converts stored folate to active folate. Therefore, when Vit B12 is deficient in cells, active folate is reduced, impairing DNA synthesis. Pancytopenia results from ineffective erythropoiesis due to impaired DNA synthesis[2].

The most common cause of Vit B12 deficiency is AIG, accounting for 15-25% of patients with Vit B12 deficiency[3]. AIG is a type of atrophic gastritis positive for APCA or IFA, autoantibodies against the proton pump (Na^+K^+ATPase) in parietal cells, which leads to malabsorption of Vit B12. AIG is known to be associated with gastric cancer, stomach neuroendocrine tumors (stomach NETs), and thyroid diseases like Hashimoto's disease[4, 5]. Therefore, when AIG is suspected, endoscopic screening and thyroid hormone measurement are necessary, in particular the former in elderly patients. In the present case, APCA was positive, with no gastric malignancy or thyroid disease complications.

Megaloblastic anemia has been frequently associated with neurological manifestations due to Vit B12 deficiency, which reduces the synthesis of S-adenosylmethionine (SAM) and lowers the ratio of SAM/SAH (S-adenosylhomocysteine), leading to inhibition of myelin methylation, demyelination of nerves and induction of neurological symptoms.

In clinical settings, the frequency of peripheral neuropathy caused by Vit B12 deficiency is 40%,

whereas SCD occurs less frequently, at only 16%[6]. Sun and colleagues previously reported a case of SCD with PA, but no cognitive impairment[7]. Lavoie presented a case of SCD associated with PA but no evidence of hematological manifestations[8].

From the retrospective viewpoint, elevated MCV levels had been present long before progression of megaloblastic anemia, suggesting that Vit B12 deficiency could be diagnosed earlier through elevated MCV levels. According to an analysis by the Department of Hematology at Tohoku University, about 20% of megaloblastic anemia is myelodysplastic syndrome (MDS). MCV measurements would be useful in differentiating MDS from megaloblastic anemia since a high MCV of around 120 fL is likely to indicate megaloblastic anemia. Generally, neurological symptoms associated with Vit B12 deficiency are common in the elderly[9], but are likely to be diagnosed as nonspecific complaints. Thus, an elevated MCV may aid the early diagnosis of Vit B12 deficiency.

Conclusion

We experienced a case of PA complicated by SCD and cognitive impairment that rapidly improved with Vit B12 replacement therapy. Elevated MCV can be a valuable marker for early diagnosis of Vit B12 deficiency in elderly people without hematological and neurological manifestations.

Conflict of interest

The authors declare that they have no conflict of interest (C.O.I).

Informed consent

Informed consent was obtained from the patient for publication of this case report and any accompanying images.

References

1) Notsu T, Adachi K, Mishiro T, et al.: Prevalence of Autoimmune Gastritis in Individuals Undergoing Medical Checkups in Japan. *Intern Med*. **58**: 1817-1823, 2019.
2) Stabler SP.: Clinical practice. Vitamin B12 deficiency. *N Engl J Med*. **368**: 149-160, 2013.
3) Cavalcoli F, Zilli A, Conte D,et al.: Micronutrient deficiencies in patients with chronic atrophic autoimmune gastritis: A review. *World J Gastroenterol*. **23**: 563-572, 2017.
4) Weise F, Vieth M, Reinhold D, et al.: Gastric cancer in autoimmune gastritis: A case-control study from the German centers of the staR project on gastric cancer research. *United European Gastroenterol J*. **8**: 175-184, 2020.
5) Cellini M, Santaguida MG, Virili C, et al.: Hashimoto's Thyroiditis and Autoimmune Gastritis. *Front Endocrinol (Lausanne)*. **8**: 92, 2017.
6) Reynolds E.: Vitamin B12, folic acid, and the nervous system. *Lancet Neurol*. **5**: 949-960, 2006.
7) Sun Z, Yu X.: A case report: subacute combined degeneration of the spinal cord and pernicious anemia caused by autoimmune gastritis. *Medicine (Baltimore)*. **101**: e29226, 2022.
8) Lavoie MR, Cohen NC, Gregory TA, et al.: Subacute combined degeneration: a case of pernicious anaemia without haematological manifestations. *BMJ Case Rep*. **13**: e234276, 2020.
9) Clarke R, Grimley Evans J Schneede J, et al.: Vitamin B12 and folate deficiency in later life. *Age Ageing*. **33**: 34-41, 2004.

亜急性連合性脊髄変性症及び可逆性の認知症を合併した73歳男性の悪性貧血の１例

佐々木慧[1]，遠藤康弘[1, 2]，原田小春[1]，寺本麻菜美[1]，佐々木誠[1]，山本眞二[3]，池脇克則[1]

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要旨：悪性貧血は，自己免疫性胃炎による巨赤芽球性貧血の一種である。今回，亜急性複合脊髄変性症と認知症を合併した悪性貧血の73歳男性の症例を報告する。診断後，ビタミンB12投与により汎血球減少や認知症を含めた神経症状は著明に改善された。

本症例では汎血球減少症や神経症状に先立ち，Mean corpuscular volume（MCV）の上昇が認められた。MCVの上昇は悪性貧血の診断に有用な早期マーカーとなる可能性が示唆された。

索引用語：悪性貧血／自己免疫性胃炎／認知症／ビタミンB12欠乏症

[1]防衛医科大学校内科学講座神経・抗加齢血管内科
[2]防衛医科大学校防衛医学研究センター特殊環境衛生研究部門
[3]やすらぎクリニック