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【 CASE REPORT 】

Pseudo-thrombotic Microangiopathy Caused by Acquired Cobalamin Deficiency Due to Unintentional Neglect

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Abstract:

Acquired vitamin B_{12} (VB_{12}) deficiency is a rare cause of thrombotic microangiopathy (TMA). We experienced an 86-year-old Japanese woman who presented with coma, renal dysfunction, and microangiopathic hemolytic anemia. Although we initially considered thrombotic thrombocytopenic purpura, we eventually diagnosed her to have VB_{12} deficiency due to inappropriate dietary care based on her low serum VB_{12} level, social history, and negative parietal cell finding and the presence of intrinsic factor antibody. Because similar cases are expected to increase in today's aging society, our experience underscores the importance of including acquired VB_{12} deficiency in the differential diagnosis of TMA, even in elderly patients without a history of gastrectomy.

Key words: neglect, plasma exchange, thrombotic thrombocytopenic purpura, vitamin B_1, vitamin B_{12}

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Introduction

Thrombotic microangiopathy (TMA) is a group of diseases defined by classic characteristics including 1) microangiopathic hemolytic anemia (MAHA), 2) thrombocytopenia, and 3) organ injury. The pathological features of TMA are vascular damage manifested by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall. Making a timely diagnosis of TMA is critically important because it is a heterogenous entity that has various causes, clinical presentations, and specific management strategies, including that of a medical emergency. To avoid any therapeutic delay in the treatment of thrombotic thrombocytopenic purpura (TTP), which is a potentially fatal condition, unexplained MAHA and thrombocytopenia are regarded as sufficient to initiate emergent plasma exchange (PE) (1).

It has recently been recognized that vitamin B_{12} (VB_{12}) deficiency can manifest as "pseudo-TMA," a combination of mechanical hemolysis, thrombocytopenia, and elevated lactate dehydrogenase that can easily be misdiagnosed as TMA (2). To avoid expensive, complicated, and potentially harmful treatment for TMA, such as plasma exchange, the recognition of pseudo-TMA due to VB_{12} deficiency and differentiation of pseudo-TMA from TMA is therefore important (2). This disease entity remains under-recognized despite the increase in the number of elderly, who are at risk of VB_{12} deficiency (3).

We herein report a case of pseudo-TMA caused by acquired VB_{12} deficiency due to unintentional neglect in an elderly individual. Given today's increasingly aged society, we believe that this case report underscores the importance of including acquired VB_{12} deficiency in the differential diagnosis of TMA in the elderly, even in patients without a history of either gastrectomy or pernicious anemia.

Case Report

An 86-year-old Japanese woman arrived by ambulance to the emergency department of Toho University's Omori Medical Center with an altered mental status. For four months she had experienced progressive general weakness and a general loss of activity, and had gradually became unable to ambulate. Two days prior to admission, it had become difficult for her to eat any food. On the morning of admission, her son called an ambulance because he found that the patient could no longer speak or respond.

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Table. Laboratory Findings.

	Day of admission	After PE (Hospital day 5)	Hospital day 75	Standard values
Leukocytes (/mm^3)	3,800	3,100	9,100	3,000-7,800
Hemoglobin (g/dL)	6.1	6.8	10.5	10.6-14.4
Hematocrit (%)	18.8	20.3	32.2	32.1-42.7
MCV (fL)	134.3	97.1	90.4	83.3-100.3
Reticulocyte (%)	2.6	0.9	N/R	0.8-2.3
Platelet (10^3/mm^3)	33	77	278	138-309
Sodium (mEq/L)	157	153	146	135-147
Potassium (mEq/L)	4.5	2.7	3.7	3.3-4.8
Chloride (mEq/L)	119	119	110	98-108
Glucose (mg/dL)	110	N/R	77	78-109
BUN (mg/dL)	63	23	35	7-24
Creatinine (mg/dL)	1.88	0.68	0.89	<0.7
AST (IU/L)	23	37	23	≤30
ALT (IU/L)	24	34	24	≤30
LDH (IU/L)	937	293	180	119-229
T-bilirubin (mg/dL)	5.1	3.4	0.4	0.2-1.2
D-bilirubin (mg/dL)	3.5	N/R	0.2	0-0.3
CK (U/L)	126	20	11	45-163
Total protein (g/dL)	5.1	4.5	5.7	6.5-8.0
Albumin (g/dL)	2.7	2.6	2.3	4.0-5.2
CRP (mg/dL)	0.4	0.1	1.2	≤0.3
PT activity (%)	43	73	92	70-120
PT-INR	1.9	1.2	1.1	N/A
APTT (s)	48.5	31	42	24-39
D-dimer (μg/mL)	9.9	14.6	1.2	≤1.0
Haptoglobin (mg/dL)	≤10	N/R	N/R	19-170
Folic acid (ng/mL)	9	N/R	10	≥4.0
Vitamin B_1 (μg/dL)	2.5	N/R	21.7	24-66
Vitamin B_{12} (pg/mL)	66	N/R	>1500	180-914

ALT: alanine aminotransferase, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CK: creatinine kinase, CRP: C-reactive protein, LDH: lactate dehydrogenase, MCV: mean corpuscular volume, N/A: not applicable, N/R: no record, PE: plasma exchange, PT: prothrombin time, PT-INR: prothrombin time international normalized ratio

The patient had a past medical history of hypertension, cerebral infarction, and asthma. She had no history of gastric disorders and had never undergone endoscopy. Although calcium antagonists, angiotensin II receptor blocker, and theophylline had been prescribed, she had discontinued these medications several months earlier because she was unable to visit her primary doctor due to difficulty in moving. She lived with her son and received welfare benefits. Her son, the only caregiver of the patient, had been unemployed for many years and used the patient's pension for their costs of living. The son prepared meals for the patient, and frequently used instant food. Although the son had noticed that the patient had become progressively more anorexic, ill, and edematous over several months, he continued to offer instant food and did not seek social/medical support until he called an ambulance. Welfare service officers and a care manager did not notice the deterioration in the patient's health status because the son did not consult them. The patient occasionally consumed alcohol and had previously been a smoker.

On physical examination, the patient had an impaired consciousness (Glasgow Coma Scale: E4V2M5). Blood pressure was 110/50 mmHg, and she had a regular pulse of 78 beats/min and a respiration rate of 18 breaths/min. Oxygen saturation under ambient air was 83%, and her body temperature was 37.2°C. Although her cardiac sounds were normal, her lung sounds were diminished. Tenderness without peritoneal signs was noted in the upper right abdomen. In addition, jaundice and systemic edema were present.

Laboratory data on admission (Table) revealed the following signs suggesting hemolytic anemia: hemoglobin of 6.1 mg/dL with 134 fL of mean corpuscular volume (MCV); serum total and indirect bilirubin of 5.1 mg/dL and 3.5 mg/dL, respectively; LDH as high as 937 U/L; and haptoglobin as low as <10 mg/dL. Numerous schistocytes were observed in the peripheral blood smear (Figure). Laboratory data were also remarkable for low platelet count (as low as 33,000/μL), hypernatremia (157 mEq/L), hypoalbuminemia (2.7 g/dL), and renal disorder (serum blood urine nitrogen and creatinine were 63.0 mg/dL and 1.88 mg/dL, respectively). Both the serum VB_1 and VB_{12} levels were as low as 2.5 μg/dL and 66 pg/mL, respectively. A portable chest X-ray and computed tomography scan of the trunk revealed cardi-

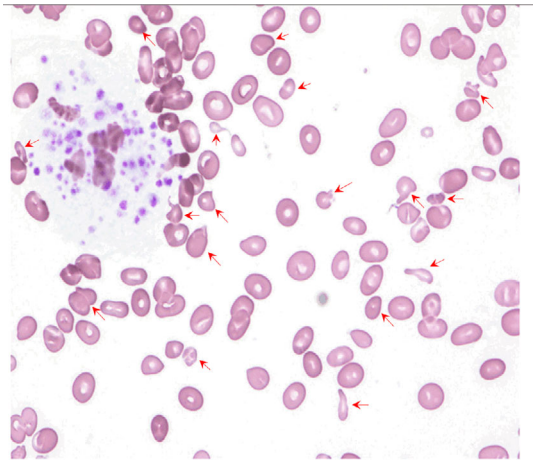

Figure. Peripheral blood smear. Note: Numerous schistocytes are evident (arrows).

omegaly, pleural effusion, and ascites. No pericardial fluid was observed. Echocardiography showed normal left ventricular contraction (ejection fraction, 68%) without any regional wall motion abnormalities.

Because of the combination of thrombocytopenia, hemolytic anemia, renal disorder, and neuropsychiatric symptoms, we tentatively diagnosed the patient to have TTP. We immediately performed PE before getting the results on ADAMTS 13 activity, because emergent PE is indicated in all patients who develop MAHA and thrombocytopenia due to unexplained causes (1). We admitted her and performed PE for five days with a total of 20 units of fresh frozen plasma. Although the level of consciousness and general status of the patient improved after the initiation of PE, the thrombocytopenia did not respond (Table). We diagnosed her with severe refractory TMA based on the standard criteria, because her platelet count did not improve to 150,000/mm^3 after a five-day course of PE (1). Although steroid pulse therapy was subsequently provided, there was no apparent improvement in platelet count. We then obtained the result that ADAMTS13 activity was normal. The ineffectiveness of PE and steroid therapy and the normal ADAMTS13 activity led us to consider the possibility of tumor-related TMA. We thus performed repeated imaging studies, tests for serum tumor markers, and cytology of pleural fluid, sputum, and urine to detect occult cancers. There were no results suggesting any malignant tumors, however.

Although we had not considered a VB_{12} deficiency as the cause of pseudo-TMA, we had immediately started the empirical intramuscular supplementation of a complex vitamin preparation that included 500 mg of thiamine and 1,000 mg of cyanocobalamin immediately after the patient's arrival because we suspected Wernicke encephalopathy in light of her social background and macrocytic anemia. We switched the intramuscular VB_{12} supplementation to oral supplementation after intramuscular supplementation for 7 days because oral administration is reported to be equally effective as intramuscular administration, assuming no problems associated with malabsorption (4). Given that the patient gradually improved after the start of VB_{12} supplementation, and both TTP and tumor-related TMA were unlikely, we finally diagnosed the patient with pseudo-TMA associated with acquired VB_{12} deficiency. Although we recommended endoscopy to rule out either pernicious anemia or atrophic gastritis, the patient and her son refused to undergo this diagnostic modality. Both serum intrinsic factor antibody and parietal cell antibody were negative.

The patient resumed eating soon after her consciousness improved. Although the patient gradually became conversable and apparently alert, her orientation to time and place continued to be impaired. We failed to evaluate her cognitive function using the Mini-mental state examination (MMSE) and Hasegawa dementia scale-revised (HDS-R) due to the patient's refusal to cooperate with such examinations. Given that her conscious and cognitive status improved to a usual level according to the son, we judged that her disorientation was most likely associated with chronic cognitive dysfunction. We could not differentiate whether the cognitive dysfunction had been caused by either dementia or irreversible sequalae. Although we started rehabilitation soon, the patient eventually needed a wheelchair to move due to muscular weakness. The patient did not complain of diplopia, involuntary movements, or sensory symptoms such as hypoesthesia/paresthesia of the extremities even after she became conversable. The patient was transferred to a nursing home 92 days after admission to continue rehabilitation.

Discussion

We experienced a case of pseudo-TMA associated with VB_{12} deficiency due to unintentional neglect. Our experience highlights the importance of, and difficulty in, differentiating between pseudo-TMA and TMA, and the cause of acquired VB_{12} deficiency in the current aged society.

Early differentiation of pseudo-TMA from TMA is important to avoid unnecessary, expensive, and invasive treatment such as PE. Considering the poor prognosis of untreated TTP, however, empirical PE has been performed in these cases (as in ours) (5, 6), because the initiation of PE before confirming decreased ADAMTS-13 activity is indicated in cases of unexplained MAHA and thrombocytopenia (1). Thus, the timely recognition of pseudo-TMA is important and therefore developing a technique to quickly differentiate pseudo-TMA from TTP is urgently needed. Several differentiation methods have been proposed; including a markedly elevated lactate dehydrogenase (LDH) (>2,500 IU/L) in the absence of reticulocytosis as well as the presence of macrocytosis are excellent markers of pseudo-TMA (7). The PLASMIC score is another useful method that uses a simple set of parameters: namely, it attributes 1 point to a platelet count <30,000 /dL, serum creatinine <2 mg/dL, MCV <99 fL, PT-INR <1.5, and evidence of hemolysis: either bilirubin >2 mg/dL, undetectable haptoglobin, or reticulocyte >2.5%.

It includes 1 point for the absence of active malignancy and another for the absence of prior solid organ or hematopoietic stem cell transplantation. A total score of 7 correlates at 96.2% with a serum ADAMTS13 activity ≤10%. A 5 to 6 score bears an intermediate risk at 56.8% whereas a 0 to 4 score correlates with a low risk of 4.3% (8). In the present case, LDH was only 937 IU/L, and the PLASMIC score was 5 (intermediate risk). Thus, it was difficult to safely rule out TTP even using these differentiation methods. We therefore believe that performing empiric PE was appropriate in this case.

Other than in congenital abnormal cobalamin metabolism due to a functional loss of the *MMACHC* gene, acquired VB_{12} deficiency rarely causes pseudo-TMA. Pernicious anemia and gastrectomy have been reported to be associated with pseudo-TMA due to VB_{12} deficiency in the elderly (6, 9). Although a case of pseudo-TMA due to acquired VB_{12} deficiency associated with neglect has been reported in pediatric patients (10, 11) we believe that this adult case offers an important clinical lesson because the patient developed pseudo-TMA because of a lack of VB_{12} due to insufficient dietary care. Because of severe anasarca (bilateral pleural effusion and ascites), low serum vitamin B_1 (VB_1), and low serum VB_{12}, patients might have malnutrition due to a persistent poor oral intake and malabsorption due to intestinal edema. In this case, the patient's son lived with her and was her sole caregiver. He did not have the ability to adequately care for his mother. He had been unemployed for many years and he lived off of the patient's public welfare and pension. Furthermore, he did not seek any medical or social support until the patient could no longer speak and he called an ambulance. Given these circumstances, we believed that the patient had thus experienced unintentional neglect.

Our report has several limitations that should be addressed. First, we could not rule out the possibility of pernicious anemia because we could not perform endoscopy due to the patient's refusal. Instead, we sought to serologically evaluate the possibility of pernicious anemia by measuring intrinsic factor antibody and parietal cell antibody using a novel enzyme-linked immunosorbent assay (ELISA). The diagnostic performance of intrinsic factor and parietal cell antibody in pernicious anemia patients using a novel ELISA yielded a sensitivity and specificity of 37% and 100%, respectively, for intrinsic factor antibodies, and a sensitivity and specificity of 81.5% and 90.3%, respectively, for parietal cell antibodies. The combined assessment of both autoantibodies increased their diagnostic performance, which yielded a 73% sensitivity for pernicious anemia while maintaining a 100% specificity (12). According to that study, the lack of serum intrinsic factor antibody and parietal cell antibody may make pernicious anemia unlikely. It is important to note, however, that we could not histologically rule out pernicious anemia in the present case.

Second, the early conversion of the route of VB_{12} supplementation from parenteral to enteral may have modified the clinical course and made the improvement unclear. Although we had converted the route of VB_{12} supplementation from parenteral to enteral within 7 days, a previous study on parenteral VB_{12} supplementation for TMA reported that only 2 out of 15 patients improved within 14 days, and 13 out of 15 patients required 14 days to 6 months for improvement (13). Considering the findings of this report, it would probably have been better to continue parenteral supplementation longer until the patient's laboratory data had completely improved. Because there was systemic edema accompanied by pleural effusion and ascites and concurrent VB_1 deficiency, malabsorption due to intestinal edema may have interfered with the intestinal absorption of orally supplied VB_{12}. Furthermore, the VB_1 deficiency itself may have modified the clinical course of the patient in terms of her level of consciousness and cognitive function.

Third, we could not measure the patient's weight change over time because she had an impaired consciousness during transportation and had difficulty maintaining a standing position after admission (she needed a wheelchair). The nutrition support team (NST) did not intervene because the patient started to consume a sufficient amount of food after her consciousness improved, so her nutritional status was not fully evaluated by NST. It is probable, however, that nutritional disorders were present because she exhibited hypoalbuminemia at the time of hospital transport and was deficient in both VB_{12} and VB_1.

Conclusion

We experienced the case of an elderly patient with a VB_{12} deficiency presenting with TMA caused by inappropriate dietary care and unintentional neglect. Our report offers an important clinical lesson because cases of elderly individuals with VB_{12} exhaustion due to inappropriate dietary care are expected to increase in today's aged society. Acquired VB_{12} deficiency should be included in the differential diagnosis of TMA, even in elderly patients without a history of gastrectomy.

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

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