

Original Article

Megaloblastic anemia with hypotension and transient delirium as the primary symptoms: report of a case

Qin Zhang, Xue-Ying Lv, Yun-Mei Yang

Department of Geriatrics, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

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Abstract: The present study describes a case of an elderly patient that was hospitalized secondary to hypotension and delirium. Physical examination at admission revealed bilateral positive Babinski's sign. Laboratory examination revealed severe anemia. Bone marrow examination showed megaloblastic changes of the granulocyte and erythroid series, as well as other dyshaematopoiesis. The conditions of the patient rapidly improved after vitamin B₁₂ treatments. Because the clinical manifestations of megaloblastic anemia are complex, this disease is often misdiagnosed in the geriatric population. Bone marrow examinations can aid in the diagnosis of anemia, but the results from these tests cannot always differentiate the type of anemia. Clinical management of the disorder is reliant upon proper classification of the type of anemia. The prognosis of megaloblastic anemia is typically good and a simple regimen of folic acid and/or vitamin B₁₂ is effective.

Keywords: Megaloblastic anemia, hypotension, delirium, vitamin B₁₂, elderly

Introduction

Megaloblastic anemia is the nutritional anemia induced by folic acid and/or vitamin B₁₂ deficiency [1]. This condition is frequently seen in children, but recent reports have revealed that this condition may also occur in elderly individuals. Because the clinical manifestations of megaloblastic anemia are complex, this disease is often misdiagnosed in the geriatric population. Bone marrow examinations can aid in the diagnosis of anemia, but the results from these tests cannot always differentiate the type of anemia. Clinical management of the disorder is reliant upon proper classification of the type of anemia. The prognosis of megaloblastic anemia is typically good and a simple regimen of folic acid and/or vitamin B₁₂ is effective [2].

Case presentation

A 75 year old male teacher was hospitalized due to "dizziness, vomiting and disturbance of consciousness for one day" on June 30, 2010. One day prior to his hospitalization, the patient reported dizziness, nausea and vomiting without an obvious cause. Subsequently he became confused, restless, and developed urinary and fecal incontinence.

His admission examination revealed a body temperature of 37.1°C, pulse of 67, respiratory rate of 16 and blood pressure of 91/49 mmHg. The patient was conscious and had no yellow staining on his skin and sclera, no swelling in superficial lymph nodes and no areas of obvious bleeding. The patient had clear breath sounds without wet or dry rales. The patient had a normal sinus rhythm and his abdomen was soft. The liver and spleen were not palpable. No swelling was found in lower extremity and bilateral Babinski's sign was positive.

The patient reported a poor vegetarian diet, which he attributed to a change in residence. In the time since his diet changed, the patient reported that he frequently experienced episodes of dizziness and bilateral weakness in both lower extremities. He had previous hospital admissions for these symptoms and had been diagnosed with cervical syndrome, for which he reported undergoing traditional Chinese medicinal treatments. The patient reported a dramatic weight loss of 10 kg in the last six months.

Routine blood examinations revealed a white blood cell count of $6.3 \times 10^9/L$, neutrophils of 85.9%, hemoglobin of 40 g/L, mean corpuscu-

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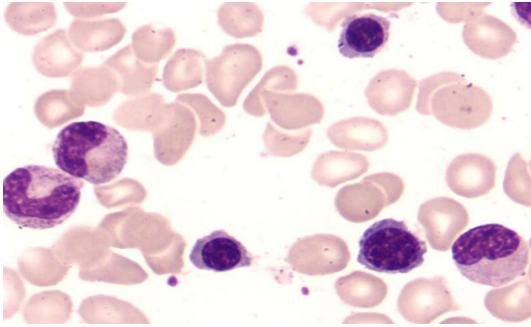


Figure 1. Changes in bone marrow on June 30: Megaloblastic changes and other dyshaematopoiesis phenomena can be found in granulocyte and erythroid series.

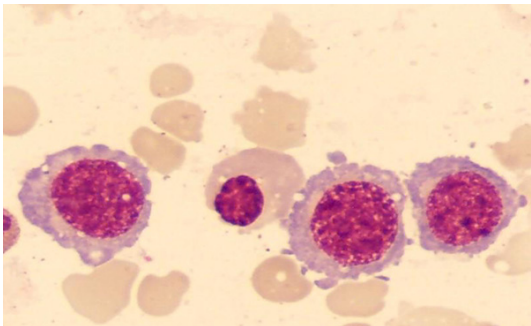


Figure 2. Bone marrow on July 9: No megaloblastic changes and other dyshaematopoiesis phenomena can be found.

lar volume (MCV) of 122.9 fl, mean corpuscular hemoglobin (MCH) of 44.7 pg, mean corpuscular width of 23.1%, platelet count of $43 \times 10^9/L$. Blood clotting function was normal, blood urea nitrogen was 9.37 mmol/L, serum sodium was 132 mmol/L, lactate dehydrogenase was 1270 U/L, hydroxybutyrate dehydrogenase was 1282 U/L. Follow-up laboratory values revealed C-reactive protein of 18.0 mg/L and the parathyroid hormone levels of 89.7 pg/mL. Routine urine examination was normal and blood biochemical analysis showed a decrease in globulin and bilirubin of 26 u. Low density lipoprotein cholesterol and very low density lipoprotein cholesterol were lower than normal values. All other biochemical indexes were normal. Rheumatoid factor (RF), anti-streptolysin-o test (ASO), antinuclear antibody (ANA) and anti-neutrophil cytoplasmic antibody (ANCA) were all negative. Cranial CT scan revealed no obvious hemorrhagic focus. The cranial MRI revealed a few ischemic foci near the front and back angles of the lateral cerebral ventricles and the

left centrum ovale. Cervical MRI revealed cervical degeneration of the discs at the C5/C6 and C6/C7 levels. This finding was also associated with central protrusion. Thoracic CT revealed a small amount of bilateral effusion in the thoracic cavity. A few infectious lesions were found in the left lung ligule and fibrous proliferative foci were found in both lungs. Ultrasound analysis of the heart revealed aorta atherosclerosis, left ventricular diastolic dysfunction and mild mitral and tricuspid regurgitation. No obvious abnormality was found in the thyroid. EEG analysis revealed a slow α active EEG. Bone puncture was carried out on the day of admission and revealed megaloblastic changes and other dyshaematopoiesis phenomena can be found in granulocyte and erythroid series (**Figure 1**).

The initial course of treatment at the hospital included intravenous fluids and a blood transfusion. After transfusion and fluid supplementation, the patient's urinary output increased and his heart rate remained normal, but his blood pressure remained low. The patient received a dopamine infusion over the night to maintain blood pressure at 90-140/60-85 mmHg. Further hospital course of treatment included 10 mg folic acid that was administered orally TID and 1 mg of vitamin B₁₂ was injected intramuscularly QD for five days. After 5 days this regimen was changed to 5 mg folic acid administered orally TID with a 1 mg intramuscular injection of vitamin B₁₂ QOD.

Routine blood analysis was reassessed on July 9 and revealed the following: white blood cell count $8.5 \times 10^9/L$, neutrophils (%) 82.8%, hemoglobin 69 g/L, platelet count $230 \times 10^9/L$, reticulocyte of 4.3%. Routine examination of bone marrow on July 9 revealed no megaloblastic changes and no other dyshaematopoiesis phenomena were found (**Figure 2**).

The patient's condition gradually improved after the initial admission. Dizziness and fatigue were alleviated and the patient's mental status and appetite improved. The patient's pain in the neck and waist region gradually disappeared, as did the hallucinations. The patient's blood pressure became more stable and the dopamine dose was gradually decreased until it was completely withdrawn on July 14, at which time oral administration of midodrine hydrochloride tablets was prescribed to maintain a stable blood pressure. Hemoglobin and platelets increased steadily. The patient began

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Table 1. Change in routine blood examinations

Date	6/29	6/30	7/1	7/2	7/5	7/7	7/9	7/10	7/12	7/27
Hemoglobin (g/L)	40	63	80	79	82	73	69	70	86	98
MCH (pg)	41.7	38	34.9	36.1	35.8	34.4	32.9	32.6	32	30.9
MCHC (g/L)	339	364	365	376	364	336	345	338	328	325
MCV (fl)	122.9	104.2	95.6	95.9	98.3	102.4	95.2	96.3	97.4	95.3
Plates ($\times 10^9/L$)	43	40	25	16	42	65	230	342	521	277
Reticulocytes (%)		0.7		0.4	1.1		4.3		3	1.3

MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume.

a small amount of activity on July 19 and was able to walk independently in the hallway as his symptoms continued to improve.

Routine blood examination repeated on July 27 revealed: hemoglobin 98 g/L, MCV 95.3 fl, MCH 30.9 pg, mean corpuscular width 17.1%, and platelets $277 \times 10^9/L$ (Table 1). Except for cholesterol, which was 2.69 mmol/L, all other blood values were normal. His blood pressure was maintained at 120-140/70-80 mmHg, and no conscious disturbances were noted. The patient was discharged on July 28.

Results

At a four month follow-up, the patient reported he was living in his original place of birth and has not had any repeated episodes of the original symptoms. He reported that he had no difficulties with activities of daily living and had returned to eating a normal and healthy diet that was not restricted to vegetarian options. He reported that he was happy to be able to walk in the park every day. This patient continued a low dose folic acid and vitamin B₁₂ regimen, and repeat blood examinations and blood pressure examinations in a local hospital were all normal at the follow-up period.

Discussion

The key characteristics of this case included: 1) Elderly male patient; 2) Primary symptoms of hypotension and delirium; 3) Severe anemia; and 4) Megaloblastic anemia as evidence through bone marrow examination. The patient's condition improved after treatment with folic acid and vitamin B₁₂.

Megaloblastic anemia is a nutritional anemia induced by deficiencies of folic acid and/or vitamin B₁₂. Vitamin B₁₂ deficiency is frequently seen in the clinic and the incidence of this disorder increases with age. Dietary vitamin B₁₂

deficiency, rare in childhood, although is common in the elderly. More than 9% of the anemia cases in elderly people are induced by vitamin B₁₂ deficiency, while 3-12% of the geriatric population has low vitamin B₁₂ levels [3-5]. The patient in this case study ate poorly and had a primarily vegetarian diet due to changes in his residence. Intestinal absorption decreases with age, so this factor along with a poor diet may have contributed to the vitamin B₁₂ deficiency. The significant 10 kg weight loss during the previous year was disconcerting, but systemic physical examination revealed that the weight loss was not likely attributable to cancer, hyperthyroidism, diabetes or other common diseases. Routine blood examination for this patient showed severe anemia and his MCV, MCH and mean corpuscular width were also significantly higher than normal levels. In addition, lactate dehydrogenase was significantly increased and mild jaundice was detected, indicating that ineffective hematopoiesis in bone marrow or hemolysis of red blood cells. These results supported the diagnosis of megaloblastic anemia, which was verified by characteristic changes in the bone marrow examination on the day of admission. The bone marrow morphology was significantly improved after treatment. After the patient was treated with folic acid and vitamin B₁₂ for 12 days, reticulocytes increased by 4.3%, hemoglobin and platelets both gradually increased, and other clinical symptoms also improved. We concluded the diagnostic treatment was effective, which strongly supported the diagnosis of megaloblastic anemia. Sustained improvements were seen at follow-up examination.

The first documented case of postural hypotension induced by vitamin B₁₂ deficiency was reported by Kalbfleish and Woods in 1962 [6], and this condition was considered to be related to autonomic neuropathy. The symptoms asso-

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ciated with postural hypotension in this case were significantly improved after vitamin B₁₂ treatment. Similar results were also reported by other investigators [7, 8]. Postural hypotension may be induced by many reasons, including hypovolemia, abnormalities in venous return and circulatory reflex disturbances that can be induced by neurological abnormalities. A previous study reported that norepinephrine released by sympathetic nerves decreased when megaloblastic anemia patients maintained a standing position. This could decrease the vasoconstriction force and subsequently result in postural hypotension [9]. However, the patient in our case demonstrated persistent low blood pressure that was not accompanied with an increase in heart rate or a decrease urine output. Additionally, the patient's blood pressure in the present case did not increase after blood volume was restored, suggesting these changes were not related to the decreased cardiac contractility or loss of blood volume. After the patient was treated with folic acid and vitamin B₁₂, his blood pressure rose steadily and thus the change in blood pressure was considered a direct result of vitamin B₁₂ deficiency and a subsequent, persistent decrease in vascular tension.

Vitamin B₁₂ is an important element for monoamine metabolism. Both vitamin B₁₂ and folic acid are involved in homocysteic acid methylation to synthesize methionine and ademetionine. Vitamin B₁₂ and folic acid deficiency can lead to disorders within the methylation process and result in the accumulation of homocysteic acid, which may subsequently lead to mental illness [10]. The neurologic manifestations of folate deficiency overlap with those of vitamin B₁₂ deficiency and include cognitive impairment, dementia, depression, and, less commonly, peripheral neuropathy and subacute combined degeneration of the spinal cord [11]. Vitamin B₁₂ deficiency has diverse cutaneous and ophthalmic manifestations [12, 13]. Vitamin B₁₂ deficiency has no or mild symptoms in the early stages, but can lead to substantial neurological impairments if left untreated. This progression can include segmental demyelination and axonal degeneration, which are characterized by weakness of lower extremities, numbness, unsteady gait, and/or psychiatric symptoms, including cognitive dysfunction, memory loss, schizophrenia, etc. Psychiatric disorders induced by vitamin B₁₂ defi-

ciency may also occur before the appearance of the anemia [14]. It has been reported that vitamin B₁₂ and folic acid deficiency can lead to conscious disturbances and delirium, which are frequently seen in elderly individuals [15, 16]. The patient in this case suffered from delirium and the possibility of parenchymal diseases was ruled out after cranial MRI and other examinations. Although the vitamin B₁₂ level was not measured, the mental status of the patient improved after he was administered vitamin B₁₂ and folic acid tablets. Differential diagnosis including vitamin B₁₂ deficiencies should be considered in older patients with psychological disturbances.

Conclusion

Bone marrow examinations can aid in the diagnosis of anemia, but the results from these tests cannot always differentiate the type of anemia. Clinical management of the disorder is reliant upon proper classification of the type of anemia. The prognosis of megaloblastic anemia is typically good and a simple regimen of folic acid and/or vitamin B₁₂ is effective.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xue-Ying Lv, Department of Geriatrics, The First Affiliated Hospital, School of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, China. Tel:+86-13758264260; Fax: +86 571-87236806; E-mail: XueyingLvdoc@yeah.net

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