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Life-threatening megaloblastic pancytopenia with normal mean cell volume: case series

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Abstract

The mean red blood cell volume (MCV) is usually increased in severe megaloblastic anemia due to pernicious anemia. However, during one year in a university hospital, three patients with life-threatening pancytopenia and normal MCV were proven to have severe vitamin B12 deficiency. The red blood cell distribution width was markedly increased (three times normal) and led to review of the blood smear and recognition of megaloblastosis as well as prominent red cell fragmentation. These three cases illustrate that vitamin B12 status should be evaluated in cases of pancytopenia, independent of the MCV value.

Keywords

Vitamin B12; Pernicious anemia; Methylmalonic acid; Homocysteine

Introduction

Severe vitamin B12 deficiency, often due to pernicious anemia, is one of the only curable causes of life-threatening anemia and pancytopenia, so it is highly beneficial to the patient to recognize the syndrome. Most clinicians will readily make a diagnosis if the mean red blood cell volume (MCV) is markedly increased. However, it is often assumed that only mild anemia or cases with B12- deficient neurological abnormalities would present with a normal MCV. In contrast, in 2004, at the University of Colorado Hospital, the only three cases of severe life-threatening anemia and pancytopenia secondary to vitamin B12 deficiency seen by the hematology service had MCV in the normal to low-normal range.

Case reports

Clinical and laboratory findings

Case 1

A 32-year-old African-American (A-A) female presented with worsening dyspnea on exertion and hemoptysis. A spiral CT scan was negative for pulmonary embolus. Her family history

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included thyroid dysfunction. A provisional diagnosis of hematological malignancy was considered because of severe pancytopenia, extremely high LDH, and early myeloid forms on her peripheral blood smear. Laboratory studies are shown in Table 1, confirming severe vitamin B12 deficiency due to pernicious anemia. Bone marrow aspirate and biopsy were megaloblastic.

Case 2

A 77-year-old A-A male presented with syncope and new skin hyperpigmentation. Two months prior, he had been hospitalized elsewhere for life-threatening microcytic (MCV 76 fL) anemia requiring five units of red cell transfusion. Upper gastrointestinal endoscopy revealed gastritis. However, severe anemia re-occurred only two months later. He was hospitalized and emergently transfused. His laboratory abnormalities are shown in Table 1, confirming pernicious anemia. Physical examination revealed a large area of darkly pigmented skin on his back which was of recent onset.

Case 3

A 46-year-old A-A male with diabetes, hepatitis C, and previously diagnosed gastritis presented with lightheadedness, ataxia, and numbness in his hands and legs. His family history was significant for scleroderma, myasthenia gravis, and Graves' disease. His laboratory findings confirmed severe vitamin B12 deficiency, as seen in Table 1. After one month on weekly B12 injections, he had complete correction of blood counts and a low-normal MCV (hematocrit 49%; MCV 83 fL).

Peripheral blood smears

The peripheral blood smears showed hypersegmented neutrophils in all three cases. Case 1 had many immature myeloid cells and megaloblastic-nucleated red blood cells. All three smears demonstrated severe anisocytosis and poikilocytosis with schistocytes, fragmented cells, and extremely large oval macrocytes. The red cell distribution width (RDW) values (Table 1) reflect this extreme variation in size and shape. The direct Coombs test was negative in all three patients.

Discussion

Severe megaloblastic anemia with normal MCV is thought to be rare in pernicious anemia, yet these three patients were the only ones known to the hematology service to be hospitalized with severe B12 deficiency in one year. A recent report of 181 Chinese patients with pernicious anemia showed that 95% had MCV above 99 fL [1], and a large series from New York showed that only 17% had MCV in the normal range [2].

RDW has been used to help classify anemias [3], and the marked elevation in RDW in our patients was a diagnostic clue pointing away from a normocytic process. The extreme values were confirmed on review since the smears revealed not only oval macrocytes but also a large number of small, fragmented cells. The smaller, fragmented cells likely decreased the MCV, which is calculated from a RBC volume histogram and is, therefore, an average of all cells. Results such as the extremely high LDH and elevated indirect bilirubin suggest that all three subjects had intramedullary hemolysis (ineffective erythropoiesis). Schistocytes, thrombocytopenia, and chemical indicators of hemolysis could even lead to an erroneous diagnosis of microangiopathic hemolytic anemia. Red cell fragmentation and marked abnormality in size and shape in severe megaloblastic anemia were noted in a recent review [4] but may not be widely recognized by generalists.

Thalassemia, or iron deficiency, can also mask macrocytosis [1–4]. However, case 3 demonstrated an increase in hematocrit to 49% with a MCV of 83 fL after B12 treatment alone, suggesting that he was iron-replete. Other clues to the diagnosis in these three subjects include the strong family history of autoimmune disease in two, prior diagnoses of gastritis in two, and the new onset of skin hyperpigmentation in one [5].

We conclude that megaloblastic pancytopenia with normal MCV and elevated RDW may present more commonly than previously recognized and should prompt expert review of the peripheral blood smear for macrocytosis and neutrophil hypersegmentation.

Learning points

- Severe vitamin B12 deficiency can cause megaloblastic pancytopenia with a normal MCV.
- High red cell distribution width is a clue to a marked variation in red cell size, ranging from macrocytes to small, fragmented cells, resulting from intramedullary hemolysis.
- A history of autoimmune disease and gastritis are potential clues to a diagnosis of pernicious anemia.

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Table 1

Clinical and laboratory data from three patients with life-threatening megaloblastic anemia

	Case 1	Case 2	Case 3
Age (years)	32	72	45
Sex	F	M	M
Race	A-A	A-A	A-A
Hct % (37–49) ^a	13.8	12.7	22.4
Hgb g/dL (12–16)	4.7	4.4	7.9
MCV fL (80–100)	92.1	86.4	84.4
RDW % (10.5–13)	38	30.5	31.5
WBC 10 ⁹ /L (4–11.1)	3.7	2.8	3.8
ANC 10 ⁹ /L (1.8–7.8)	0.6	1.9	1.7
Platelets 10 ⁹ /L (150–400)	105	39	164
Reticulocytes % (0.5–2.4)	2.9	0.5	0.7
LDH U/L (98–192)	4240	2527	2223
Total bilirubin mg/dL (0–1)	1.8	2.1	0.9
Indirect bilirubin mg/dL (0–0.7)	1.3	1.5	0.6
D dimer < 500 (ng FEU/mL)	2820	1723	-
Serum B ₁₂ pg/mL (211–911)	95	< 30	10
Serum folate ng/mL (> 5.3)	11.4	12.2	> 20
MMA nmol/L (0–400)	1330	22250	11450
Homocysteine umol/L (5–15)	99	-	-
Ferritin ng/mL (10–388)	69	177	879
Antibodies	APC + IF+	IF+	-

A-A, African-American; RDW, red cell distribution width; APC+, antiparietal cell antibodies positive; IF+, anti-intrinsic factor antibody positive

^a numbers in parenthesis are normal ranges from the University of Colorado Hospital Laboratory