

# "Normal" Mean Corpuscular Volume Does Not Exclude the Diagnosis of Thalassaemia

ACW LEE

**Abstract** The mean corpuscular volume (MCV) measured by automated blood cell counter is a convenient way of recognising microcytosis which is a hallmark feature in the diagnosis of thalassaemic syndromes. Two children with severe thalassaemia syndrome but normal MCV measurements are described. A 17-month-old girl with homozygous  $\beta$ -thalassaemia and a 3-year-old girl with haemoglobin H-Constant Spring disease presented with anaemia. Results from the automated blood cell counter showed haemoglobin of 7.0 g/dL and 8.0 g/dL (normal, 11.0-15.0), respectively, with corresponding MCV of 80.5 fL and 79.3 fL (normal, 70.0-90.0), respectively. Microcytosis and hypochromia, however, were prominent on microscopic examination of the peripheral blood smear, which led to the correct diagnosis. Paediatricians and family physicians should be alerted to the potential pitfalls when interpreting the results provided by automated blood cell counters. Microscopic examination of the peripheral blood smear is indispensable in the evaluation of anaemic children.

**Key words** Anaemia, hypochromic microcytic; Erythrocyte indices; Haemoglobin H disease; Mean corpuscular volume; Thalassaemia, beta

## Introduction

Automated blood cell counters or analysers are now a standard setup in most haematology laboratories, providing rapid results on blood cell indices with high-volume output. With advancements in new physical principles for cellular analysis and software improvements, the results generated from these machines are generally accurate and relevant for clinical management. However, how the blood sample has been obtained, the anticoagulant admixed with the sample, the lag time between sampling and analysis, and the intrinsic constraints of the analytical methods may affect the findings and interpretation of the results.<sup>1</sup>

Mean corpuscular volume (MCV) measures the size of

an "average" red blood cell. In the laboratory evaluation of patients with anaemia, the MCV is a commonly used and important index for classification and thus guiding further management.<sup>2</sup> Traditionally, the MCV was calculated as a ratio of haematocrit/red blood cell count. In modern automated counters, individual red cell volume can be measured by either electrical impedance or light defraction, and the MCV computed by the measurements of thousands of red blood cells that pass through a small aperture.

In the presence of significant variation in red cell sizes and shapes, a microcytic, hypochromic anaemia may be masked when only the computed indices are examined. Direct visualisation of the peripheral blood smear under the microscope is still an indispensable examination in the evaluation of anaemic illnesses. The following two cases are illustrative.

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Children's Haematology and Cancer Centre, Mount Elizabeth Hospital, Level 4, 3 Mount Elizabeth, Singapore

ACW LEE (李志偉) MBBS, FHKAM(Paed)

Correspondence to: Dr ACW LEE

Received May 18, 2014

## Case Reports

### Case 1

A 17-month-old girl of South Asian origin attended a

private paediatric practice because of pallor. She was the first child of the family and the perinatal period was uneventful. She had been well and thriving normally in the first year of life, but her weight gain slowed down after the first birthday. The family history was negative for anaemic disorders. The attending paediatrician noted the child to be pale and hence a test for complete blood counts was ordered. The results were tabulated in Table 1. On the finding of a normal MCV of 80.5 fL, the paediatrician dismissed the diagnosis of thalassaemia. Nonetheless, a referral to the paediatric haematologist was made.

The peripheral blood smear was retrieved and examined under the microscope (Figure 1). The red blood cells showed severe anisopoikilocytosis with prominent microcytosis, hypochromia, and polychromasia. Normoblasts constituted 10% of the nucleated cells. The white blood cells and platelets were normal, save for occasional myelocytes. Based on the blood smear findings, the paediatric haematologist made a working diagnosis of severe thalassaemia syndrome. Subsequent laboratory confirmation included haemoglobin electrophoresis, which revealed HbF of >98% with absence of HbA, and  $\beta$ -globin gene analysis, which showed the patient to be double heterozygous for IVS1-nt1(G>T) mutation and 619bp deletion.

### Case 2

A 3-year-old girl of Chinese descent presented with signs of pallor after an antecedent upper respiratory infection with persistent coughs upon recovery. Her prior health and development was unremarkable. There was no family history of anaemia. She was pale on examination but

there was no jaundice, lymphadenopathy, or hepatosplenomegaly. The results from complete blood counts were tabulated in Table 1.

Despite a seemingly normal MCV of 79.3 fL, review of the peripheral blood smear by the paediatric haematologist revealed prominent anisopoikilocytosis, microcytosis, hypochromia, target cells, basophilic stippling, and polychromasia. A thalassaemic syndrome was highly suspected. Further testing with supravital staining demonstrated the presence of haemoglobin H granules in 56% of the red cells, and the haemoglobin electrophoresis showed the presence of haemoglobin H, haemoglobin Barts, and haemoglobin Constant-Spring. Thus, haemoglobin H-Constant Spring disease was diagnosed.

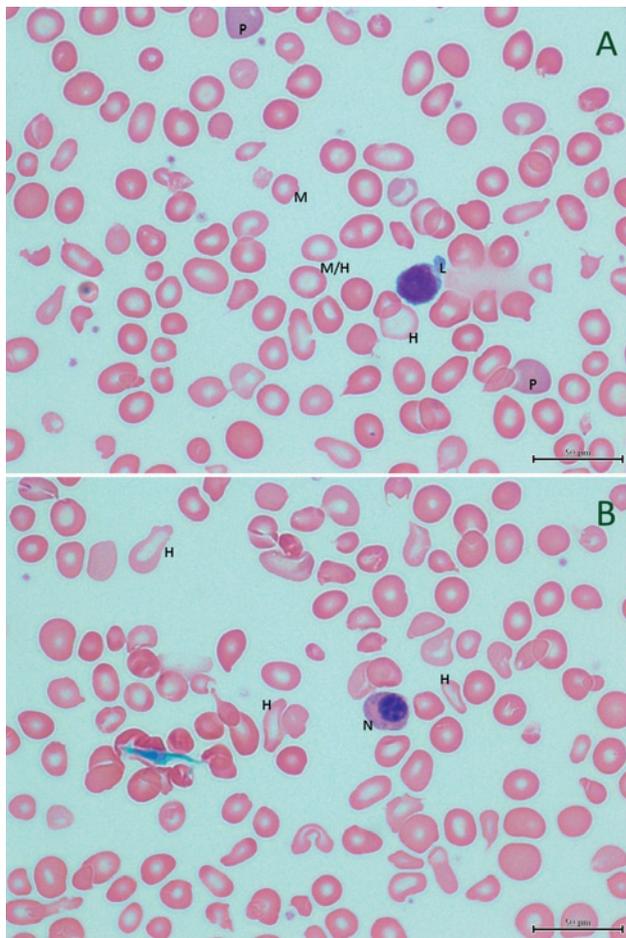
### Discussion

Anaemic illnesses are commonly classified into microcytic, normocytic, and macrocytic anaemia according to the red blood cells sizes. Each type of anaemia is associated with a different set of differential diagnosis and thus the classification is useful in guiding further laboratory investigations.<sup>2</sup> This is especially relevant in paediatric practice in the Oriental and Southeast Asian regions where microcytic, hypochromic anaemia in the forms of iron deficiency anaemia and thalassaemia syndromes prevail.<sup>3</sup> Other causes of microcytic anaemia include sideroblastic anaemia, lead poisoning and some cases of anaemia of chronic disease and hereditary spherocytosis.<sup>4</sup> Thus, the finding of microcytosis is quite common in paediatrics and the office settings.

**Table 1** Haematological parameters as reported from the automated blood cell counter (Advia® 2120 Hematology System, Siemens, New York)

Age	Case 1 17 months	Case 2 38 months	Reference	Units
Haemoglobin (Hb)	7.0	8.0	11.0-15.5	g/dL
Red cell count (RBC)	2.85	4.02	4.00-5.10	$\times 10^{12}/L$
Haematocrit (Hct)	22.9	31.9	33.0-43.0	%
Mean corpuscular volume (MCV)	80.5	79.3	70.0-90.0	fL
Mean cell haemoglobin (MCH)	24.7	19.9	23.0-31.0	pg
Mean cell haemoglobin concentration (MCHC)	30.7	25.0	31.0-36.0	g/dL
Red cell distribution width (RDW)	28.8	25.4	11.0-25.6	%
Platelet	123	275	140-460	$\times 10^9/L$
White cell count (WBC)	11.06	11.65	6.00-17.00	$\times 10^9/L$

Microcytosis is traditionally discerned under the microscope. The diameter of normal red cells is between 6.2-8.2  $\mu\text{m}$ , which is about the same size of a small lymphocyte. Hence, by examining the peripheral blood smear and comparing the sizes of the red cells and lymphocytes, a visual differentiation of the different classes of anaemia can be made. However, the measurement of MCV as provided by the automated blood cell counter is



**Figure 1** Peripheral blood smear (x100) of Case 1, (A) photomicrograph showing red cells that are microcytic (M), hypochromic (H), or microcytic-hypochromic (M/H). A small lymphocyte (L) is shown for size comparison. There are also polychromatic red cells (P) that are larger in size. Note the prominent variation in sizes and shapes (anisopoikilocytosis) of the red cells. (B) Photomicrograph showing the marked variation in red cell dimensions. Hypochromatic cells (H), in which the central pallor is greater than  $\frac{1}{3}$  of the diameter, have marked variation in shapes. A circulating normoblast (N) or nucleated red cell is shown.

now often used as a surrogate index for classifying anaemia in busy clinical and office settings, partly because the result comes with each measurement of haemoglobin and partly because experienced personnel who can read peripheral blood smear is not always available.

The two cases reported here have illustrated the pitfall of using the MCV measurement alone when interpreting the results of automated blood cell counts in children with anaemia. A positive family, the presence of jaundice and/or hepatosplenomegaly, and facial skeletal changes, when positive, may be clues to the underlying thalassaemic syndromes. However, direct examination of the peripheral blood smear is still the gold standard in the detection of microcytic, hypochromic anaemia and the exclusion of spherocytic disorders and other more sinister diseases.

The reason for the deceptively normal MCV may be understood by examining the cells on the peripheral blood smear. In these two cases, there is a sizable portion of red cells that are large and polychromatic (Figure 1), which probably represents the younger population of red cells. Mathematically, cells with diameters two times larger have volumes eight times of the comparison cells. As little as 11% of such larger cells in the circulation can double the volume of the rest of the red cell mass. This is why the microcytosis is masked by the MCV measurement but is otherwise obvious under the microscope. Reticulocytes, not measured in both of the cases, is expected to be high based on the red cell morphology. Recent blood transfusion and co-existing conditions that increase red blood cell sizes such as folic acid or cobalamin deficiency have to be taken into consideration when a dimorphic population of microcytic and macrocytic red cells are encountered.

In conclusion, clinicians working with children should be aware of the limitations of computed red cell indices such as the MCV provided by automated blood cell counters. Examination of the peripheral blood smear in the properly staffed laboratory or by the paediatric haematologist is essential when children with anaemic disorders are evaluated.

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