Elevated Hemoglobin and Macrocytosis: A Neglected Association to Become a Diagnostic Tool (A Case Report)

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INTRODUCTION
The hemoglobin (Hb), hematocrit (Hct), and red blood cells (RBCs) have been historically essential in morphologic classification and diagnosis of anemias. Likewise, the RBC indices (RBCI) such as mean corpuscular Hb (MCH, picograms per cell), MCH concentration (MCHC, grams Hb per deciliter), and, especially, mean corpuscular volume (MCV) that defines the size (volume) of RBCs have been equally important in anemia assessment. While MCV represents perhaps the most valued index in hematological practice, its exact effects on Hct and Hb levels, especially in polycythemia cases, have long been underappreciated and completely disregarded in clinical practice. An illustrative case is presented. This case report follows the CARE Guidelines.

CASE REPORT
A 79-year-old man with a history of congestive heart failure, atrial fibrillation, bladder cancer, lumbar spondylosis, gout, and depression was referred for evaluation of elevated Hb and Hct (Table 1). His Hb and Hct levels have fluctuated over a 2-year period from 17.4 to 18.1 g/dL (reference range, 13.0-17.0 g/dL) and from 52.7% to 54.4% (reference range, 39%-51%), correspondingly. The RBCs varied from 4.28 to 5.03 × 1012 per liter (reference range, 4.10-5.70 × 1012 per liter). At the time of evaluation, the patient’s RBC distribution width was 12.8% (reference range, 12.0%-16.5%) and mean corpuscular volume (MCV) was elevated at 110 fL (reference range, 80-100 fL). MCH was 36.3 pg per cell (reference range, 27-31 pg per cell) and MCHC was 33 g Hb per deciliter (reference range, 31-37 g Hb per deciliter). He had a normal white blood cell count of 4.5 × 109 per liter (reference range, 3.7-11.1 × 109 per liter), normal differential and platelet count of 124 × 109 per liter (reference range, 140-400 × 109 per liter). The reticulocyte count was 1.72% (reference range, 0.70%-2.40%), absolute count 80 × 109 per liter (reference range, 25-115 × 109 per liter). The patient never smoked and had normal oxygen saturation and no evidence of lung disease or sleep apnea. Additional tests were performed but failed to confirm the diagnosis of polycythemia vera (PV). There was no splenomegaly, his erythropoietin level was normal, and JAK2 V617F gene was unmutated. The patient’s treatment consisted of metoprolol, clonazepam, hydrocodone, venlafaxine, trazodone, allopurinol, tamsulosin, and furosemide.

The patient’s records showed that his MCV was slowly rising over 20 years. Of note, while the MCV was elevated during the entire follow-up period (Table 2), the increase in total Hbs/Hcts was observed for only 2 years preceding the evaluation. During that time, the patient was receiving a loop diuretic that, upon careful review, caused his RBC count to increase from a mean baseline of 4.54 × 1012 per liter prior to the diuretic use to 4.79 × 1012 per liter during the treatment. The patient was observed for 18 months. Following the diuretic cessation, the RBC count, while remaining normal, declined to the patient’s previous baseline with concomitant Hb/Hct normalization.

The cause of increased MCV, although extraneous to the issue under discussion, was addressed by extensive and repeated diagnostic procedures over the years. Seventeen years prior to the patient’s presentation, a bone marrow study showed normal trilineage hematopoiesis with mild relative erythroid predominance and focal mild increase in reticulin staining. Cytogenetic studies were normal and flow immunophenotyping failed to identify abnormal cell populations. The patient had no known history of drug or alcohol abuse, or kidney, thyroid or liver disease. He had a
normal testosterone level and lipid profile [cholesterol 4.73 mmol per liter (reference range, < 5.17 mmol per liter), triglycerides 1.74 mmol per liter (reference range, < 5.63 mmol per liter)], and took no medications known to cause macrocytosis. He demonstrated no conditions that can cause spurious macrocytosis such as cold agglutinins, monoclonal proteins, hyperglycemia or hyperleukocytosis. The diagnosis of pernicious anemia was repeatedly dismissed based on the patient’s normal vitamin B12 (and folate) levels, lack of anemia, and macrocytosis persisting for as long as 20 years.

DISCUSSION

The cause of elevated Hb/Hct, the laboratory finding in question, was patently nontrivial in this case and necessitated an unconventional approach. As noted above, the patient’s Hb/Hct elevation occurred concomitantly with macrocytosis (Table 2). When present together, these abnormalities can pose a clinical challenge. The ordinary cause of high Hct is elevated RBC count.4 Because it was normal, the lasting increase in MCV was felt to be pertinent to the patient’s Hct elevation. Indeed, the high Hct ought to be attributed to the large RBC size as the classical formula $Hct = RBC \times MCV$ overtly demonstrates: the higher the MCV (the larger the RBC size), the higher the Hct (and vice versa).

Curiously, this fact, though obvious and rightly emphasized previously,5 has been completely overlooked and discounted in practice. It is also important to point out that MCV affects not only Hct, but also Hb. The fundamental link between MCV and Hb was established almost a century ago6 but remained completely obscured. This link was validated in a more recent study where MCV was shown to vary in a strict linear relationship with average content of Hb of RBCs (MCH).7 As the result, macrocytes accommodate a greater amount of Hb compared with normocyttes or microcytes. Such a congruence of MCV with Hb content of RBCs (MCH) is sustainable owing to essentially constant Hb concentration per RBC (MCHC)7 (Table 2). While these findings proved to be important for evaluation of anemias, it has not been previously recognized that, by contributing to a total Hb/Hct level, MCV could be clinically relevant in the cases of elevated Hb/Hct.

The MCV elevation was not the only factor that triggered Hb/Hct raise in this case. The treatment with loop diuretic for 2 years was deemed to have caused chronic dehydration leading to relative RBC elevation. The latter in conjunction with elevated MCV forced the Hb/Hct levels upward of normal range and was masquerading polycythemia vera (PV). It is worth noting that, while the World Health Organization’s (WHO) classification of PV identifies erythrocytosis with high levels of Hb/Hct,8 this case corroborates

<table>
<thead>
<tr>
<th>Date</th>
<th>Summaries from initial and follow-up visits</th>
<th>Diagnostic testing (including dates)</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Patient with multiple medical problems noticed to have borderline macrocytosis (MCV, 100 fL and transient thrombocytopenia (136 × 10^9 per liter).</td>
<td>Evaluation of macrocytosis with bone marrow biopsy (01/19/01) showed no apparent signs of myelodysplasia, normal cytogenetics and flow cytometry.</td>
<td>Complete blood cell count monitoring without further diagnostic intervention was recommended.</td>
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<td>2001-2015</td>
<td>Gradual increase of MCV without other RBC parameter changes was noticed: 102 fL in 2006, 104 fL in 2009, 106 fL in 2013 and 110 fL in 2015. The treatment with diuretic for CHF initiated in 2015.</td>
<td>Several evaluations over the years failed to elucidate the cause of elevated MCV (see text).</td>
<td>The patient’s RBC parameters were observed without the treatment or any dietary or lifestyle changes.</td>
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<tr>
<td>March 2016-Nov 2017</td>
<td>An asymptomatic elevation of Hb and Hct in addition to macrocytosis was identified.</td>
<td>A thorough evaluation with multiple blood tests and spleen ultrasound (see text) failed to establish the cause of elevated Hb and Hct.</td>
<td>A hematology consultation was requested for an indeterminate cause of elevated Hb/Hct.</td>
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<tr>
<td>Nov 2017</td>
<td>An initial evaluation of the patient’s medical, family and social history, medications and physical exam by hematologist failed to reveal an apparent cause of elevated Hb/Hct.</td>
<td>A comprehensive, longitudinal and comparative review of the RBC counts and RBC indices was performed.</td>
<td>The cause of elevated Hb/Hct was identified as a combined effect of relative RBC elevation due to diuretic use and elevated MCV. Discontinuation of the diuretic was recommended.</td>
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<td>2017-2019</td>
<td>Following discontinuation of the diuretic, the patient’s RBC count returned to previous baseline with concomitant Hb/Hct normalization.</td>
<td>No further testing was recommended.</td>
<td>No further interventions were recommended.</td>
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CHF = congestive heart failure; Hb = hemoglobin; Hct = hematocrit; MCV = mean corpuscular volume; RBC = red blood cell.
that the latter may not be a reliable surrogate marker for absolute erythrocytosis.9

Although the etiology of elevated MCV presents a separate issue and is peripheral to its effect on Hb/Hct, it was of special interest in this case. Macrocytosis of such a long duration is rarely seen. Additionally, its cause remained hard to determine despite the extensive and repeated diagnostic procedures over the years. The likelihood of a normal variant or genetic predisposition10,11 appeared to be low because the macrocytosis evolved over time. An acquired myelodysplastic syndrome, however, remained a plausible cause of the macrocytosis despite its remarkably long timespan.10

The present case illustrates a common scenario of how elevated MCV can contribute to high Hb/Hct levels, but it requires awareness and clinical acumen to resolve. While the described modifying MCV effect may have little clinical significance when short-lived, it caused a lasting diagnostic dilemma in this case. Such subtle RBC parameter dynamics may not be routinely perceived as important, but they are common and vastly underappreciated. Because macrocytosis occurs frequently in practice, and because RBC count tends to fluctuate for various reasons, their joint effect on Hb/Hct is clinically more prominent than generally recognized. In fact, even minor upward or downward trends in MCV readings can affect Hb/Hct in a clinically significant way.

As RBCI have become readily available with automated cell counters, their accurate assessment is paramount, especially in cases like this, and requires awareness and clinical acumen to resolve. While the described modifying MCV effect may have little clinical significance when short-lived, it caused a lasting diagnostic dilemma in this case. Such subtle RBC parameter dynamics may not be routinely perceived as important, but they are common and vastly underappreciated. Because macrocytosis occurs frequently in practice, and because RBC count tends to fluctuate for various reasons, their joint effect on Hb/Hct is clinically more prominent than generally recognized. In fact, even minor upward or downward trends in MCV readings can affect Hb/Hct in a clinically significant way.

As RBCI have become readily available with automated cell counters, their accurate assessment is paramount, especially in cases like this, and requires exclusion of the false readings due to spurious macrocytosis (SM) and/or spurious erythrocytosis. As mentioned before, the potential causes of SM such as RBC clumping (cold agglutinins or monoclonal proteins), RBC swelling (blood sample dilution from hyperglycemia),12 and increased blood turbidity (hyperleukocytosis)13 were ruled out. A simple review of a peripheral blood smear can reliably identify SM in most instances. Spurious erythrocytosis may be caused by hemoconcentration due to burns, emesis, diarrhea, or diuretics as occurred in this case. A comprehensive history will usually identify the cause of spurious erythrocytosis, thus obviating the need for costly RBC mass measurements with radioisotope studies. One of the limitations of this case presentation is that the macrocytosis remained incompletely explained even after excluding all conceivable causes. On the other hand, if not for the durable macrocytosis, the long-hidden cause of Hb/Hct elevation could have been overlooked.

CONCLUSION

The essential link between the size (volume) of RBCs and the RBC cellular Hb content, despite its far-ranging clinical applications, has been discounted for almost a century. This case opportune highlights the fact that macrocytes, by virtue of their larger volume, display a higher Hb content per cell than normocytes, and, as the result, contribute to overall higher Hb/Hct readings. In addition, the case demonstrates that macrocytosis is capable of forcing Hb/Hct above the normal range even in the absence of erythrocytosis (elevated RBC count). Because the described effect has a profound importance in clinical practice, general physicians and hematologists must be mindful about the MCV in every case of abnormally high Hb/Hct that can cause potential errors in interpretation of blood tests, misdiagnosis of PV, and unwarranted and costly workup. ♦

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### Author Contributions

Leonid L Yavorkovsky, MD, PhD, contributed entirely to this study including identifying the case and writing the manuscript.
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References