Difficult Decisions

Macrocytosis – how far to investigate?

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Laboratory automation nowadays throws up data, unsolicited by the clinician, that thrusts itself upon one's attention. A request for a haemoglobin is far more readily disposed of by feeding the blood sample to an automated counter and retrieving the printed result 20 seconds later rather than by actually measuring only the haemoglobin concentration. Up to 15 pieces of information may be contained on the print out including several pieces of trivia deemed interesting by the manufacturers that are best ignored. Among the more useful pieces of information is the mean red cell corpuscular volume (MCV).

What is macrocytosis?

This is not as silly a question as it appears. There is no consensus about the size of the normal red blood cell. Cell counters are set by the operator and the results can vary considerably on different machines with the same blood. Some parameters can be checked independently of the cell counter such as the haemoglobin level but other parameters such as the number of red cells per μl can only be numerated on other cell counters. The haematocrit can be measured reproducibly but invariably includes trapped plasma and the amount of trapped plasma varies with red cell shape. Thus the normal MCV has been claimed to vary between 76 to over 100 femtolitres (fl). This is clearly too wide a range and will result in iron deficiency being missed at the lower end and significant macrocytosis being missed at the upper end.

It is incumbent on the manager of a haematology laboratory, having set the cell counter, to determine a normal range by collecting blood samples on a single occasion from about 50 healthy young adults and measuring these on the machine. When this was done in the author's department the MCV ranged from 80–90 fl on each occasion that the exercise was performed. The haematocrit had been set to exclude 2.5% of

trapped plasma in the red cell column. The mean MCV was in the region of 85 fl.

One of the virtues of automated cell counters are that, when properly managed, their results are reproducible and changes in MCV over long periods of time are significant. Thus it may not matter a great deal how the machine is set provided that these settings are maintained and with these settings, a normal range has been determined. An MCV above this normal range is macrocytosis.

When is macrocytosis worth investigating?

Whatever the normal range of the MCV in a healthy young population, patients have a wider range. An increase in MCV by up to about 4 fl above the upper limit is so common as to be almost non-specific. Unless there is a good reason for expecting macrocytosis minor increases are best left alone in the first instance. However minor increases in the MCV may assume greater significance in the presence of peripheral neuropathy, or of a smooth tongue, or of a facies and a voice that suggests hypothyroidism and so on.

How to investigate?

Not uncommonly, investigation of a patient with modest macrocytosis fails to reveal any specific cause. This is particularly so in women of mature age who complain of lack of energy and in whom a modestly raised MCV (6–10 fl above the normal range) is the only abnormality.

Macrocytosis is physiological in the new-born and in pregnancy.¹ It is normal for the MCV to increase by about 4 fl in pregnancy but in a few women the increase can be as high as 20 fl. These women are normoblastic and the MCV returns to the normal range post-natally. The commoner causes of a raised MCV that should not be missed are: (a) megaloblastic anaemia; (b) alcoholism; (c) hypothyroidism; (d) myelodysplastic syndrome; and (e) medication, particularly with cytotoxic drugs.

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Alcoholism should be the first diagnosis in an adult with a raised MCV and a normal haemoglobin concentration. But even if the patient is clearly consuming more alcohol than his physician, other causes of macrocytosis should be looked for.

All patients who are hypothyroid have abnormally large red blood cells. Even those with a normal MCV show a fall of 5 to 6 fl 2–3 months after becoming euthyroid.²

Drug therapy is a very common cause of macrocytosis particularly long term drugs such as chlorambucil, melphalan and drug combinations in those receiving intermittent courses for lymphoma, leukaemia and myeloma. There is a suspicion that some anti-depressants have a similar effect as do most anticonvulsants used in epilepsy.

Almost all patients with megaloblastic anaemia due to deficiency of cobalamin or folate are macrocytic as are patients with myelodysplastic syndrome which includes preleukaemic states.

Thus having taken a good history and examined the patient, investigations should include request for thyroid stimulating hormone (TSH) serum cobalamin and red cell folate. It is as well to repeat the blood count and ask for a reticulocyte count since a young red cell population is a macrocytic one.

Should a marrow aspiration be done?

There is often a reluctance to proceed to a marrow aspiration, certainly at an early stage of the investigation. The patient does not like it and as the physician usually does not do the test himself, it involves a request to the haematologist. If the intention is to obtain a firm diagnosis of megaloblastic haemopoiesis then in the absence of a characteristic blood film, the only way to achieve this end is by examining the marrow. To be meaningful it must be done before giving cobalamin and/or folate therapy. Although one

expects low serum cobalamin and/or low red cell folate levels in a patient with megaloblastic anaemia, misleading results not uncommonly emerge from even the best laboratories. It is as well to know the marrow morphology.

The myelodysplastic syndromes comprise a group of disorders in which haemopoiesis is abnormal with developing pancytopenia. About a quarter of the patients proceed to manifest acute leukaemia but the other three quarters will die over several years of infection, bleeding etc. Patients are generally over the age of 50, they are usually macrocytic and many develop a transfusion requirement. Some are sideroblastic, marrow may show excess blasts, neutrophils are poorly granulated and 'monocytosis' may be present in the blood. A marrow is often useful in reaching a diagnosis.

Primary marrow failure (aplastic or hypoplastic anaemia) is macrocytic and here too a marrow is decisive.

The less common causes of macrocytosis

At this point it is permissible to rest on one's laurels. Macrocytosis has been associated with neoplasia, non-alcoholic liver disease, chronic airway disease, mongolism, copper deficiency³ and was even reported to be familial. Spurious macrocytosis can be associated with cold agglutinins, uncontrolled diabetes and therapy with hydroxyurea.

If one of the commoner causes is not present the cause of the macrocytosis is likely to remain uncertain.⁴ The largest group here, as mentioned, is in mature women in whom one suspects, but cannot prove, that the macrocytosis is due to hormonal factors. In older subjects time may show the emergence of other features of the myelodysplastic syndrome.

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