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Unexplained Macrocytosis in Elderly Patients

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Summary

One hundred and twenty-four patients over the age of 75 years were assessed for the cause of their macrocytosis (MCV > 95 fl). A definitive diagnosis was reached in 75/124 (60%) by non-invasive techniques. The remainder underwent a bone marrow biopsy yielding a definitive diagnosis in a further six patients who had an identifiable myelodysplastic syndrome (MDS). A high proportion of the remainder had morphological abnormalities which fitted with no recognized pathological entity. It is suggested that these may represent MDS in evolution.

Introduction

The advent of automatic cell counters has made the red cell indices including mean cell volume (MCV) widely available. An elevated MCV (i.e. macrocytosis) can be caused by several medical conditions and a variety of drugs. In this study we have considered patients aged 75 years and above, who were found to have a raised MCV with or without anaemia. Where conventional haematological and biochemical tests failed to elucidate the cause of the elevated MCV, patients were classified as having unexplained macrocytosis. The latter group had bone marrow aspirate (+/− trephine) in an attempt to define the cause of the macrocytosis.

Patients and Methods

We studied 124 patients aged 75 years and above, who were found to have a raised MCV as defined by MCV > 95 fl when measured on a Coulter Counter STCK-R. All patients underwent full clinical assessment, paying particular attention to drug history and alcohol consumption. Clinical manifestations of disease that could be responsible for macrocytosis, e.g. hypothyroidism, are generally more difficult to evaluate in elderly people. Investigations performed on all patients included:

1. Blood film examination
2. Serum vitamin B_{12}
3. Serum and red cell folate
4. Thyroid function tests (thyroxine and thyroid-stimulating hormone)
5. Liver function tests, including gamma glutamyl transferase.

Significant haemolysis was excluded by the examination of the blood film in association with the liver function tests. A reticulocyte count and Coombs test were only performed if indicated following the above investigations. Although reticulocytosis is often cited as a cause for a raised MCV, it is a rare cause in our experience. In a similar study, Keenan [1] reported only two cases of haemolysis in a group of 80 patients. Where these investigations failed to elucidate the cause of the raised MCV, a bone marrow examination was performed. Forty-nine patients proceeded to bone marrow examination and all had marrow aspirates. Trephine biopsy was obtained in 38 patients. In the remaining 11 patients, trephine biopsy was unsuccessful.

Marrow aspirates were examined morphologically after Giemsa staining and in addition all aspirates were stained to assess iron stores. Where a trephine biopsy was available, histological sections were examined.

Results

Out of 124 patients included in the study, the cause of the raised MCV was determined in 75 patients by non-invasive techniques (Table I). Fifteen patients were found to have hypothyroidism, in 17 patients macrocytosis was believed to be related to ethanol intake, fifteen patients had folic acid deficiency, another fifteen had vitamin B_{12} deficiency, and three patients had combined vitamin B_{12} and folate deficiency.

Two patients were found to have chronic liver disease, three patients were taking drugs (anti-epileptics) which could account for the raised MCV, and five patients were found to have malignant disease (three non-haematological, one acute myeloid leukaemia and one non-Hodgkin's lymphoma).

In the remaining 49 patients, where the raised MCV could not be explained by non-invasive techniques, bone marrow biopsy (aspirate +/− trephine) was performed.

The results of the bone marrow examinations were as follows (Table II): six patients could be classified as having a myelodysplastic syndrome (MDS) according to the F.A.B. classification [1], five patients had refractory anaemia (RA) and one patient had refractory anaemia with ring sideroblasts (RARS). The mean haemoglobin (Hb) for this group was 8.5 g/dl (range 6.1–10.6 g/dl) and the mean MCV is 100 fl (range 96–105 fl).

Nineteen patients showed some dysplastic features on marrow examination (8/19 had megaloblastic changes in erythroid precursors and 11/19 had hypogranularity of the myeloid precursors and dyserythropoietic

Table I. Diagnosis following evaluation of macrocytosis by non-invasive techniques

Cause of macrocytosis	No. of patients	Mean Hb (g/dl)	Mean MCV (fl)
Ethanol	17	13.6	100
Hypothyroidism	15	11.96	101
Vitamin B_{12} deficiency	15	11.4	104
Folate deficiency	15	12.4	103
Malignant disease	5	9.9	99
Combined vitamin B_{12} and folate deficiency	3	13.3	102
Anti-epileptic drugs	3	12.6	97
Chronic liver disease	2	12.7	98
Unexplained	49	12.0	100

changes) but would not fit the diagnostic criteria of any category of the F.A.B. classification. In addition one patient in this group (1/19) was found to be iron deficient. This was not suspected before the bone marrow examination in view of the raised MCV. The mean Hb of this group was 12.8 g/dl (range 10.7–15.0 g/dl) and the mean MCV was 99.2 fl (range 95–110 fl).

In the remaining 24 patients, bone marrow examination showed no morphological abnormality. Two patients in this group (2/24) were iron deficient. The mean Hb for this group was 12.3 g/dl (range 8.4–15.6 g/dl) and the mean MCV 99.7 fl (range 95–109 fl).

Discussion

Haemopoietic marrow undergoes progressive involution in distribution and cellularity with advancing age [3, 4]. Various laboratory and clinical observations led to the conclusion that marrow reserves decline with age [5]. Although the debate as to whether this deterioration in marrow function has its origin in the haemopoietic micro-environment rather than the haemopoietic stem cell itself remains to be settled, recent evidence from long-term *in vitro* bone marrow cultures favours that the haemopoietic micro-environment is to blame for the age-related deterioration [6, 7]. The precise factors responsible for this nonpathological age-related deterioration in bone marrow function, however, remain unknown.

Table II. Diagnostic categories following bone marrow biopsy (49 patients)

Diagnosis	No. of patients	Mean Hb (g/dl)	Mean MCV (fl)
Myelodysplastic syndrome:	6	8.5	100
Refractory anaemia (RA)	5		
Sideroblastic anaemia (RARS)	1		
No diagnostic features	24*	12.3	99.7
Dysplastic features:	19	12.8	99.2
Megaloblastic	8		
Dyserythropoietic hypogranularity	11†		

*Two patients were iron deficient. †One patient was iron deficient.

Age-related changes in full blood count and red cell indices have not been clearly defined. Munan *et al.* [8] demonstrated a gradual decline in Hb level from the sixth decade. In common with other groups, the decline was shown to be more marked in men. However, since the fall in Hb level was noted to be more marked over the age of 70 years, the possibility of inclusion of unwell individuals plus the small sample size of the very old may account for this observation. Other investigators have demonstrated no significant age-related decline in Hb level in the elderly [9, 10].

Age-dependent reference ranges for red cell indices are even less well defined than for Hb level. Although some investigators demonstrated a small rise in MCV with increasing age, they stressed that this is of little clinical significance and that other causes for macrocytosis should always be considered in the elderly [11–13].

In this study, an elevated MCV (>95 fl), though neither sensitive nor specific for any one condition, was a useful parameter directing further investigations which ultimately yielded a definitive diagnosis in 81/124 patients (65%). The yield was even higher (75% in the subgroup of patients with MCV > 100 fl. At higher MCV volume (>100 fl) more patients are likely to be found to be vitamin B_{12} and/or folate deficient 37.8% vs. 26.6% for MCV > 95 fl). In the remaining 43 patients, three were found to be iron deficient and no other definitive diagnosis could be reached. However, the bone marrow was morphologically abnormal in 19/43 (44%). The abnormality was principally in the form of dysplastic changes involving one or more of the haemopoietic cell lines. Although none of the 19 patients fitted the diagnostic criteria of the F.A.B. classification for myelodysplastic syndromes, it is possible that they represent early stages of myelodysplasia, which could evolve into a frank MDS with time. In favour of this hypothesis is the observation by Dotty *et al.* [14] who showed that macrocytosis predates the onset of MDS and/or acute leukaemia related to chemo/radiotherapy.

In addition, Joseph *et al.* [15] reported on refractory unexplained macrocytosis as an early sign of smouldering leukaemia and they suggested that refractory macrocytosis has the same significance as unexplained neutropaenia and or thrombocytopaenia.

Furthermore, the most frequent morphological abnormalities of the red cells reported in patients with MDS are acanthocytosis and macrocytosis due to increase in cholesterol/phospholipid quotient in the red cell membrane [16].

We conclude that macrocytosis (MCV > 95 fl) is a useful and simple parameter indicative of an abnormality for which a definitive diagnosis could be reached in most cases. The probability of achieving a definitive diagnosis increases with higher degrees of macrocytosis (MCV > 100 fl). Where macrocytosis remains unexplained after all appropriate tests—including a bone marrow biopsy—have been performed, we believe this could be an early sign of MDS. Follow-up of patients with unexplained macrocytosis with normal or non-specific dysplastic features in bone marrow for evidence of evolution to a distinct type of MDS as classified by the F.A.B. group should help elucidate this hypothesis.

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