Anaemia in the post-menopausal woman

Anaemia is a commonly encountered clinical entity. It can affect women of all ages and is not an ultimate diagnosis. An underlying aetiology should always be sought.

Dr Kaushik Guha Specialist Registrar in Cardiology, Royal Surrey County Hospital, Egerton Road,Guildford,Surrey, GU2 7XX.
email kguha@doctors.org.uk

Anaemia is an often encountered clinical entity, which is frequently overlooked. Even when recognised it is under investigated and poorly managed. The definition of anaemia for this article is a haemoglobin of less than 12.0g/dL.[1] Microcytosis is defined as a mean corpusclar volume (MCV) of less than 76fL and macrocytosis is defined as a MCV greater than 100fL.[2]

Pre-menopausal women

The commonest anaemia encountered in the pre-menopausal population is likely to be microcytic anaemia. This is a generic term for any type of anaemia characterised by small red blood cells and the most common cause is iron deficiency. Haemoglobinopathies, considered in the context of today's multicultural society, and anaemia of chronic disease must also be borne in mind.[3,4] In terms of chronic disease, a microcytic or normocytic anaemia may be the first presentation of chronic disease. In the pre-menopausal age group this includes infectious diseases, rheumatological auto immune mediated disease and renal disease.

Iron deficiency should not be considered as a satisfactory terminal diagnosis. This should prompt a consideration of the underlying aetiology. Firstly dietary intake must be questioned. There is a increasing promotion of veganism and vegeteranism. This is allied with certain ethnicities who are vegan due to secular beliefs. The main foodstuffs containing iron include red meat, green leaf vegetables and fortified cereals. A thorough food history must therefore be taken to elicit an accurate estimate of iron intake.

Coeliac disease

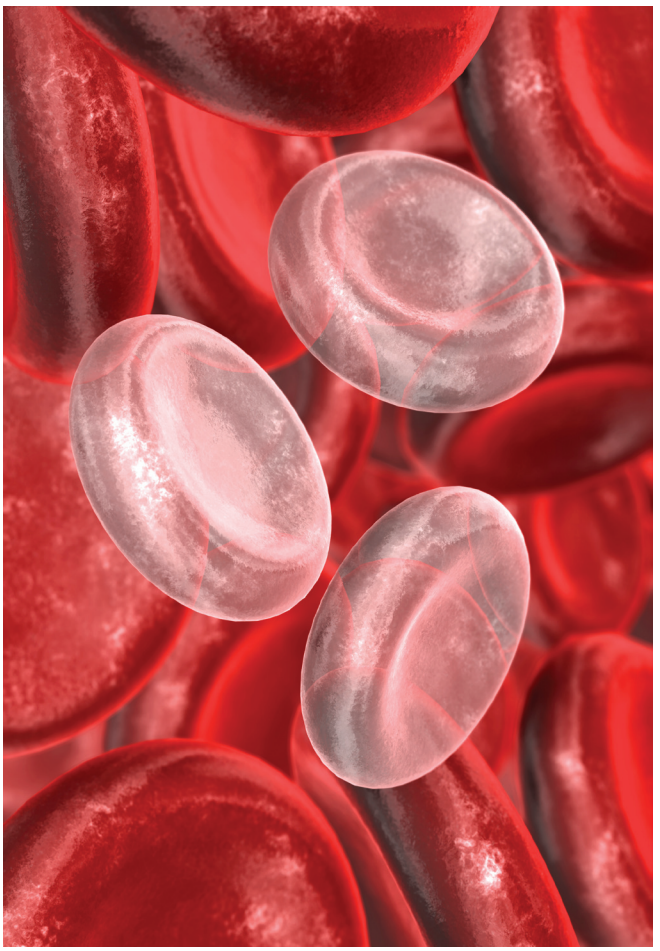
Gastroenterological causes must also be considered including coeliac disease, parasitic disease and occult malignancy. Coeliac disease is characterised by gliadin insensitivity mediated by T cells. This is accompanied with an upregulated autoimmune response, which manifests with the classic symptoms of abdominal pain, bloating and diarrhoea on encountering gluten containing food. This should be further investigated via an antitissue transglutaminase (anti TTG) and if necessary endoscopy and subsequent duodenal biopsy.[5] Prevalence has been estimated at around 6% in the adult female population with anaemia.[6] The management of coeliac disease is a sound patient-doctor partnership including the strict avoidance of gluten containing food and appropriate patient education.

Infectious diseases

Infectious diseases may also present with microcytic anaemia. It should be remembered that urbanisation has led to widespread immigration leading to multicultural societies. Worldwide the leading cause of microcytic anaemia is postulated to be hookworm infection. It is estimated to affect up to one billion people.[7] Other tropical diseases include schistosomiasis and amoebiasis. These should form part of the differential in patients who have travelled to endemic regions.

Malignancy

Occult malignancy is rare in the pre-menopausal population, but should be considered as part of the differential, especially for those who fail to respond



to treatment. Malignancies that should be considered are those of gynaecological origin including cervical and ovarian. The other neoplastic disease to consider is colorectal carcinoma. This should be remembered in patients with strong family history and a confirmed diagnosis of Familial Adenomatous Polyposis (FAP) or Hereditary Non-Polypoid Colon Cancer (HNPCC).[8]

Gynaecological causes of a microcytic anaemia are commonest in the population. Normally it is the coupling of menorrahgia with inadequate iron intake. A detailed gynaecological history should be sought.

Macrocytic anaemia may be encountered. The commonest causes of macrocytic anaemia included thyroidal disease, B_{12} and folate deficiency, myelodysplasia, alcohol consumption and haemolysis.[9] The commonest likelihood in this age group is likely to be autoimmune mediated hypothyroidism and alcohol misuse, which manifests as anaemia via occult B_{12} and folate deficiency.

Post-menopausal women

A discovery of anaemia in the post menopausal population must be investigated to find a satisfactory cause. Microcytic anaemia may well be secondary to occult neoplastic disease. Other common causes include surreptitious gastrointestinal haemorrhage and drug induced mucosal haemorrhage. Iron deficiency should be extensively investigated for an underlying cause as it is likely to represent significant underlying disease.[10,11] This applies to those patients deemed suitable for therapeutic intervention eg. oeso-phagogastroduodenoscopy. For more elderly patients or patients with a plethora of comorbidities a more conservative approach may be desirable. Other common causes of microcytic and normocytic anaemia include renal anaemia. This may be readily found incidentally with increased awareness of the sub classification of renal disease. Angina and intermittent claudication may signify anaemia on a background of atherosclerotic disease.

Macrocytic anaemia include the causes detailed above. A clear history may not be available and hypothyroidism can present insidiously in the elderly. This is also the case with B_{12} and folate deficiency. Myelodysplasia is more common and needs to be considered as part of the differential. Lastly drug-induced anaemia is also common and must be remembered.

History and examination

A thorough history and examination is mandatory. Concerning features elicited in the history should be remembered and elicited. Examination should both look for signs of anaemia. Examination should also pick up potential clues for aetiology and end organ complications of anaemia. This includes koilonychia, glossitis, macroglossia, lymphadenopathy and hepatosplenomegaly. A digital rectal exam should also be part of the anaemia examination. Attention should also concentrate on the cardiovascular system looking for signs of high output heart failure. Lastly, a basic thyroidal examination may reveal classic signs of cognitive impairment, slow relaxing ankle jerks and hair loss.

Investigations

Investigations can be divided between serum, invasive and specialised. Serum studies should include full haemitinics. This includes full iron studies in conjunction with B_{12} and folate measurement. Ferritin should not be used as an exclusive marker due to the fact that it is an acute phase reactant and will be elevated in acute phase reactions and pro-inflammatory states, this also holds true for other molecular markers of iron status. Other serological measurements, which may be necessary include thyroid function tests, liver function tests, serum immunoglobulins, lactate dehydrogenase, serum electropheresis and tissue trasnglutaminase. Erythrocyte sedimentation rates can be falsely elevated in anaemia.[12] Haemoglobin electropheresis is also necessary in selected patients to exclude haemoglobinopathies.

A relatively simple and inexpensive investigation is a blood film. A blood film may reveal poikilocytes and target cells. It may also reveal a mixed dimorphic picture in patients with a combination of iron and B_{12} or folate deficiency. There are several other abnormalities that may be discovered on examination of blood film, which may be indicative of the underlying aetiology.

Faecal occult blood testing is now established as part of the investigative process for occult blood loss. It has been evaluated and is now established as part of the NHS service framework for colorectal carcinoma screening.[13]

Invasive investigations include those tailored to pin pointing of the actual source of anaemia. Gastroenterologically this includes OGD and colonscopy. It may also entail mesenteric angiography and other radiographic studies including computed tomography, barium and gastrograffin studies. Relevant biopsies may be taken and are necessary for appropriate diagnoses of malignancy and coeliac disease.

More specialised investigations may include bone marrow biopsy. This should be undertaken by a haematologist and may be necessary to establish exactly what is the aetiology of the anaemia. This is especially true for haematological patients in which BM biopsy forms part of the staging process. It is also true for more complex patients eg. patients with sero positive rheumatoid arthritis using both methotrexate and non steroidal agents.[14]

Management

The management of macrocytic anaemia relies on the correct identification of the aetiology. It then depends on successful treatment of the condition. This may entail B_{12} and folate replacement. If undertaken folic acid should be started prior to B_{12} replacement due to the risk of subacute combined degeneration of the cord. There is a growing literature that high dose B_{12} may be as efficacious as the traditional route of intramuscular B_{12} replacement.[15,16]

In terms of iron deficient anaemia, an underlying aetiology should always be sought. Once a diagnosis is firmly established, iron replacement therapy can be instituted. The traditional mode of therapy is oral iron replacement. It should be remembered that oral iron is more readily absorbed with vitamin C at cellular level as a co-transporter within the duodenum. This is most applicable for patients with established inadequate nutritional intake and may have undiagnosed scurvy.

Oral iron replacement therapy is cheap and readily available, but is poorly tolerated in a significant minority of patients.[17,18] It is well recognised to cause gastrointestinal disturbance, which becomes more prevalent in an elderly population. The elderly are most susceptible to these complications and hence leads to poor concordance. The response to iron supplementation should be monitored and a failure of correction should include the review of concordance of prescribed therapy.

Intravenous iron replacement has been shown to be more efficacious in numerous patient populations. Though more costly initially, it achieves better longer term outcomes and is better at retarding the long term sequelae of anaemia. The strongest evidence base lies within those patients with renal anaemia. This has now been firmly established as the optimal method of management and is well recognised to improve the marked cardiovascular comorbidity of patients with advanced renal failure. There is emerging data that intravenous iron replacement should be considered in patients with complex comorbidities including congestive cardiac failure and oncology patients.[19,20] All three categories of patients may need intravenous iron therapy in conjunction with an erythropoietin stimulating agent (ESA).[21]

Intravenous iron replacement necessitates intravenous access and is successfully undertaken in a day unit

setting. There is a risk of anaphylaxis associated with all three available intravenous iron preparations in the UK. Both iron sucrose and iron dextran have a test dose requirement but this is not the case for the newer preparation ferric carboxymaltose.[22,23] Iron sucrose is the most widely prescribed intravenous iron in the UK but it is limited to a maximum single dose of 200 mg. A total dose infusion (<20mg/kg body weight) can be given of iron dextran but this requires a lengthy infusion of 4–6 hours. Ferric carboxymaltose can be given at high doses ie <1,000 mg a week (max dose 15mg/kg body weight/ week) over the much shorter time of 15 minutes.

Conclusion

Anaemia is a commonly encountered clinical entity. It can affect women of all ages and is not an ultimate diagnosis. An underlying aetiology should always be sought. The aetiology may become clear with basic investigations. Once the aetiology has been correctly diagnosed, definitive management should be focused on the underlying condition.

I have no conflict of interest

References

1. World Health Organization. (2008) Worldwide Prevalence of anaemia (1993–2005). Geneva; World Health Organization.
2. Hoffbrand AV, Pettit JE, Moss PAH. Essential haematology. 4th edn. Oxford: Blackwell Science 2001
3. De Maeyer EM,Adiels Tegman M. The prevalence of anaemia in the world. *World Health Stat Q* 1985; **38**: 302–16
4. British Society of Haematology Working Group. Investigation of Haemoglobinopathies; *Brit J Haem* 1998; **101**; 783–92
5. Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross sectional study of undiagnosed celiac disease in primary care. *Eur J Gastro and Hep*; 2003; **15**; 407–13
6. Unsworth DJ, Lock RJ, Harvey RF. Improving the diagnosis of celiac disease in anaemic women. *Brit J Haem* 2000; **111**; 898–901
7. Stoltzfus RJ, Dreyfuss ML. Guidelines for the use of iron supplements to prevent and treat iron deficiency anaemia. Washington: International Life Sciences Institute Press, 1997
8. Offitt K. Genetic Prognostic Markers for Colorectal Cancer. *NEJM* 2000; **342**: 124–25
9. Hoffbrand V, Provan D. ABC of clinical haematology: Macrocytic Anaemias. *BMJ* 1997; **314**: 430
10. Clark SF. Iron Deficiency Anaemia. Nutrition Clin Prac 2008; **23**: 128–41
11. Rockey DC, Cello P. Evaluation of the Gastro Intestinal Tract in Patients with Iron Deficiency Anaemia. *NEJM* 1993; **329**: 1691–95
12. Kanfer EJ, Nicol BA. Haemoglobin Concentration & erythrocyte sedimentation rate in primary care patients. *J R Soc Med* 1997; **90**;(1): 16–18
13. NHS Bowel Cancer Screening Programme. NHS; 2007
14. Doube A, Davis M, JG Smith, et al. Structured Approach to the investigation of anaemia in patients with rheumatoid arthritis. *Ann Rheum Dis*; 1992; **51**(4): 469–72
15. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998; **92**: 1191–98
16. Butler CC, Vidal-Aball J, Cannings-John R, et al. Oral B12 versus intramuscular B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. *Fam Pract* 2006; **23**; 279–85
17. Wilson JX. Regulation of Vitamin C Transport. *Ann Rev Nutr* 2005; **25**; 105–25
18. Smith DL. Anaemia in the Elderly. *AAFP* 2000; **62**: 1565–72
19. O'Meara E, Murphy C, McMurray JJ. Anaemia and heart failure. *Curr Heart Fail Rep* 2004; **1**: 176–82
20. Bolger AP, Bartlett FR, Penston HS, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure *J Am Coll Cardiol* 2006; **48**: 1225–27
21. Rizzo JD, Lichtin AE, Woolf SH, et al. Use of Epoetin in Patients With Cancer: Evidence-Based Clinical Practice Guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *Journal of Clin Oncology* 2002; **20**: 4083–107
22. Silverstein SB, Rodgers GM. Parenteral Iron Therapy. *Am J Haem* 2004; **76**; 74–78
23. Ferinject. Summary of product characteristics. http://emc.medicines.org.uk/document.aspx?documentId=20987