Management of Anemia in the Elderly

JMAJ 52(4): 219–223, 2009

Masatsugu OHTA*1

Abstract

Anemia is an important disease often found in the elderly. Iron deficiency anemia and secondary anemia are relatively frequent. Patients with iron deficiency anemia should be examined for the presence of gastrointestinal disease, including malignant disease, as a possible underlying condition. In addition, secondary anemia may result from chronic infectious disease, chronic inflammatory disease such as collagen disease, chronic renal failure, and endocrine disease. It is also important to differentiate anemia from myelodysplastic syndrome, which has been occurring at increasing frequency together with aging. This syndrome is considered to be clonal hematopoietic disorders that originate from abnormality at the hematopoietic stem cell level, and currently there is no standard treatment for this condition. There is also so-called senile anemia derived from age-related physiological degeneration of bone marrow function, renal function, and other organ functions. When anemia is found in the elderly, it is important to determine if it is explained by physiological changes or if there is an underlying disease the treatment of which can improve the anemia.

Key words Anemia in the elderly, Iron deficiency anemia, Secondary anemia, Myelodysplastic syndrome, Unexplained anemia

Introduction

Anemia is an important disease often found in the clinical practice of hematological disorders in the elderly. In terms of frequency, iron deficiency anemia and secondary anemia are high, and the presence of underlying malignant tumor is not rare (Fig. 1). In elderly patients with anemia, it is important to promptly examine the presence of underlying disease and provide proper treatment.

Definition of Anemia

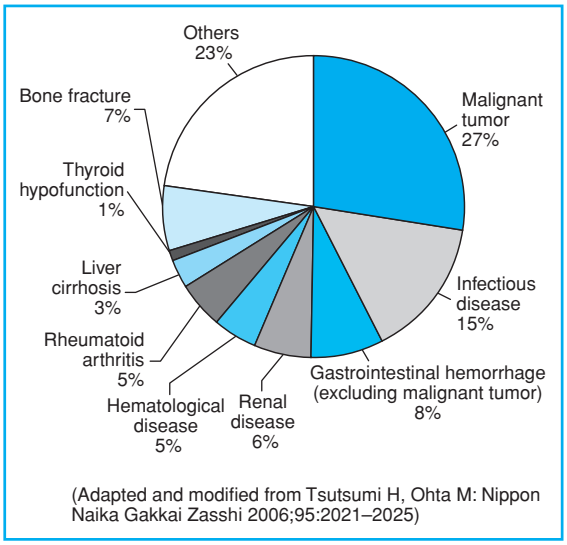
According to WHO criteria, anemia in adults is defined as a hemoglobin level of 13 g/dl or lower for men and 12 g/dl or lower for women.[1] However, in the elderly, organ function declines with age should be taken into account. In actuality, erythroid progenitor cells in the bone marrow decrease with advancing age.[2] Shirakura et al. in Japan examined peripheral blood in nursing home residents aged 60 years or older, and defined obvious anemia in the elderly as a hemoglobin level of less than 11.0 g/dl, regardless of gender. This is considered to be a practical criterion when dealing with anemia in the elderly.

Symptoms of Anemia

Patients with anemia show a variety of symptoms, including facial pallor, orthostatic hypotension, or edema resulting from decreased red blood cells, fatigability, malaise, headache, vertigo, syncope, tinnitus, or chest pain due to insufficient oxygen supply, palpitation or shortness of breath by compensatory mechanism. Since organ insufficiency of the elderly as a result of aging, even hemoglobin levels of 9–10 g/dl may result in the manifestation of severe anemic symptoms.

In addition, co-morbidities may worsen in the anemic state. For instance, in the presence of

*1 Vice-Director, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan (maohta@tmghig.jp).
This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol.137, No.6, 2008, pages1185–1188).



(Adapted and modified from Tsutsumi H, Ohta M: Nippon Naika Gakkai Zasshi 2006;95:2021–2025)

Fig. 1 Underlying diseases in elderly patients with anemia

Data are from an analysis of 1,053 inpatients aged 60 years or older who had a hemoglobin level of less than 11.0 g/dl in Tokyo Metropolitan Geriatric Hospital and Gunma University Kusatsu Hospital.

Table 1 Classification of secondary anemia

Anemia of chronic disorders (ACD)
1. Chronic infectious disease Lung abscess, pulmonary tuberculosis, pneumonia, subacute bacterial endocarditis, meningitis, chronic osteomyelitis, chronic urinary tract infection, chronic pelvic infection, chronic fungal infection, AIDS, etc. 2. Chronic inflammation Rheumatoid arthritis, adult Still's disease, systemic lupus erythematosus (SLE), mixed connective tissue disease, polymyositis, vasculitis, etc. 3. Malignant tumor Cancer, bone marrow infiltration of cancer
Anemia due to renal disease (renal anemia)
Chronic renal failure
Anemia due to hepatic disease
Chronic hepatitis, liver cirrhosis, hemochromatosis, etc.
Anemia due to endocrine disease
Hypothyroidism, adrenal gland dysfunction, hypopituitarism, hyperparathyroidism, gonadal hyperfunction, gonadal hypofunction, etc.

cardiac insufficiency, progress in anemia compensatorily induces continuing increases in cardiac output, often resulting in acute cardiac failure. Anemia may also exert an adverse effect on depressive state and decreased cognitive ability.

Considerations in Differential Diagnosis of Anemia in the Elderly

Important past histories include gastrointestinal disease, collagen disease, chronic infectious disease such as tuberculosis, endocrine disease including thyroid dysfunction, renal disease, and genitourinary disease.

Where gastrointestinal disease is concerned, attention should be paid to the presence/absence of ulcers, benign tumor, malignant tumor, hemorrhoids, hepatitis, and liver cirrhosis. Diseases relatively common in the elderly, such as hiatal hernia and diverticulosis, may cause anemia. Caution is also required in order not to miss the presence of gastritis or gastric ulcers caused by nonsteroidal anti-inflammatory drugs. A history of gastrectomy or duodenectomy is also important to be considered the possibility of iron deficiency anemia or vitamin B_{12} deficiency anemia.

Family histories of jaundice, anemia, gallstones, and splenectomy should be examined.

Taking a life history is important in elderly patients. Unbalanced diets, particularly low intake of meat and fish, are likely to result in iron deficiency. Attention to possible folic acid deficiency is necessary when food intake is extremely unstable in patients with dementia or paralysis, or alcohol consumption is high. In addition, if a caregiver is an elderly individual with dementia, attention should be paid whether an adequate nutritional management is provided to the recipient of care.

Types of Anemia in the Elderly[3]

Iron deficiency anemia

When the presence of iron deficiency is apparent, it is important to search for the cause. Since most cases are derived from chronic hemorrhage, determination of the source of bleeding should be attempted. Repeated testing of stools for occult blood is necessary. Genitourinary examination is also necessary. In elderly patients, examination of tumor markers and endoscopic study should be considered, with the possibility of gastrointestinal malignancy borne in mind. Secondary anemia and iron deficiency are frequently combined in the elderly, and the iron

Table 2 Diagnostic criteria for myelodysplastic syndrome

1. Chronic anemia is the major clinical finding, and bleeding tendency and fever are also observed.
2. Hematologic examination and bone marrow examination reveal all of the following.
   (1) Cytopenia of 1–3 blood cell series in the peripheral blood.
   (2) Dysplastic features of the blood cell morphology in the peripheral blood and bone marrow.
   (3) 30% or fewer blasts in both the peripheral blood and bone marrow.
3. There is no other disease causative of cytopenia.
   Other causative diseases include leukemia, aplastic anemia, PNH, myelofibrosis, ITP, megaloblastic anemia, bone marrow metastasis of cancer, malignant lymphoma, multiple myeloma, hypersplenism, SLE, hemophagocytic syndrome, infection, and drug-induced hematological disorder.
4. The presence of the following findings increases the certainty of diagnosis.
   (1) Normocellular or hypercellular bone marrow
   (2) Chromosomal abnormality of bone marrow cells
   (3) Cytochemical abnormality of blood cells (ringed sideroblasts, PAS-positive erythroblasts, peroxidase-negative neutrophils, decreased NAP score)
5. When making a diagnosis, myelodysplastic syndrome is suspected by agreement with items 1 and 2, other diseases are excluded by agreement with item 3, and the diagnosis is made more certain by agreement with item 4.

[Extracted from the 2002–2004 General Report of Investigative Research on Idiopathic Hematopoietic Disorder Supported by the Health Labour Sciences Research Grants (Research Project for Overcoming Intractable Diseases) issued in March 2005.]

saturation rate is often decreased to 15% or lower. In the diagnosis of iron deficiency anaemia, decreased serum ferritin is an important index. A definitive diagnosis of iron deficiency anemia can be made when the ferritin level is less than 12 ng/ml, and total iron binding capacity 360 μg/dl or higher.

The relationship between iron deficiency anemia and *Helicobacter pylori* has recently been attracting attention, after the observational finding of low serum ferritin levels in *H. pylori*-infected individuals.[4] Although it is speculated that prolonged infection with *H. pylori* causes a decrease in iron storage in the body, its mechanism is not well understood.

Secondary anemia

Secondary anemia is a collective term for anemia attributable to some underlying disease other than hematological disease (Table 1).[5] The causative conditions include infectious disease, collagen disease, renal disease, hepatic disease, endocrine disease, and malignant tumor. Anemia from chronic infectious disease, chronic inflammation, and malignant tumor is also referred to as anemia of chronic disorders (ACD) on the basis of the common pathology.

It has become apparent that hepcidin, a peptide produced mainly in the liver, is involved in the manifestation of ACD, serving as a negative regulator in the iron metabolic control mechanism of the body.[6] Hepcidin is thought to induce ACD by inhibiting the absorption of iron from the gastrointestinal tract and the release of iron from macrophages resulting decrease in iron available for erythropoiesis.[7] It has been suggested that inflammatory cytokines such as IL-6 and IL-1β, which are activated by infectious disease, chronic inflammation, etc., are involved in the production of hepcidin.

The severity of anemia of this type is usually mild to moderate. Anemic symptoms are often minimal, with the hemoglobin level around 8–11 g/dl because of the compensatory mechanism. As a principle, the underlying disease should be treated. Most cases of mild to moderate anemia observed in the elderly are secondary anemia, and therefore the presence of underlying disease should be borne in mind when examining the patient.

Megaloblastic anemia

Vitamin B_{12} deficiency often begins about 5 years after a patient has undergone gastrectomy. Since the response to vitamin B_{12} supplementation is poor in the elderly, it is not rare that more frequent administration of this vitamin is required in the elderly as compared with younger patients. Concomitant iron deficiency is often seen in the process of restoring erythropoiesis after vitamin B_{12} supplementation, requiring caution not to overlook its occurrence.

Although pernicious anemia is generally rare, the diagnosis is more frequent in the elderly in combination with other autoimmune disease. If the patient has no history of gastrectomy, anti-intrinsic factor antibody and parietal cell antibody should be examined. It is considered that atrophic gastritis underlies the manifestation of pernicious anemia. Concomitant gastric cancer is also found in about 10% of patients.

Folic acid deficiency is likely to occur in alcoholics or bedridden patients with nutritional deficit. Caution is necessary in older patients who are confined to bed at home.

Myelodysplastic syndrome (MDS) (Table 2)

Myelodysplastic syndrome is characterized by morphological dysplasia in the blood cells of each series (myelocytic, erythroblastic, megakaryocytic) and ineffective hematopoiesis, and is considered to be a clonal hematopoietic disorder derived from abnormality at the hematopoietic stem cell level.[8] In most cases, this condition occurs in elderly people in their 60s to 90s, and anemia is present in 80–90% of patients. This is an important disease that requires differential diagnosis from anemias in the elderly.

Although the classification of myelodysplastic syndrome has been changed from the FAB classification to the WHO classification,[9] international consensus is required for the assessment of morphological dysplasia. Since currently there is no established standard treatment, determination of the procedure to choose the proper treatment according to the disease type and prognostic scoring is required.[10] Improvement of bone marrow failure is expected from newly developing agents such as DNA methyltransferase or histone deacetylase inhibitors. Patients with a chromosomal abnormality in a poor-prognosis group show extremely poor response to chemotherapy when their condition has developed into acute leukemia. Therefore, in the elderly, priority is given to conservative treatments with quality-of-life considerations.

When patients with anemia do not respond to drug therapy and become transfusion-dependent, precaution is necessary as to organ damage due to iron overload.[11,12] Formerly, intravenous deferoxamine was the only iron-chelating agent available in Japan. It was not easy to use in actual clinical practice, particularly in elderly patients, because of the issues of patients' compliance and adverse reactions. However, in June 2008, an oral iron-chelating drug, deferasirox, was marketed in Japan, increasing expectations for more effective iron-removing effect.[13]

Senile anemia

When close investigation fails to determine the cause of anemia in elderly patients with prolonged mild to moderate normochromic anemia with a hemoglobin level of 9–11 g/dl, and when examination performed about every 3 months for more than a year has revealed no marked changes in the hemoglobin level, this anemic condition is called senile anemia for the sake of convenience.

This type of anemia responds poorly to erythropoietin, and slightly hypoplastic or dysplastic marrow is present. It is possible that physiologic changes due to age-related degeneration of bone marrow function, renal function, and androgen production capacity etc. serve as the cause.[14] However, there may be various hidden pathological conditions in the background, and they sometimes surface over the course of time. In some cases, it becomes apparent from follow-up observation that the condition is anemia associated with malignant tumor, MDS, or collagen disease.

Conclusion

Clinical features of anemia in the elderly have been reviewed. In elderly patients, past medical history and drug history are diverse, and it is sometimes difficult to obtain accurate information. In addition, elderly patients tend to have multi-organ dysfunction in the background, making it important to understand the pathological condition accurately. When the presence of anemia becomes apparent, it is critical to find out if it represents physiological changes or if it is a pathological condition derived from an underlying disease and can be improved by treatment of the causative disease.

References

1. Price EA, Schrier SL. Anemia in the elderly: introduction. Semin Hematol. 2008;45:207–209.
2. Shayne M, Lichtman MA. Hematology in older persons. In: Lichtman MA, Beutler E, Kipps TJ, et al. ed. Williams Hematology, 7th ed. New York: McGraw-Hill; 2006:111–121.
3. Patel KV. Epidemiology of anemia in older adults. Semin Hematol. 2008;45:210–217.
4. Cardenas VM, Mulla ZD, Ortiz M, et al. Iron deficiency and Helicobacter pylori infection in the United States. Am J Epidemiol. 2006;163:127–134.
5. Means Jr RT. Anemias secondary to chronic disease and systemic disorders. In: Greer JP, Foerster J, Rodgers GM, et al. ed. Wintrobe's Clinical Hematology 12th ed. Philadelphia: Lippincott Wiliams & Wilkins; 2009:1221–1238.
6. Nemeth E, Valore EV, Territo M, et al. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. Blood. 2003;101:2461–2463.
7. Ganz T: Anemia of chronic disease. In: Lichtman MA, Beutler E, Kipps TJ, et al. ed. Williams Hematology, 7th ed. New York: McGraw-Hill; 2006:565–570.
8. Corey SJ, Minden MD, Barber DL, et al. Myelodysplastic syndromes: the complexity of stem-cell diseases. Nat Rev Cancer. 2007;7:118–129.
9. Swerdlow SH, Campo E, Harris NL, et al. (eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC; 2008:88–107
10. Jädersten M, Hellström-Lindberg E. Myelodysplastic syndromes: biology and treatment. J Intern Med. 2009;265:307–328
11. Takatoku M, Uchiyama T, Okamoto S, et al. Retrospective survey of Japanese patients with transfusion-dependent MDS and aplastic anemia highlights the negative impact of iron overload on morbidity/mortality. Eur J Haematol. 2007;78:487–494.
12. Pietrangelo A. Iron chelation beyond transfusion iron overload. Am J Hematol. 2007;82:1142–1146.
13. Metzgeroth G, Dinter D, Schultheis B, et al. Deferasirox in MDS patient with transfusion-caused iron overload — a phase-II study. Ann Hematol. 2009;88:301–310.
14. Makipour S, Kanapuru B, Ershler WB. Unexplained anemia in the elderly. Semin Hematol. 2008;45:250–254.