The Clinical and Economic Burden of Anemia

Robert E. Smith Jr, MD

Abstract

Anemia is a prevalent condition that goes underrecognized and undertreated, yet still carries substantial costs for payers and is a burden on the health and quality of life of those diagnosed. Clinicians should recognize anemia of chronic diseases, such as cancer, chronic kidney disease, and human immunodeficiency virus infection, as a surrogate for more severe illness. Because of its prevalence and the health consequences associated with anemia, better detection and response is needed in vulnerable patient populations. Clinicians need to be more cognizant of the symptoms of anemia and more vigilant in its treatment to ensure better outcomes both clinically and financially.

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For author information and disclosures, see end of text.

Introduction

Anemia is a prevalent yet underrecognized and undertreated condition that imposes substantial costs to payers[1,2] and negative consequences on the health and quality of life (QOL) of affected individuals.[1,3-8] When anemia is associated with another disease, such as a cancer or kidney disease, it has adverse effects on the underlying disease, including worsening of symptoms,[1,4,7,9] more rapid disease progression,[7,10] and a poorer prognosis.[1,7,10-21] Anemia is usually correctable, with resulting improvement in the health of the patient. Yet, clinicians concentrating on other aspects of a disease will often fail to recognize the need to treat the anemia associated with it, if the anemia is not alleviated by treating the primary disorder. For improved patient care, clinicians need to better understand that anemia is a predictor of a worse prognosis and higher treatment costs[1,2]—independent of the cost of anemia treatment—across a diverse group of disease processes.

Definition of Anemia

Anemia is a condition in which the number of circulating red blood cells, the concentration of hemoglobin (Hb), or the percentage volume of packed red blood cells in a centrifuged blood specimen (hematocrit [Hct]) is lower than normal.[12] The World Health Organization criteria for anemia are Hb less than 12 g/dL in premenopausal women and less than 13 g/dL in men and postmenopausal women.[12,22,23] Anemia can be an isolated condition, such as that caused by a nutritional deficiency (eg, iron, folate, vitamin B_{12}),[23,24] or it may develop secondary to another disease or its treatment.[23,25-27]

Anemia of chronic disease is the term used to describe anemia occurring in the setting of another illness that resolves if the underlying illness can be successfully treated. It is thought that this type of anemia is the consequence of a cytokine storm related to immune activation associated with the underlying disease, be it an infection, an inflammatory process, or a cancer.[3,28]Acute or chronic immune activation causes inflammatory cytokine production, which reduces iron availability, impairs erythroid progenitor cell proliferation and erythropoietin production, and shortens red blood cell life span.[3,29] When the comorbidity is kidney disease, accumulation of uremic toxins can also contribute to decreased erythropoiesis in addition to the decreased erythropoietin production.[3] All of these changes result in anemia.[3,29]

Epidemiology

According to the Centers for Disease Control and Prevention (CDC), 5.5 million annual ambulatory care visits have anemia as their primary cause[30]; most often the anemia is due to a nutritional deficiency. A chronic disease is the second most prevalent cause of anemia,[3] but the estimates of the particular disease responsible varies widely (Table).

Although anemia of chronic disease is common, it is underrecognized and undertreated.[3] A claims database study examined approximately 2.3 million Medicare and commercial health plan members with solid tumors, chronic kidney disease (CKD), human immunodeficiency virus (HIV) infection, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), or congestive heart failure.[2] Anemia was diagnosed in 3.5% of the patients, and of those, only 15% received an identified treatment for it.[2]

Anemia Prevalence and Causes

Cancer

Anemia occurs in up to 77% of patients with cancer,[3] and is often overlooked, in part because many patients will not report fatigue (suggesting anemia) unless they are asked.[4] Indeed, up to 60% of anemic cancer patients may receive no treatment for anemia.[31] Anemia associated with a cancer can be due to many causes, such as blood loss, iatrogenic or otherwise, hemolysis, nutritional deficiency, marrow tumor, chemotherapy drugs, or hematophagic histiocytosis, but is most often caused by inflammatory cytokine production, which suppresses erythropoietin production and erythroid progenitor cell proliferation,[3,32] and impairs iron metabolism due to upregulation of the iron-distributing regulator hepcidin.[3,29]

Table. Underlying Causes of the Anemia of Chronic Disease[3]

Associated Diseases	Estimated Prevalence, %[a]
Infections (acute and chronic) Viral, including HIV Bacterial Parasitic Fungal	18-95
Cancer Hematologic Solid tumor	30-77
Autoimmune Rheumatoid arthritis Systemic lupus erythematosus, connective-tissue diseases Vasculitis Sarcoidosis Inflammatory bowel disease	8-71
Chronic rejection after solid-organ transplantation	8-70
Chronic kidney disease and inflammation	23-50

HIV indicates human immunodeficiency virus.
[a]Values shown are ranges. Epidemiologic data are not available for all conditions associated with the anemia of chronic disease. The prevalence and severity of anemia are correlated with the stage of the underlying condition and appear to increase with advanced age.
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Chronic Kidney Disease

Anemia is also undertreated in CKD patients,[13] especially those not undergoing dialysis. Of the approximately 20 million people in the United States with CKD, it is estimated that 2 million to 4 million have anemia.[13] A large health maintenance study found 23% of patients with CKD had an Hct value less than 30%, and of those, only 30% were being treated for anemia.[3] Other estimates of anemia prevalence in large CKD cohorts have ranged from 47% to 78%.[10,33] Anemia has been found to increase as the glomerular filtration rate (GFR) declines, with anemia prevalences of 27% at GFR >60 mL/min/1.73 m^2 and 76% at GFR <15 mL/min/1.73 m^2.[5] Even after renal transplantation, anemia was reported in 38.6% of recipients.[34] The causes of anemia in CKD include insufficient erythropoietin production, iron or other nutritional deficiency, inflammation, and shortened red blood cell survival.[13]

HIV/AIDS

Estimates of anemia prevalence in HIV-positive patients in the early 1990s reached 90%, then decreased to about 46% with the widespread adoption of highly active antiretroviral therapy (HAART).[7] Anemia still occurs at high rates when HIV therapy regimens include zidovudine (AZT).[7] The incidence of anemia increases with disease progression from HIV infection to autoimmune immunodeficiency syndrome (AIDS), with a correlation between CD4 T-lymphocyte counts and Hb levels.[7,16] The causes of anemia in HIV/AIDS may include inflammatory cytokine production and suppression of hematopoiesis, decreased erythropoietin production and nutritional deficiency states in addition to renal disease,[7] as well as the myelotoxic effects of AZT and other drugs.[7,16] The use of HAART without AZT has been found to prevent or ameliorate anemia in some patients.[7]

Cardiovascular Disease

Anemia occurs frequently in cardiovascular disease, especially congestive heart failure.[35,36] Estimates of anemia

prevalence range from less than 10% in mild heart failure to greater than 40% in advanced heart failure.[29] Anemia in congestive heart failure may be caused by excessive cytokine production, among other factors such as renal insufficiency.[36]

Hepatitis C

Anemia is common in hepatitis C infection,[26,37] occurring in up to 67% of patients.[26] In this condition, anemia is also associated with certain treatments used to combat the virus.[26,37] Hemolytic anemia is a known adverse effect of ribavirin,[26,37] and interferon may also induce anemia by a variety of mechanisms.[26]

Inflammatory Bowel Disease

Approximately one third of IBD patients have recurrent anemia,[28] making it the most common IBD complication.[37] In studies of Crohn's disease, the prevalence of anemia ranged from 10% to 73%, 9% to 74% in ulcerative colitis studies, and 17% to 41% in studies with IBD type unspecified.[38] Anemia in IBD is caused by blood loss, iron malabsorption, and inflammation,[37] and the inflammatory etiology is a classic example of the anemia of chronic disease.

Rheumatoid Arthritis

Anemia occurs in 30% to 60% of RA patients, with approximately one quarter of cases caused by iron deficiency, and three quarters attributed to chronic disease.[39] The 2 types can be distinguished by the serum ferritin level; a ferritin level greater than 50 mcg/mL suggests anemia of chronic disease, whereas a lower level suggests iron deficiency anemia.[39] In RA, iron deficiency anemia is usually caused by blood loss resulting from menstruation or gastrointestinal bleeding induced by nonsteroidal anti-inflammatory drugs.[39] The anemia of chronic disease in RA is usually caused by inflammatory cytokines, which inhibit normal red blood cell formation and erythropoietin production.[39]

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) normally causes elevated Hb levels, even to the level of secondary polycythemia, due to reduced tissue oxygenation. Nevertheless, anemia occurs at a high rate in COPD. In a Medicare claims database study of 132,424 patients with COPD, Halpern et al found that 21% had anemia.[1] Anemia in COPD may be caused by inflammation and resistance to erythropoietin due to inflammatory cytokines.[1]

Diabetes

Anemia can also occur in diabetes mellitus, especially in more advanced stages with diabetic complications.[10,29,40] In advanced diabetes, protein glycosylation leads to increased intrarenal pressure, decreased ability of the kidneys to produce erythropoietin, and anemia.[20,41] This anemia occurs much earlier in the course of diabetic CKD than in CKD patients without diabetes.[20] Diabetic neuropathy may also trigger anemia in kidney disease through renal denervation, thereby reducing signals for the kidneys to produce erythropoietin.[20,41] Thus, diabetes contributes to the development of anemia via the complications of diabetic nephropathy and neuropathy.[41] In addition, certain medications used to treat diabetes (eg, thiazolidinediones, metformin) further increase the risk of anemia.[41]

Aging and the Elderly

Anemia occurs frequently in the elderly.[36,42] In a National Institute of Aging database, 12.5% had anemia.[42] Data from the third National Health and Nutrition Examination Survey (NHANES, 1988-1994) showed that 11% of men and 10% of women aged 65 years or older had anemia and its prevalence was greater than 20% in those aged 85 years or older.[24] Causes of anemia could be divided into thirds: one third of persons had a nutritional deficiency; one third had anemia of chronic disease, CKD or both; and one third had unexplained anemia.[24] According to a CDC/National Center for Health Statistics statement entitled "Anemia or Iron Deficiency," 19% of nursing home residents in 2004 had anemia.[30] Some estimates of anemia prevalence in nursing homes (which may include anemia of chronic disease), however, are as high as 63% of residents.[23]

Surgery

Anemia is also common in the context of surgery, occurring both pre- and postoperatively.[43] The prevalence of perioperative anemia is difficult to establish because of the varied patient populations and reasons for surgery.[43] Recent evidence has shown a wide range in anemia prevalence, from 5% to 90% of surgical patients.[43] Studies comparing pre- and postoperative rates found substantial increases, from 34% to 56% for preoperative anemia to 84% to 90% for postoperative anemia.[43] Preoperative anemia, which may remain unrecognized and untreated unless the surgeon specifically screens for it, can be caused by acute or chronic blood loss, iron deficiency, renal insufficiency, malignancy, or such chronic diseases as IBD or RA.[43] Postoperative anemia can result from coagulation defects, iatrogenic phlebotomy, a

blunted erythropoietic response, infection, or other factors.[43]

Critical Care

Anemia is one of the most common medical complications in critical care.[21] Epidemiologic studies in the United States and Europe have shown that the majority of critically ill patients have anemia on admission to the intensive care unit.[44] In critical illness, anemia may be caused by ongoing blood loss in addition to inflammatory cytokines blunting erythropoietic response and inhibiting erythrocyte production.[45]

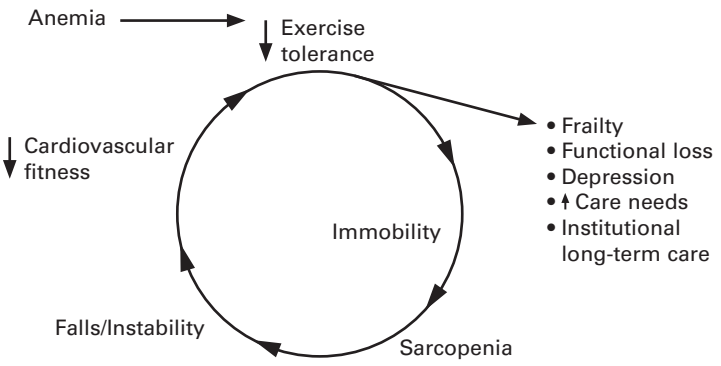
Clinical Consequences of Anemia

Anemia impairs the delivery of oxygen to tissues, necessitating compensatory increased cardiac output.[3] Tissue hypoxia resulting from anemia can impair the function of major organs.[13] Anemia is associated with poorer outcomes and increased mortality in a wide range of conditions.[1,3] In pregnancy, iron deficiency anemia increases the risk of preterm delivery and low birth weight and may reduce neonatal iron stores.[46] In surgical patients, preoperative anemia increases transfusion requirements.[43] Perioperative anemia has also been correlated with increased morbidity, mortality, and length of hospital stay.[43] Importantly, anemia can increase the risk of hypoxemia with general anesthesia[43]; therefore, it is essential for surgeons and anesthesiologists to assess the severity of any anemia before surgery. Anemia may also contribute to surgical delirium and hemorrhage.[43] If a patient has anemia during recovery from surgery, anemia-related fatigue can negatively affect health-related quality of life (HRQOL).[43]

In the elderly, who may have declining functional reserves in various organs, anemia is associated with physical decline.[22,36] A prospective study of 1146 individuals aged 77 years or older found that those with anemia had significantly greater declines in physical performance over 4 years than those without anemia (adjusted mean decline 2.3 vs 1.4; P = .003).[22] In elderly patients, anemia increases the risk of falls, weakness, muscle wasting, and immobility[36]; cardiovascular and neurologic impairments[36]; depression and dementia[36]; hospitalization and mortality[42]; and ultimate dependency on long-term care or institutionalization (Figure 1).[36]

Anemia can manifest clinically as fatigue or lethargy, depression, and impaired cognitive function,[13,31] and severe anemia can cause pallor and palpitations.[12] However, mild cases of anemia may be asymptomatic, detectable only with laboratory testing,[12] and easy to overlook, especially when serious underlying diseases receive priority.

Figure 1. Association of Anemia With Morbidity



Anemia causes reduced exercise tolerance, leading in turn to relative immobility, muscle wasting (sarcopenia), falls, and diminished cardiovascular fitness that further reduces exercise tolerance. This downward spiral produces the consequences listed on the right: frailty, dependency, depression, and the need for expensive services to support the person with these conditions.

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Anemia as a Surrogate for Severe Disease

Anemia of chronic disease can act as a surrogate for a more severe form of the comorbid disease. The symptoms of the primary disease can worsen when anemia is present,[1,4,7,9] and disease progression can accelerate.[7,10] When present in conditions such as cancer, CKD, or congestive heart failure, anemia is associated with poorer prognosis.[3] In a variety of conditions, anemia is a risk factor for increased mortality.[1] Anemia of chronic disease also contributes to poorer QOL.[4-8] Moreover, improved Hb values, which may result from treatment with erythropoiesis-stimulating agents (ESAs), have been associated with improved QOL in patients with cancer, CKD, HIV/AIDS, RA, IBD, heart failure, and diabetes, and in surgical patients.[3,4,7,12,13,20,25,27,31,36,38,42,43,47] Thus, recognition and treatment of anemia is essential for optimal patient care in a wide range of conditions.

Cancer

Anemia is associated with poor survival and may negatively affect survival in patients with cancer.[32] A systematic review of 60 studies found the relative risk of death in patients with cancer increased by 65% in the presence of anemia.[11] Anemia

exacerbates fatigue in patients with cancer,[32] and studies have shown a clear association between lower Hb concentrations and greater fatigue.[4] In a standardized survey of anemic cancer patients compared with nonanemic cancer patients, and persons without cancer in the general population, the anemic cancer patients had significantly worse fatigue scores than the nonanemic cancer patients, and both groups also had worse scores compared with the general population (P <.001).[9] Anemia-related fatigue can lead to reduced ability to work and activities of daily living and social isolation in cancer patients.[31] Many studies also have shown relationships among chemotherapy-induced anemia, fatigue, and QOL.[4]

Chronic Kidney Disease

In patients with CKD, anemia has been associated with lower HRQOL scores, which continue to decline over time.[6] Anemia in kidney disease is also associated with cognitive impairment,[5,13] sleep disturbance,[5] and CKD progression.[10] Anemia is a pathogenetic factor for cardiovascular disease in CKD patients, increasing the risk of cardiovascular morbidity and mortality.[10,12] In CKD, anemia contributes to reduced exercise tolerance,[5] left ventricular hypertrophy, angina, and worsening congestive heart failure.[13,15]

After renal transplantation, anemia is associated with poorer graft function[14,34] and significantly predicts graft failure.[14] In one study of transplant recipients with a serum creatinine greater than 2 mg/dL (indicating poor graft function), 63% had anemia compared with 32% of those with a serum creatinine less than or equal to 2 mg/dL (P <.01).[34]

Finally, as CKD progresses, anemia contributes to mortality.[12,14,15] In a study of dialysis patients, each 1-g/dL decrease in mean Hb was independently associated with increased mortality.[15] In another study, anemia significantly predicted mortality in renal transplant recipients.[14]

HIV/AIDS

Anemia is associated with more rapid disease progression from HIV to AIDS and decreased survival at all CD4 T-lymphocyte counts.[7,16,48] The risk of death is up to 70% greater in anemic patients with AIDS compared with their nonanemic counterparts.[7] With anemia in HIV, the need for transfusions is greater and QOL poorer, largely due to fatigue.[7]

Cardiovascular Disease

Anemia is an independent risk factor for death after myocardial infarction (MI).[12,17] In a random sample of patients hospitalized with acute MI, those with an Hct value between 30% and 35% had a 1-year mortality of 31%, and those with an Hct value less than 30% had a 1-year mortality of 42%.[17] Anemia complicates coronary artery bypass surgery, increasing the risk of postoperative adverse events.[18] Anemia also complicates heart failure. A meta-analysis of chronic heart failure studies (n = 153,180) found anemia increased mortality risk.[19] A recent study demonstrated that patients with heart failure and anemia had unadjusted survival at 3 years of 50% versus 74% in nonanemic patients (P = .0003).[35] Anemia was also a powerful predictor of rehospitalization in heart failure.[29] Finally, in heart failure registry outpatients, reduced Hb levels were associated with poorer QOL.[8]

Inflammatory Bowel Disease

For patients with IBD, chronic fatigue may be as great a concern as abdominal pain or diarrhea.[28] As with other conditions in which anemia of chronic disease occurs, anemia may contribute substantially to fatigue.

Chronic Obstructive Pulmonary Disease

In COPD, anemia was associated with several indicators of worse disease. Patients with COPD and anemia have poorer 6-minute walking distance and dyspnea scores and increased hospitalization and mortality rates.[1] In the Medicare study by Halpern et al, the mortality rate was 262 deaths per 1000 person-years in those with anemia versus 133 deaths in those without anemia (P <.001).[1]

Diabetes

As noted earlier, the presence of diabetes increases the risk of anemia. Anemia in diabetes also increases the risks of other morbidity and mortality. Anemia doubles the risk of diabetic retinopathy.[20] In patients with diabetes, anemia also contributes to cardiovascular disease,[20] which is the leading cause of death in diabetes.[20,49]

Neurologic Disorders

Secondary cerebral injury from hypoxia increases the importance of addressing anemia in the critical care of neurologic conditions.[21] Anemia is consistently associated with worse clinical outcomes in this setting.[21]

Economic Costs of Anemia

It is difficult to isolate and quantify the economic costs of anemia because of the varied settings in which it occurs. Analyses of the cost of treatment of anemia associated with other disorders must consider drug acquisition expenses, drug

administration costs, hospital charges, inpatient physician fees, transfusion costs, laboratory testing costs, and indirect costs.[13] The influence of anemia on the cost of treating the associated disease and on disease progression must also be considered. In general, anemia increases the costs of care for patients with associated conditions. Government databases and research studies have provided data for specific situations.

Large claims analyses have demonstrated increased healthcare utilization and expenditures when anemia coexists with several major disorders.[1] For example, a 2005 study of approximately 2.3 million health plan members found that patients with a systemic disorder condition (CKD, solid-tumor cancers, HIV, RA, IBD, or congestive heart failure) who were also anemic had twice the average annualized costs of nonanemic patients with the same condition.[2] Here again, anemia was a surrogate for more severe disease with consequent higher costs.

Cancer

In a systematic review of 24 studies in patients with cancer and chemotherapy-related anemia, costs attributable to anemia were estimated at $22,775 to $93,454 per year (2006 dollars).[50]

Chronic Kidney Disease

A study in predialysis patients with CKD found that those with untreated anemia had an unadjusted incremental monthly cost increase of $1089 compared with those who did not have anemia (cost ratio 1.8:1; P <.0001).[51] In a 6-month follow-up study in 28,985 patients with end-stage renal disease (ESRD) initiating dialysis, each month that the Hb level was less than 11 g/dL was associated with an incremental increase in medical costs of 8.9%.[52] Of course, treatment of anemia alone entails costs. In 2007, costs for intravenous iron supplementation in ESRD were $255 million; costs for treatment with ESAs were $1.8 billion.[53]

Cardiovascular Disease

A study in patients with symptomatic heart failure found that those with anemia had adjusted total costs of $22,926 per year versus $17,189 in patients without anemia (P = .04).[35] In patients undergoing percutaneous coronary interventions, preexisting anemia was the third most powerful predictor of hospital costs.[54] An additional $250 in hospital costs was associated with each Hct point below normal range.[54]

Chronic Obstructive Pulmonary Disease

In the study by Halpern et al, unadjusted analysis found more than twice the average annual Medicare payments for patients with COPD and anemia compared with those without anemia (P <.001).[1] After adjustment for markers of disease severity and preceding healthcare utilization, anemia was independently associated with $3582 per patient in annual payments.[1] **Figure 2** illustrates the impact of anemia on Medicare reimbursements for specific healthcare costs.[1]

Aging and Falls

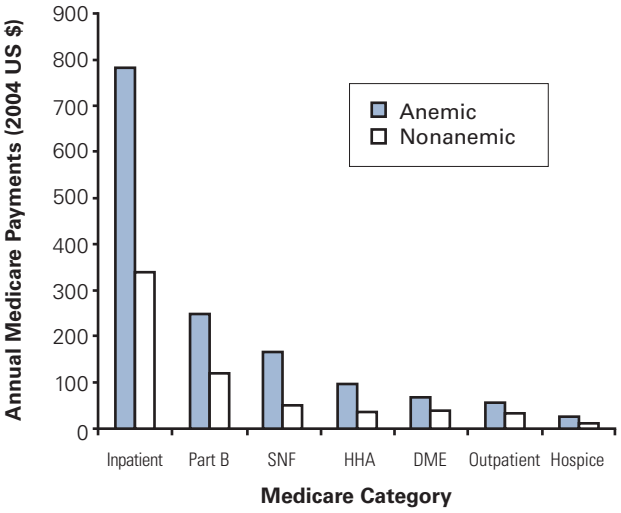
Anemia can contribute to the total cost of falls in the elderly. A retrospective analysis of claims for injurious falls from more than 30 health plans (mean patient age, 76 years) found that anemia increased costs by $1855 per patient per month, and $2811 for hip-specific falls.[55]

Indirect Costs

Fatigue and other limitations related to anemia have untold effects on indirect costs for employed individuals and, in the case of disabled patients, their caregivers.[13,36] Indirect costs may include disability payments, lost workdays, reduced productivity at work, and travel expenses for healthcare appointments.[36]

Subsequent articles in this supplement will provide greater detail on the evolving understanding about the ben-

Figure 2. Impact of Anemia on Annual Medicare Payments for Patients With Chronic Obstructive Pulmonary Disease by Category



DME indicates durable medical equipment; HHA, home health assistance; SNF, skilled nursing facility.
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efits and risks of anemia therapies, governmental regulations and professional association recommendations regarding the use of ESAs in the correction of anemia, and the role of managed care in optimizing healthcare for individuals with anemia and comorbid disorders.

Conclusions

The prevalence and consequences of anemia require better detection and response in vulnerable patient populations. Anemia has enormous impact on health, QOL, medical costs, and productivity. Clinicians should recognize anemia of chronic disease as a surrogate for more severe illness in cancer, CKD, HIV, cardiovascular disease, IBD, RA, hepatitis C, diabetes, and COPD. Untreated comorbid anemia can accelerate disease progression, lead to poorer outcomes, and substantially increase costs. Therefore, clinicians should be more vigilant of anemia and the symptoms of anemia in the setting of a systemic disease.

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Authorship Information: Concept and design; analysis and interpretation of data; and critical revision of the manuscript for important intellectual content.

Address correspondence to: Robert E. Smith Jr, MD, South Carolina Oncology Associates, 166 Stoneridge Dr, Columbia, SC 29210. E-mail: rsmith@sconcology.net.

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