Anemia in patients with Takayasu arteritis: prevalence, clinical features, and treatment

Ying ZHANG, Di ZHANG, Yi QU, Peng FAN, Ya-Xin LIU, Hui-Min ZHANG, Lei SONG, Wen-Jun MA, Hai-Ying WU, Jun CAI, Fang LUO#, Xian-Liang ZHOU#, De-Yu ZHENG, Li-Sheng LIU

Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Abstract

Background Anemia is a common comorbidity of patients with Takayasu arteritis (TA). This study evaluated the prevalence, clinical characteristics, and treatment in Chinese TA patients with anemia. Methods This retrospective study included 533 consecutive patients hospitalized for TA from January 2009 to April 2018. Anemia was diagnosed on the basis of hemoglobin level, according to World Health Organization criteria. Results A total of 194 patients (36.4%) were diagnosed with anemia. Most had mild anemia (177, 91.2%). Female patients were predominant (92.8% of anemic patients). Normocytic anemia (62.9%) was the most common pattern. Anemic patients were more likely than non-anemic patients to have dizziness (29.4% vs. 21.2%), low body mass index (22.0 ± 3.6 vs. 22.9 ± 3.4 kg/m²), and active disease stage (64.9% vs. 50.1%); pulmonary involvement (12.4% vs. 26.8%), pulmonary hypertension (12.9% vs. 20.1%) and pulmonary hypertensive-target drugs (2.8% vs. 11.6%) were less common among anemic than non-anemic patients (all P < 0.05). Larger left ventricular end-diastolic diameter and lower left ventricular ejection fraction were observed in anemic patients. Over a median follow-up of four months, the increase of hemoglobin in anemic patients was associated with the use of iron supplementation. Conclusions Anemia is a very common concurrent condition in TA, especially in young, female patients. Patients with anemia are more likely to be in the active disease stage. Iron supplementation helps increase hemoglobin.

Keywords: Anemia; Disease activity; Oral iron supplementation; Takayasu arteritis

1 Introduction

Takayasu arteritis (TA) is a type of large-vessel vasculitis that generally affects the aorta and its main branches. Pulmonary artery can also be involved. The active stage of TA arises most commonly in young females of reproductive age.

Anemia is a common condition with a wide variety of causes, including long-term infection, malnutrition, solid or hematological malignancies, and connective tissue disorders. Anemia has a higher prevalence among preschool children, young females, and elderly individuals than among others.

According to the 2004 statistics of the Ministry of Health of the People’s Republic of China, the overall prevalence of anemia in the Chinese population was 15.2%. Because anemia is common in the general population, anemia is often recognized as a comorbidity rather than a complication in TA patients. There is limited information from a large population on the influence of anemia on TA, although several studies have reported anemic TA patients with severe inflammation and poor general condition.[1-2] Studies in other populations have showed that anemia is linked to adverse outcomes. Anemia is associated with the mortality in patients with left ventricular dysfunction.[3] Anemia is a risk factor for cardiovascular disease outcomes in a community cohort aged from 45 to 64 years.[4] In TA, anemia is also linked with a history of cardiovascular diseases.[5] In rheumatoid arthritis (RA), anemia is linked with active disease stage, and control of inflammation improves anemia.[6]

In this retrospective study, we investigated the prevalence, clinical characteristics, and treatment of anemia in a large population of TA patients in China.
2 Methods

This study protocol was approved by the Institutional Ethics Committee of Fuwai Hospital. Because of the retrospective design of this study, written informed consent was waived.

We retrospectively reviewed the medical records of 533 TA patients admitted to our hospital from January 2009 to April 2018. All patients fulfilled the criteria for TA established by the American College of Rheumatology.[7] Angiographic classification was made according to the Hata and Numano criteria.[8] Disease activity was determined according to the criteria of the National Institutes of Health.[9] Patients with a history of thalassemia or gastrointestinal tract bleeding were excluded.

Clinical characteristics, including demographic information (sex, age at first hospitalization), clinical course (symptoms, signs, age at symptom onset, disease duration), comorbid diseases (hypertension, dyslipidemia, diabetes mellitus, stroke, renal dysfunction), and medical therapy (prednisone, aspirin, statins, anti-hypertension drugs, iron supplementation), were extracted from the electronic medical records.

Prednisone is the fundamental anti-inflammatory drug in our expertise. The initial dose of prednisone is related to body weight; 0.5–1.0 mg/kg daily was used.

The following laboratory parameters were measured with the same type of machines using fasting venous blood samples: white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean cell hemoglobin (MCH), MCH concentration (MCHC), standard deviation in red blood cell distribution width (RDW-SD), platelet, mean platelet volume (MPV), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, and N-terminal brain natriuretic propeptide (NT-proBNP).

Anemia was diagnosed on the basis of hemoglobin level (< 130 g/L in men and < 120 g/L in non-pregnant women), according to World Health Organization cutoff points.[10] Mild anemia was defined for both sexes as hemoglobin ≥ 90 g/L and below the cutoff, moderate anemia as hemoglobin ≥ 60 and < 90 g/L, and severe anemia as hemoglobin < 60 g/L. CRP was considered elevated at levels > 8 mg/L. Elevated ESR was defined as > 20 mm/h in females and > 15 mm/h in males. Fecal occult blood test was referred to determine gastrointestinal bleed. In the follow-up period, the first recheck of blood indices after discharge was recorded.

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography. Pulmonary hypertension was defined if the pulmonary artery systolic pressure was above 35 mmHg.[11] Fifty-eight patients underwent [18F]-fluorodeoxyglucose positron emission tomography/computed tomography (18F-PET/CT). Patients were defined as PET-active if the maximum standardized uptake value (SUV) of region of interest is higher than average liver uptake.

Statistical analysis was performed with SPSS 19.0. Continuous variables were presented as mean ± SD or median (Q1-Q3) and were compared with independent t-test or the Mann–Whitney U test. Categorical variables were presented as number (percentage) and were compared with the chi-square test or Fisher’s exact test. Multivariable linear regression model was used to assess the association between change of hemoglobin and the use of iron supplementation at discharge. Age and sex were forced in the model. Other factors (iron supplements, prednisone, elevated ESR) with a P value < 0.2 in univariate analysis were entered into the model. A two-sided P value < 0.05 was considered statistically significant.

3 Results

3.1 General clinical features

The clinical features of patients with and without anemia are listed in Table 1. A total of 194 patients (36.4%) were classified as anemic. Female patients were predominant (92.8%) in the anemic group. The anemic patients had a short duration from symptom onset to assessment. Anemic patients had a lower BMI (22.0 ± 3.6 kg/m²) than non-anemic patients. Dizziness, which was the most common chief complaint (29.4% of patients), was experienced more commonly among patients with anemia (P = 0.035). Blood pressure discrepancy between arms (71.6%) were more prevalent among patients with anemia. Type V arteritis was most common (40.8% of patients), followed by type I (30.9%). Pulmonary artery involvement was less prevalent among anemic than non-anemic patients. A higher percentage of anemic patients (64.9%) than non-anemic patients (50.1%) were in the active stage according to the criteria of the National Institutes of Health (P = 0.001). Patients with anemia were more likely to have an active result of 18F-PET/CT (80.0% vs. 52.6%, P = 0.041).

3.2 Anemia pattern and severity

A total of 177 (91.2%) had mild anemia and 17 (8.8%) had moderate anemia. None of the patients presented with severe anemia. Normocytic anemia was most common (122 patients, 62.9% of anemic patients), followed by hypochromic,
Table 1. Demographic information and clinical features of the patients with Takayasu arteritis.

| Anemia, | Non-anemia, | P value |
|---------|-------------|---------|
| n = 194 | n = 339     |         |
| Female  |             |         |
| 180 (92.8%) | 266 (78.5%) | < 0.001* |
| Age at enrollment, yrs | 35.9 ± 13.7 | 37.7 ± 13.0 | 0.139 |
| Under 30 yrs | 78 (40.2%) | 101 (29.8%) | 0.014* |
| Age at symptom onset, yrs | 26.3 ± 10.4 | 27.2 ± 10.2 | 0.377 |
| Duration of clinical course, median (Q1-Q3), months | 54.8 | 79.4 | 0.030* |
| Body mass index, kg/m² | 22.0 ± 3.6 | 22.9 ± 3.4 | 0.021* |
| BMI < 18.5 kg/m² | 26 (13.4%) | 33 (9.7%) | 0.194 |
| Daily prednisone dose, mg | 25.5 ± 8.4 | 23.5 ± 8.2 | 0.026* |

Table 2. Laboratory findings in TA patients according to presence of anemia.

| Variables      | Anemia      | Non-anemia  | P value |
|----------------|-------------|-------------|---------|
| BUN, mmol/L   | 5.01 (4.11−6.41) | 4.97 (3.97−6.10) | 0.918 |
| Creatinine, mg/dL | 61.0 (52.4−71.4) | 64.6 (54.0−75.0) | < 0.001* |
| WBC, 10⁹/L | 7.12 (5.89−8.52) | 7.08 (5.89−8.71) | 0.665 |
| Platelet, 10⁹/L | 41.1 (33.4−44.4) | 46.4 (34.3−50.4) | < 0.001* |
| Hemoglobin, g/L | 111 (102−117) | 136 (127−147) | < 0.001* |
| NT-proBNP, pg/mL | 576.4 (287.4−1187.2) | 490.6 (91.4−819.7) | 0.001* |

Values are median (Q1−Q3); *P < 0.05. BUN: blood urea nitrogen; CREA: creatinine; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HCT: hematocrit; MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; MPV: mean platelet volume; NT-proBNP: N-terminal brain natriuretic propeptide; RBC: red blood cell count; RDW-CV: coefficient variation of red blood cell distribution width; RDW-SD: standard deviation in red blood cell distribution width; WBC: white blood cell count; TA: Takayasu arteritis.

microcytic anemia (51 patients, 26.3%) and normochromic, microcytic anemia (19 patients, 9.8%). Megaloblastic anemia was seen in only two patients (1.0%). Among patients with moderate anemia, 82.6% had hypochromic, microcytic anemia and 17.6% had normocytic anemia.

3.3 Laboratory findings

The level of ESR and BNP was higher in anemic patients than in non-anemic patients. Variables related to erythrocyte measurements, including decreased RBC, Hemoglobin, hematocrit, MCV, MCH, MCHC and increased RDW-SD and MPV were observed in anemic patients (Table 2).

3.4 Echocardiography findings

Anemic patients had larger left ventricular end-diastolic diameter (48.3 ± 6.9 vs. 46.5 ± 8.1 mm, P < 0.05) and lower left ventricular ejection fraction (61.6% ± 10.5% vs. 64.2% ± 8.5%) than non-anemic patients. The ratio of mitral regurgitation was higher (25.3% vs. 13.0%). The frequency of pulmonary hypertension was lower (12.9% vs. 20.1%; Table 3).

3.5 Treatment and short-term follow-up

Compared with anemic patients, the use of pulmonary
Factors that reached a $P$ value < 0.2 in univariate analysis were included in the multiple regression model. Age and sex were forced in the model. CI: confidence interval; SE: standard error of the regression coefficient.

| Increase of hemoglobin | B     | 95% CI          | SE  | Beta | $P$ value | $t$  |
|-----------------------|-------|-----------------|-----|------|-----------|-----|
| Iron supplements      | 7.779 | (2.07, 13.487)  | 2.87| 0.273| 0.008     | 2.71|
| Prednisone            | 0.451 | (-7.889, 8.792) | 4.194| 0.012| 0.915     | 0.108|
| Female                | 2.566 | (-7.215, 12.347)| 4.919| 0.053| 0.603     | 0.522|
| Elevated ESR         | -5.944| (-12.682, 0.795)| 3.389| -0.178| 0.083     | -1.754|
| Age                   | -0.197| (-0.401, 0.007) | 0.103| -0.211| 0.059     | -1.916|

Factors that reached a $P$ value < 0.2 in univariate analysis were included in the multiple regression model. Age and sex were forced in the model. CI: confidence interval; SE: standard error of the regression coefficient.
active disease in TA patients because MPV was negatively associated with CRP and ESR; the level of MPV increased after anti-inflammation therapy. We also observed increased RDW and decreased MPV in anemic patients. We speculated IDA existed in our population due to the followings. A total of 26.3% of the anemic TA patients had hypochromic, microcytic anemia, which was a main type of IDA. Women at reproductive age are at risk of IDA in general population, and young women took up a high part in anemic patients. A study showed that patients with iron deficiency had lower classical hematologic indices including MCV, hemoglobin and MCH. In our practice, patients with lower level of hemoglobin and MCV were more likely to initiate iron supplementation. The initiation of iron supplementation at discharge was associated with increased hemoglobin. Our anemic patients had elevated RDW, which is a marker of iron deficiency.

Anemia may have adverse effects on heart function. Hemodynamic compensation for anemia (increased output and increased heart rate) and non-hemodynamic compensation (increased erythropoietin and increased oxygen extraction, activated sympathetic and renin-angiotensin-aldosterone systems) may result in cardiac enlargement, left ventricle hypertrophy and mitral regurgitation. Decreased ejection fraction or higher level of BNP was more frequent in anemic patients than in non-anemic patients. These changes may be related to the high ratio of cardiovascular diseases in anemic people. The present study showed that anemia was associated with less pulmonary artery involvement, less ratio of pulmonary hypertension and less use of pulmonary hypertensive-target drugs. This may be a compensation for hypoxia in TA patients with pulmonary artery disorders. Hypoxia may increase the level of erythropoietin, which promotes the proliferation and differentiation of erythroid precursors, causing an elevation of red blood cell mass. As we diagnosed anemia due to the WHO criteria, patients with pulmonary disorder were more likely to be in the non-anemic stage. However, studies have reported that patients with pulmonary hypertension have iron deficiency without anemia due to elevated hepcidin, iron deficiency without anemia may cause dyspnea and decreased activity endurance. In addition, chronic anemia, especially genetic anemia, can result in pulmonary hypertension by the effect of intravascular hemolysis, pulmonary thromboembolism and response to hypoxia caused by anemia. However, the clinical feature of our anemic TA patients is different from that of the patients with genetic anemia. Most of our anemic TA patients had mild anemia, and the anemia could be corrected after proper anti-inflammation therapy and iron supplementation. We considered that anemia did not raise pulmonary hypertension in TA patients.

ESR is influenced by anemia. In the present study, the level of ESR was higher in anemic patients than in non-anemic patients, but the level of CRP was similar. Anemic patients were more likely to be in the active disease according to the criteria of the National Institutes of Health and the results of 18F-PET/CT. Active disease stage and anemia could both contribute to raised ESR. Physicians should interpret the clinical value of raised ESR carefully for individual TA patients.

Several limitations should be addressed. First, we did not assess the data related to indices of iron, folate and vitamin B12, which were not routinely checked in our patients, so the proportion of IDA in TA could not be determined. Second, we assessed the blood indices, ESR and CRP at only two time points, the effect of dynamic changes of these parameters were unknown. Third, only 110 anemic patients came back to our center for a recheck of blood indices. There might be bias, although the blood indices during hospitalization of anemic patients with and without a follow-up did not have significant differences (data not shown). With the large sample size of TA patients, this study offers an overview of anemia in TA patients.

In conclusion, anemia was common among TA patients and was more common in young, female patients. Anemic patients were more likely to be in the active disease stage. Anemia affects cardiac function. Oral iron supplementation helped increase hemoglobin.

Acknowledgment

This study was funded by the National Key Research and Development Program of China (2016YFC1300100) and CAMS Innovation Fund for Medical Sciences (2016-I2M-1-002). The authors have no conflicts of interest to declare.

References

1. Kato H, Onishi Y, Nakajima S, et al. Significant improvement of Takayasu arteritis after cord blood transplantation in a patient with myelodysplastic syndrome. Bone Marrow Transplant 2014; 49: 458–459.
2. Gaballah M, Goldfischer R, Amo dio JB. The utility of MRI in the diagnosis of Takayasu arteritis. Case Rep Pediatr 2017; 2017: 7976165.
3. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001; 38: 955–962.
4. Sarnak MJ, Tighiouart H, Manjunath G, et al. Anemia as a
risk factor for cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. J Am Coll Cardiol 2002; 40: 27–33.

5 Liu Q, Dang A, Lv N, et al. Anaemia and low body mass index are associated with increased cardiovascular disease in patients with Takayasu arteritis. Clin Exp Rheumatol 2016; 34: S16–S20.

6 Pereira ICP, Sousa NCF, Pereira DMS, et al. Treatment with either leflunomide or adalimumab reduces anaemia in patients with rheumatoid arthritis. An Acad Bras Cienc 2018; 90: 2161–2166.

7 Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990; 33: 1129–1134.

8 Hata A, Noda M, Moriwaki R, et al. Angiographic findings of Takayasu arteritis: new classification. Int J Cardiol 1996; 54 Suppl: S155–S163.

9 Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. Ann Intern Med 1994; 120: 919–929.

10 Nutritional anaemias. Report of a WHO scientific group. World Health Organization Technical Report Series 1968; 405: 5–37.

11 Chen Z, Li J, Yang Y, et al. The renal artery is involved in Chinese Takayasu's arteritis patients. Kidney Int 2018; 93: 245–251.

12 Clemente G, Hilario MO, Lederman H, et al. Takayasu arteritis in a Brazilian multicenter study: children with a longer diagnosis delay than adolescents. Clin Exp Rheumatol 2014; 32: S128–S133.

13 Liu Q, Dang AM, Chen BW, et al. The association of red blood cell distribution width with anemia and inflammation in patients with Takayasu arteritis. Clin Chim Acta 2015; 438: 205–209.

14 Peeters HR, Jongen-Lavrencic M, Raja AN, et al. Course and characteristics of anaemia in patients with rheumatoid arthritis of recent onset. Ann Rheum Dis 1996; 55: 162–168.

15 Peng YF, Guo J, Deng YB. The role of mean platelet volume in patients with Takayasu arteritis. Ann Clin Biochem 2017; 54: 273–278.

16 Nguyen PH, Gonzalez-Casanova I, Nguyen H, et al. Multicausal etiology of anemia among women of reproductive age in Vietnam. Eur J Clin Nutr 2015; 69: 107–113.

17 Theurl I, Aigner E, Theurl M, et al. Regulation of iron homeostasis in anemia of chronic disease and iron deficiency anemia: diagnostic and therapeutic implications. Blood 2009; 113: 5277–5286.

18 Akkermans MD, Uijterschout L, Vloemans J, et al. Red blood cell distribution width and the platelet count in iron-deficient children aged 0.5-3 years. Pediatr Hematol Oncol 2015; 32: 624–632.

19 Metivier F, Marchais SJ, Guerin AP, et al. Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant 2000; 15 Suppl 3: S14–S18.

20 Pereira AA, Sarnak MJ. Anemia as a risk factor for cardiovascular disease. Kidney Int Suppl 2003: S32–S39.

21 Go AS, Yang J, Ackerson LM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation 2006; 113: 2713–2723.

22 Ebert BL, Bunn HF. Regulation of the erythropoietin gene. Blood 1999; 94: 1864–1877.

23 Rhodes CJ, Howard LS, Busbridge M, et al. Iron deficiency and raised hepcidin in idiopathic pulmonary arterial hypertension: clinical prevalence, outcomes, and mechanistic insights. J Am Coll Cardiol 2011; 58: 300–309.

24 Verdon F, Burnand B, Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ 2003; 326: 1124.

25 Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. Blood 2016; 127: 820–828.