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【 CASE REPORT 】

Simultaneous Presentation of Giant Cell Arteritis and Myelodysplastic Syndrome in an Elderly Japanese Man

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Abstract:
An 81-year-old Japanese man presented with constitutional symptoms and anemia and was diagnosed with giant cell arteritis (GCA) and myelodysplastic syndrome (MDS) simultaneously. His symptoms and anemia improved promptly with steroids; however, the MDS rapidly progressed to overt leukemia. While MDS patients are at an increased risk of autoimmune diseases, an association with GCA has rarely been reported. This case illustrates the importance of considering GCA as a cause of anemia in elderly patients if MDS is already diagnosed, even in countries where the prevalence of GCA is very low. The simultaneous development of GCA and MDS suggests a common pathogenetic link between these two diseases.

Key words: giant cell arteritis, myelodysplastic syndrome, elderly, anemia

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Introduction

Anemia is a common medical problem in elderly patients, with the prevalence increasing with age (1). The causes of anemia in elderly patients are wide-ranged and often multifactorial, although chronic diseases are the most common causes. A number of chronic diseases that may lead to anemia of chronic disorder (ACD) are more prevalent in older populations than in younger ones and should always be considered in the differential diagnosis of anemia of elderly patients.

Giant cell arteritis (GCA) is a chronic autoimmune vasculitis that affects large- and middle-sized arteries of older adults (2, 3). In the absence of typical clinical manifestations, such as headache, of which two-thirds of patients complain, and scalp or temporal artery pain, observed in 40-70% of cases, the diagnosis is often difficult, especially in regions like Asia, where the prevalence of GCA is very low (2-4). Many patients with GCA have various constitutional symptoms, and most patients have moderate normocytic ACD (3).

Myelodysplastic syndrome (MDS) is a clonal stem cell disorder that leads to cytopenias of various degrees (5). MDS generally affects older people, with a median age at the diagnosis of 65-70 years, and is an important hematological disorder that causes anemia in elderly patients. In addition to hematological abnormalities, patients with MDS are known to have a wide spectrum of immune abnormalities (6, 7) and to be frequently complicated with various autoimmune conditions, and a pathogenetic link between MDS and autoimmune diseases has been postulated (8-12).

We herein report a case of MDS with single lineage dysplasia (MDS-SLD) that simultaneously developed ACD due to GCA (13), illustrating a possible pathogenetic link between the MDS and GCA and the importance of a thorough investigation of the etiology of anemia in elderly patients.

Case Report

An 81-year-old Japanese man who had been treated for unstable angina by his family doctor started to have appetite loss and general malaise in October 2015, and a blood test taken 1 month later revealed anemia, with a hemoglobin (Hb) concentration of 8.0 g/dL (previously 12.2 g/dL at 3 months earlier). He had no fever, body weight loss, head-

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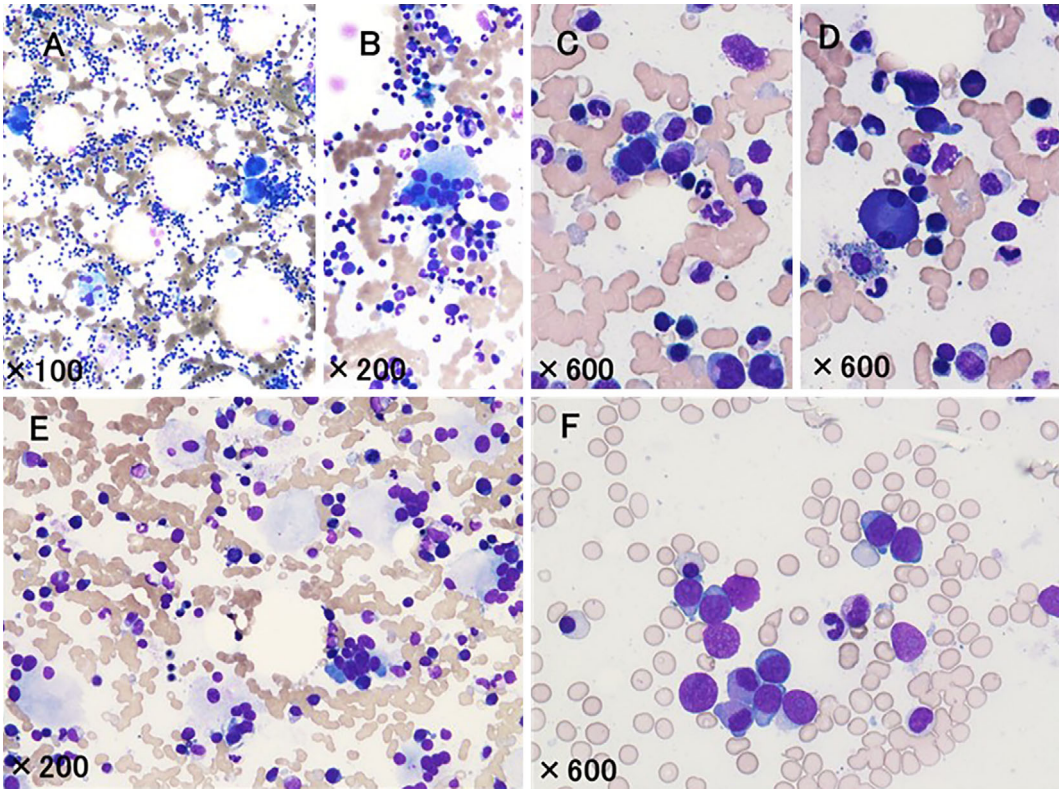

Figure 1. **Bone marrow findings at the diagnosis of myelodysplastic syndrome and at the time of transformation to overt acute leukemia. (A-D) The bone marrow smear at presentation shows slightly hyperplastic marrow with an increased number of megakaryocytes (A) with marked dysplastic changes, such as separated nuclei (B) and small, hypolobulated (C), and separated, binuclear (D) megakaryocytes (Wright-Giemsa stain). Dysplastic changes in the erythroid and myeloid cells are not apparent, and there is no increase in the number of blasts. (E and F) The bone marrow at the time of leukemic transformation shows a marked increase in the numbers of dysplastic megakaryocytes (E) and blasts (F) (Wright-Giemsa stain).**

ache, muscle pain, jaw claudication, or visual changes. An endoscopic examination of the upper and lower gastrointestinal tract was essentially normal. He was referred to our hospital for the evaluation and treatment of the anemia. He had received coronary stenting 10 years earlier and was taking isosorbide, valsartan, nicorandil, ticlopidine, low-dose aspirin, pravastatin, and allopurinol. He had quit smoking 17 years earlier.

On referral, the findings of a physical examination were unremarkable, and there was no thickening of the superficial temporal arteries, scalp tenderness, or muscle tenderness. A complete blood count showed the red blood cell count to be 3.06×10^{12}/L with 2.31% reticulocytes, the Hb 7.9 g/dL, the hematocrit 25.6%, the white blood cell (WBC) count 5.6×10^{9}/L with 0.5% blasts, and the platelet count 138×10^{9}/L. Other laboratory tests were as follows: serum albumin level, 2.7 g/dL; lactate dehydrogenase, 158 U/L (reference range: 118-223); serum iron, 19 μg/dL (reference range: 54-200); serum ferritin, 869 ng/mL (reference range: 49.4-430); and C-reactive protein (CRP), 8.38 mg/dL. Anti-nuclear, anti-CCP, anti-DNA, ant-SS-A/Ro, and anti-SS-B/La antibodies, proteinase-anti-neutrophil cytoplasmic antibody (PR3-ANCA), and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) were all negative. Computed tomography of the neck, chest, and abdomen with and without contrast enhancement did not detect any abnormal findings, including those of large vessels.

The bone marrow (BM) was slightly hyperplastic with an increased number of megakaryocytes showing marked dysplastic changes (Fig. 1A-D). Dysplasia of erythroid and myeloid cells was not apparent, and myeloblasts accounted for 1.6% of all nucleated cells. Based on these findings, the patient was diagnosed with MDS-SLD. The karyotype of the BM cells was 46,XY [20].

Although he only had mild constitutional symptoms, which could be attributed to the anemia, his laboratory findings of elevated CRP, low serum iron, and high serum ferritin levels suggested complication of chronic inflammation. Ultrasonography did not reveal any signs suggestive of polymyalgia rheumatica (PMR) but did show narrowing of the temporal arteries. Magnetic resonance imaging (MRI) showed thickening and enhancement of the bilateral temporal arteries (Fig. 2A). These findings were highly suggestive of GCA, and a biopsy of the superficial temporal artery was performed. Hematoxylin and Eosin staining of the specimen showed stenosis of the arterial lumen, tortuous internal elas-

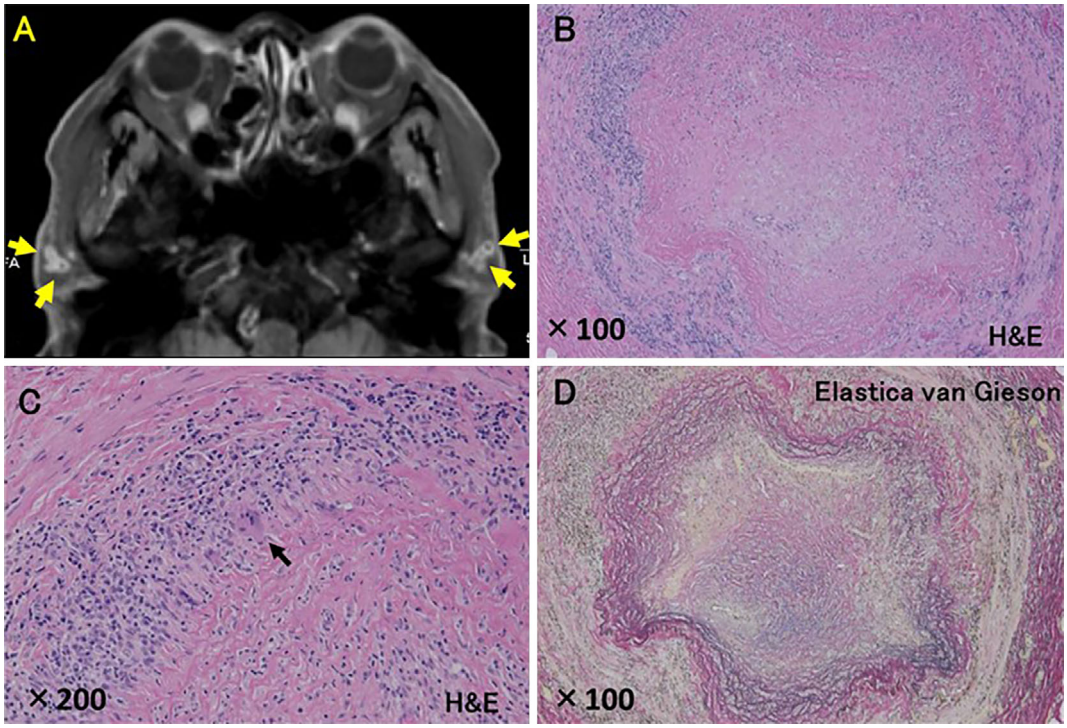

Figure 2. **Gadolinium-enhanced magnetic resonance imaging and biopsy specimen of the temporal arteries. (A) Magnetic resonance imaging shows thickening and enhancement of the bilateral temporal arteries (arrows). (B and C) Hematoxylin and Eosin staining of the biopsy specimen of the temporal artery shows stenosis of the arterial lumen, tortuous internal elastic lamina, and lymphocytic infiltration and multinuclear giant cells (arrow) at the junction of the media and intima. (D) Elastic van Gieson stain shows degradation and disruption of the internal elastic lamina.**

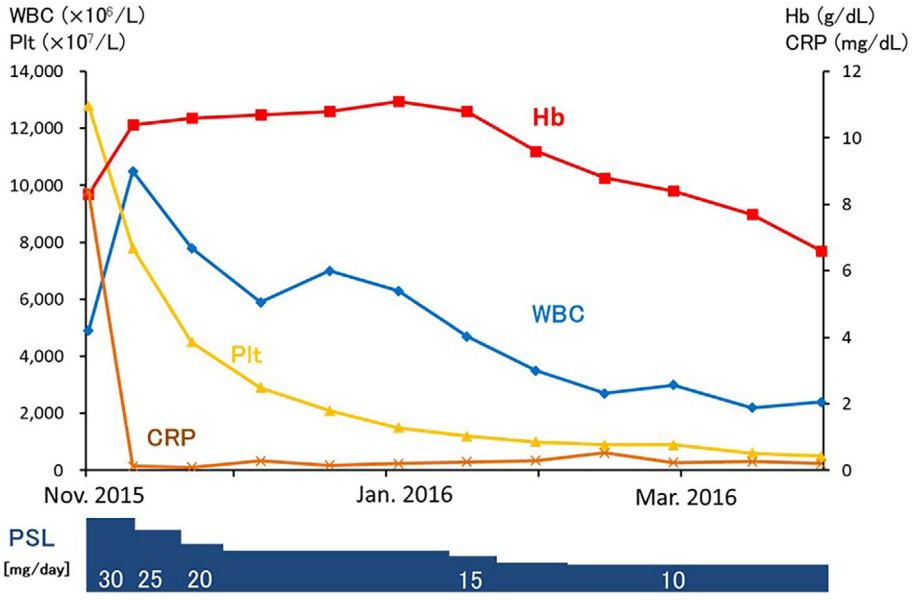

Figure 3. **The clinical course. The polygonal lines indicate the hemoglobin (Hb) level, the white blood cell count (WBC), the platelet count (Plt), and the C-reactive protein (CRP) level. The daily dose of prednisolone (PSL) given is shown at the bottom.**

tic lamina, and lymphocytic infiltration and multinuclear giant cells at the junction of the media and intima (Fig. 2B and C). Elastic van Gieson stain showed degradation and disruption of the internal elastic lamina (Fig. 2D). These histological findings were diagnostic of GCA and the patient was judged to have MDS and GCA simultaneously.

Oral prednisolone at 30 mg/day was started, which led to the rapid improvement of his symptoms, and a reduction in

the CRP level and amelioration of the anemia followed (Fig. 3). However, WBC and platelet counts soon started to decrease progressively with increases in the peripheral blasts, and 5 months after the presentation, the Hb decreased to 8.1 g/dL, the WBC count to 1.8×10^9/L with 24.0% blasts, and the platelet count to 12×10^9/L. BM aspiration revealed marked increases in the dysplastic megakaryocytes, as seen before; however, blast cells accounted for 46% of all nucleated cells, and the patient was diagnosed as having progressed to acute myeloid leukemia (AML) (Fig. 1E and F). He did not wish to receive chemotherapy for the AML and was transferred to another hospital to receive supportive care.

Discussion

GCA is a disease of elderly patients and develops almost exclusively in subjects over 50 years of age (14). The incidence of GCA increases with increasing latitude in the northern hemisphere and is highest in Scandinavian countries and lower in southern European countries, Africa, Arab nations, and Asia (14). GCA is particularly uncommon in Asian populations; a nationwide survey found that the annual prevalence of GCA among persons ≥50 years of age was 1.47 per 100,0000 population in Japan, compared to 200 per 100,000 in Olmsted County, USA (4, 15). Clinicians therefore often fail to consider GCA in general practice, especially in the absence of typical clinical features, in regions such as Asia, where GCA is very rare. Accordingly, while anemia is seen in most patients with GCA, it is often not considered in the differential diagnosis of anemia in such regions (2, 3). The present case presented with both ACD due to GCA and MDS simultaneously, emphasizing the importance of checking the complete list of differential diagnoses for anemia, including diseases that are rare for a given region, even when another cause of anemia is evident.

MDS is known to be complicated with various autoimmune diseases in 7.5-20% of patients (8, 9, 11). In such circumstances, MDS is generally diagnosed concomitantly with or shortly before the symptoms or signs of the autoimmune disease (16). A French nationwide retrospective survey of 99 MDS and 24 chronic myelomonocytic leukemia patients associated with systemic inflammatory and autoimmune diseases (SIADs), including 9 cases of GCA, reported that hematological disease and SIAD were diagnosed simultaneously in 31% of patients (12). On the other hand, GCA patients are reported to be at an increased risk of developing malignancy, suggesting a common etiology between MDS and GCA (17, 18). However, partly due to its rarity, a literature review in 2006 reported only seven patients in whom MDS and GCA occurred concurrently (19). The current understanding of the mechanism underlying GCA is that it is crucial that dendric cells at the adventitia-media border be activated and recruit CD4+ T cells and macrophages into the vascular wall (2, 3). CD4+ T cells then secrete cytokines, including interferon-γ, and the macrophages form multinucleated giant cells and secrete interleukin-1 and interleukin-6 and metalloproteases. The impaired function of T cells and monocytes in MDS patients may influence these consequences and contribute to the development of GCA (6, 7). Despite the abovementioned possible association between GCA and malignancies, among 39 patients with biopsy-proven GCA and malignancies, only 1 presented with both disorders simultaneously, suggesting that GCA presenting simultaneously with a malignancy is a rare event (17). The present case was diagnosed simultaneously with MDS and GCA when MDS started to obviously progress, strongly suggesting a possible pathogenetic association between the two disorders.

Polymyalgia rheumatic (PMR) is another autoimmune disorder that mainly affects elderly patients and often overlaps with GCA, and these two disorders are considered to be different manifestations of the same disease process (2). PMR is also reported to be complicated with MDS, and relatively small studies have reported that PMR was complicated in 0.9-2.9% of MDS patients (8, 9, 11, 20). A population-based case control study using data of federally funded health insurance in the United State reported a mild association between MDS and PMR compared with population-based controls with an odds ratio of 1.47 (10). These findings similarly suggest a pathogenetic association between MDS and PMR/GCA.

The anemia improved promptly with steroid therapy in the present case. This improvement was considered to reflect the alleviation of the ACD; however, the anemia soon worsened again, with declines in the WBC and the platelet counts, probably due to the rapid progression of MDS to overt AML surpassing the beneficial effect of the steroid therapy. This observation may be compatible with the notion that the initial response of autoimmune disease complicated with MDS to steroid therapy is favorable; however, the treatment of autoimmune complications has no effect on MDS (12, 19).

Autoimmune diseases associated with MDS often have an atypical presentation and do not meet the diagnostic criteria (12). The present case presented with nonspecific constitutional symptoms only; however, ultrasonography of the temporal arteries performed to rule out PMR/GCA eventually led to the diagnosis, illustrating the importance of always considering the possibility of relevant conditions even in regions where the prevalence of that condition may be very low. Furthermore, as both MDS and GCA mainly affect elderly patients, the possibility of coexisting GCA should be considered when encountering MDS patients, even in the absence of typical signs and symptoms.

The authors state that they have no Conflict of Interest (COI).

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