Clinical Case Reports

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CASE REPORT

Rapidly progressed aortic stenosis in a patient with previous diagnosis of polycythemia vera and post-polycythemia vera myelofibrosis

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Key Clinical Message

Polycythemia vera (PV) is a chronic myeloproliferative disease that is often complicated with thromboembolism. However, aortic stenosis (AS) could be a manifestation of the cardiovascular complications of PV possibly through shear stress and atherosclerosis. We report a rare case of rapidly progressed AS in a patient with PV.

Keywords

Aortic stenosis, hyperviscosity, polycythemia vera.

Case Report

A 69-year-old woman was emergently admitted to a hospital with the chief complaint of exertional dyspnea. She was diagnosed with severe AS and was transferred to our hospital. She had a past medical history of PV that was diagnosed in another institution, and had been treated at the Department of Hematology in our hospital since 1994. The hemoglobin value was around 16.0 g/dL and hematocrit between 45% and 54% under treatment with phlebotomy. The Janus kinase 2 mutation (JAK2 V617F mutation) was observed in the patient. She had a uterine myoma resected in 1988, surgically treated right breast cancer in 1993, and she had experienced two transient ischemic attacks (in 1994 and 2005). No significant family history or hereditary diseases were identified. The patient underwent echocardiography for an evaluation of chest oppression in 2009, which revealed mild AS. In August 2013, shortness of breath on exertion appeared and worsened gradually. Finally, she was emergently admitted to a hospital in October 2013 and was transferred to our hospital.

The physical examination upon admission revealed the following: height 153.0 cm, body weight 43.0 kg, body mass index 18.4, Glasgow Coma Scale 15, blood pressure 106/62 mmHg, pulse rate 64/min, body temperature 36.6 degrees centigrade, and respiratory rate 16/min. Cardiac auscultation revealed a third heart sound and a Levine *III*/VI systolic murmur that was loudest at the second intercostal space in the right sternal border and radiated over the entire precordium and into both carotid arteries. A Levine *II*/VI harsh pan-systolic murmur was also audible at the apex. Moist rales were heard over the lower lung field. Splenomegaly of >10 cm distance of the tip of the spleen from the left costal margin, hepatomegaly and lower extremity edema were noted. The chest radiograph showed cardiomegaly with a cardiothoracic ratio of 58%. The electrocardiogram revealed sinus rhythm with a heart rate of 97 and a negative T wave in *I*, aVL and V4-6, which suggested left ventricular hypertrophy. Blood examinations indicated an elevated white blood cell count (30,500/μL, percentage of white blood cells differential count; neutrophils 74.4%, lymphocytes 6.0%, monocytes 7.2%, eosinophils 0.6%, basophils 1.2%, blasts 0.6%, promyelocytes 0.2%, myelocytes 7.6%, and metamyelocytes 2.8%), anemia (hemoglobin concentration 8.3 g/dL; hematocrit 25%), and increased levels of lactate

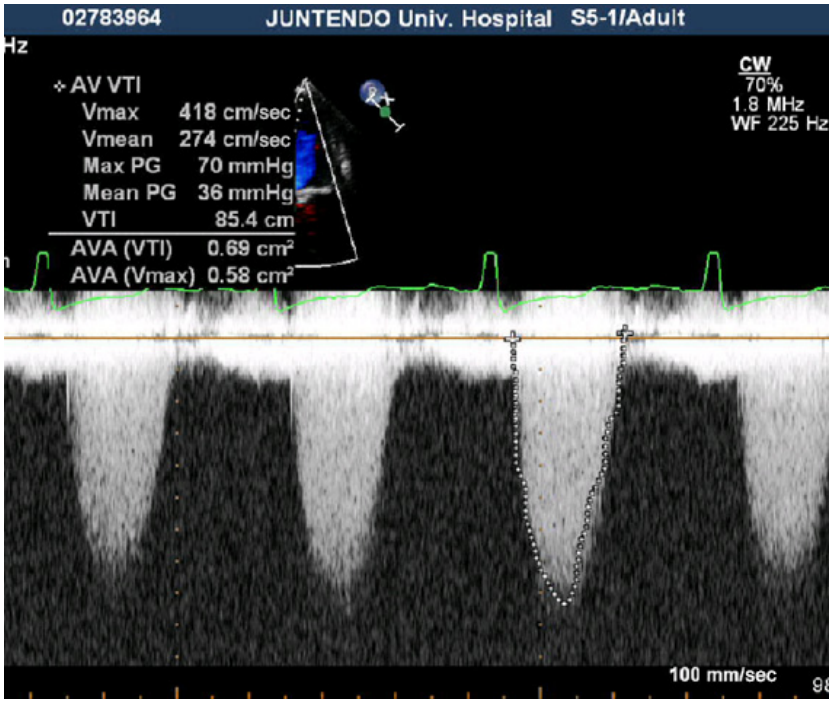

Figure 1. Echocardiographic finding at admission. In the view of apical three chambers, severe aortic stenosis was observed.

dehydrogenase (448 U/mL). Platelet count was within normal range (170,000/μL). The serum concentration of ferritin was 1326 ng/mL. The value of brain natriuretic peptide (BNP) was 716 pg/mL. Echocardiography revealed reduced left ventricular systolic function with a left ventricular ejection fraction (LVEF) of 28%. The aortic valve was tricuspid with severe calcification, and there was severely limited motion of the leaflets (Fig. 1). The peak flow velocity of the aortic valve was 4.2 m/sec, the peak transvalvular pressure gradient of the aortic valve was 70 mmHg, and the aortic valve area, which was estimated using the continuity equation, was 0.7 cm^2, which indicated the diagnosis of severe aortic stenosis [1]. Other findings included moderate to severe mitral regurgitation and moderate tricuspid regurgitation. The coronary angiography showed no abnormal findings.

The patient was diagnosed with acute decompensated heart failure due to severe AS. We started oxygen therapy and intravenous administration of diuretics. In addition, a blood transfusion for anemia, and bi-level positive airway pressure therapy for pulmonary congestion were performed. Acute heart failure was compensated 10 days after admission. We considered aortic valve replacement to be the most appropriate option for treating the AS. However, the patient was at high risk of open heart surgery because of the existence of PV that had a risk of progression to leukemia. The stress of the operation and the hypothermal condition during the cardio-pulmonary bypass could impair the natural killer cells, which could induce the transition to leukemia [2]. Thus, our heart team considered the risk of surgical aortic valve replacement to be greater than the benefit. We selected balloon aortic valvuloplasty (BAV). On the 20th day after admission, BAV was performed, which could reduce the severity of AS. However, restenosis of the aortic valve was observed a few days after BAV. Although the patient's general condition gradually improved, it was insufficient for discharge. Therefore, transcatheter aortic valve implantation (TAVR) was selected. After 2 months, the patient underwent successful TAVR; the only complication was splenic infarction that recovered without any invasive treatment. After discharge, the patient had no signs or symptoms of heart failure, and the patient received blood transfusions for myelofibrosis-induced anemia in our hospital.

Discussion

Polycythemia vera is a chronic myeloproliferative disease that is characterized by an abnormal increase in red blood cell count. The mean survival period of PV patients without treatment has been reported to be 6–18 months from diagnosis, whereas that of patients with appropriate treatment has been reported to be 9.1–14.1 years [3, 4]. Thus, PV is considered to have a relatively good prognosis. However, some cases developed leukemia or

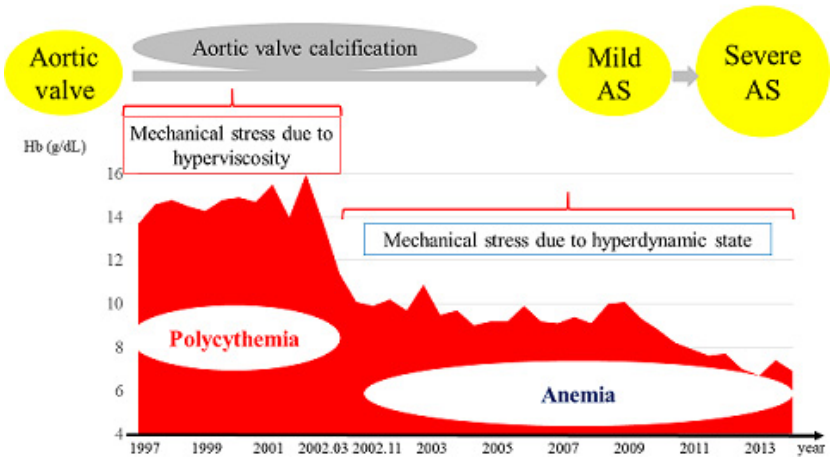

Figure 2. Clinical course of progression of aortic stenosis accompanied by the course of polycythemia vera. Aortic valve calcification might be induced by shear stress generated by hyperviscosity due to polycythemia, inflammation, and angiogenesis. In anemic phase, mechanical stress due to hyperdynamic state by anemia was considered to be related to the progression of aortic stenosis.

myelofibrosis; the incidence rate of 9% (myelofibrosis) and 3% (leukemia) in PV patients [5]. More importantly, a considerably high proportion of PV patients also have cardiovascular disease, which can be fatal. A previous report suggested that 29% of PV patient deaths originate from cardiovascular disease, mainly thromboembolic events caused by hyperviscosity due to polycythemia [6]. In 1992, Reisner et al. reported in a clinical study that 77% of cases of PV patients had valvular heart disease [7]. Fazio et al. also reported that the prevalence of AS in PV patients was 25.5%, which is higher than the prevalence of thrombotic events (13.4%) [8].

Aortic stenosis is a serious valvular heart disease with a high mortality rate, and the prevalence of this disease has increased with an aging society. Numerous factors are associated with the occurrence and progression of this disease, such as the atherosclerotic risk factors of age, diabetes, hypertension, dyslipidemia and smoking as well as the risk factors of inflammation, rheumatic fever, and hyperparathyroidism [9]. In addition to these risk factors, hemodynamic issues caused by hematologic diseases, such as polycythemia or anemia, are risk factors for AS [8, 10]. Regarding the progression of AS, Kearney et al. reported that 35% of the patients with mild AS progress to severe AS during a mean follow-up period of 6.5 years [10]. Another report showed that the clinical course of mild AS was relatively benign, with a 5-year cardiac mortality and aortic valve replacement rate of 26% [11]. Our case had no traditional atherosclerotic risk factors, except for age. However, the severity progressed from mild to severe within 4 years, which is a relatively short period compared with that in previously reported cases [10, 11]. Potential explanations for the rapid progression of AS include following pathophysiological conditions of progressive PV accompanied by myelofibrosis. First, hyperviscosity caused by polycythemia could increase shear stress on the aortic valve and induce aortic valve calcification, although quantitative assessment for shear stress induced by PV was not estimated in this report. Second, post-PV myelofibrosis diagnosed with criteria of the International Working Group for Myelofibrosis Research and Treatment [12], caused anemia that was observed from 2002 in this case. Anemia might increase mechanical stress on the aortic valve via the persistent hyper-hemodynamic state that compensates for the inadequate circulatory volume, which could result in a calcified aortic valve [13]. Additionally, previous reports demonstrated that circulating inflammatory biomarkers such as, C-reactive protein (CRP) and vascular endothelial growth factor (VEGF) were elevated in PV patients [14, 15]. Considering the effect of chronic inflammation and VEGF on developing atherosclerosis [16, 17], the hemodynamic mechanical stress accompanied by inflammation and angiogenesis could contribute to occurrence and progression of AS (Fig. 2).

In conclusion, we report a case of rapidly progressing AS in a patient with PV and post-PV myelofibrosis. In this case, it was speculated that AS was initiated and progressed due to the hemodynamic stress and chronic inflammation on the aortic valve caused by PV and post-PV myelofibrosis. Based on our case and previous reports, careful observation is required with respect to the incidence of both thromboembolisms and AS as the cardiovascular complications in PV patients.

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Conflict of Interest

None declared.

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