Did Angiodysplasia Associated with Heyde's Syndrome Disappear Spontaneously?: A case report

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Case Report

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Abstract

Background: Heyde’s syndrome can be easily overlooked or misjudged in clinical practice because it shares common clinical manifestations with multiple diseases and because of the limited accuracy of the corresponding examinations for diagnosing Heyde’s triad. Moreover, aortic valve replacement is often delayed in these patients because of the contradiction between anticoagulation and haemostasis. Herein, we present a rare case of atypical Heyde's syndrome. The patient's severe intermittent gastrointestinal bleeding was not completely cured even after a local enterectomy. In the absence of direct evidence of acquired von Willebrand syndrome (AVWS) or angiodysplasia, her long-standing gastrointestinal bleeding was finally stopped after receiving transcatheter aortic valve implantation (TAVI).

Case presentation: A 64-year-old female suffered from refractory gastrointestinal bleeding and exertional dyspnoea. Local enterectomy was performed owing to persistent haemorrhage and repeated transfusions; subsequently, histological examination revealed angiodysplasia. Heyde's syndrome was not suspected until 3 years later, at which time the patient started bleeding again and was also found to have severe aortic valve stenosis on echocardiography. TAVI was consequently performed when the patient was in a stable condition even there was no evidence of angiodysplasia and AVWS at that time. The post-procedure and follow-up were uneventful.

Conclusions: The visible characteristics of angiodysplasia or a shortage of HMWM-vWFs should not be indispensable for the clinical diagnosis of Heyde's syndrome. Enterectomy could be a bridging therapy for aortic valve replacement in patients with severe haemorrhage, and TAVI may benefit high-risk patients who are stable.

Background

The incidence and mortality of Heyde's syndrome have both been on the rise for nearly a decade(1). The most prominent pathophysiological mechanism of this syndrome is deemed an acquired deficiency in high-molecular-weight multimers of von Willebrand factor (HMWM-vWFs). Despite the lack of guidelines for Heyde's syndrome, the diagnosis is generally based on a triad of aortic stenosis (AS), refractory gastrointestinal bleeding (GIB), and associated angiodysplasia or acquired von Willebrand syndrome (AVWS)(2). However, because it shares common clinical manifestations with multiple diseases and because the corresponding diagnostic examinations have limited accuracy, it is easy to omit or misdiagnose this disease. Moreover, aortic valve replacement is often delayed because of the contradiction between anticoagulation and haemostasis(3). Herein, we summarize a case of Heyde's syndrome in which the patient’s severe intermittent gastrointestinal bleeding was not completely cured even after intestinal resection. However, transcatheter aortic valve implantation (TAVI) could dramatically improve the recurrent bleeding even if angiodysplasia or AVWS could not be proven.

Case Presentation

A 64-year-old woman had been experiencing frequent chest distress and shortness of breath during moderate activity. She had no medical history of heart disease but did have hypertension for ten years.

In February 2014, she suffered repeated episodes of tarry stools accompanied by palpitations, chest tightness, and dizziness without any apparent inciting factors. Gastroduodenoscopy and colonoscopy did not locate any bleeding lesions, while subsequent capsule endoscopy and double balloon enteroscopy identified haemorrhage and multiple haemangiomas in the jejunum respectively (Fig. 1).

Nevertheless, the patient had minimal haemostatic effects following endoscopic argon plasma coagulation and conventional medication. She then had to receive a transfusion of several units of blood, during which her haemoglobin fluctuated between 74 and 124 g/L (normal 110–150 g/L). Several months later, as she required repeated transfusions due to her persistent haemorrhage, an exploratory laparotomy was performed to resect several suspicious lesions in her small intestine. The relevant histological examination showed chronic mucosal inflammation with multiple erosions, which was consistent with a haemangioma. Thus, thalidomide (25 mg/d) was prescribed to prevent postoperative neoangiogenesis, and her GIB consequently ceased for some time.

In May 2017, the patient received an emergency coronary angiography because of syncope during exercise, and the patient's coronary angiography revealed a diffuse stenosis of 40% in the middle right coronary artery but no other critical lesions. The patient started having melena again after the procedure, which was likely related to the dual antiplatelet prophylactic therapy prescribed prior to coronary angiography; however, the melena was effectively controlled with conventional medications, such as proton pump inhibitors (PPIs) and octreotide.

Afterwards, the patient was referred to our department due to worsening exertional dyspnoea, thoracalgia, and orthostatic hypotension. Her clinical signs of AS and systemic congestion were obvious, whereas her laboratory tests were unremarkable other than an Hb level of 76 g/L and an NT-proBNP level of 392 (normal < 125) pg/mL. The transthoracic echocardiography (TTE) results showed severe calcified AS, the mean and peak transvalvular pressure gradients were 48 and 84 mmHg, respectively; the aortic valve area was 0.80 cm2; and there were no signs of obstructive hypertrophic cardiomyopathy (HCM) (Fig. 2a-c).

In August 2018, the patient was stable and underwent TAVI with a VENUS-A 26 prosthetic aortic valve; no paravalvular leak occurred after the procedure. Interestingly, arteriovenous malformations are difficult to detect via superior mesenteric artery angiography before TAVI. The patient's peak aortic valve pressure gradient improved from 88 mmHg to less than 5 mmHg postoperatively, and she did not develop enterorrhagia or major bleeding during the perioperative period. For her antithrombotic strategy, clopidogrel was prescribed for 1 year, in addition to the long-term use of Pradaxa.

At the 1-year follow-up, the TTE results confirmed a well-seated prosthesis with a peak transvalvular pressure gradient of 12 mmHg and an aortic valve area of 4.11 cm2, but there was a simple left ventricular outflow tract obstruction (LVOTO) present, which was not accompanied by a systolic anterior

motion of the mitral valve or HCM (Fig. 2d-e). She did not have any further significant haemorrhagic or ischaemic events or events secondary to the triad of AS.

Discussion

Epidemiology and Pathophysiology

With the ageing of society, the prevalence of Heyde's syndrome in patients with severe AS is increasing annually and has reached 1.87%-3.2%, resulting in increasing disease mortality(1). The corresponding dominating mechanism is the excessive proteolysis of HMWM-vWFs by ADAMTS-13 in the context of the high shear stress related to stenotic valves, which not only predisposes patients to bleeding but also induces submucosal arteriovenous malformations in the digestive tract(4, 5).

Diagnosis

It is generally believed that the diagnosis of Heyde's syndrome should be based on a triad of AS, refractory GIB, and associated angiodysplasia or AVWS. Additionally, other primary diseases that can cause GIB should be excluded, such as tumours; primary digestive, haematological or autoimmune diseases; and the side effects of drugs.

For AS, the risk of complicating haematochezia in patients with severe AS is known to be 100 times that in non-AS patients(6). As our patient had suffered from continuous dyspnoea, chest pain, palpitations, and even syncope during mild to moderate exercise, her diagnosis of AS should have been recognized earlier after excluding severe coronary heart disease, and combined with her symptoms of GIB, it should be further differentiated from Heyde's syndrome in a timely manner.

For angiodysplasia, locating the culprit lesion can be challenging. Despite the rapid development of endoscopic diagnostic technologies, including double balloon enteroscopy, in the past decade, 35% of angiodysplasia cases have gone undiagnosed(3). Although the gold standard diagnostic method is mesenteric arteriography, the average localization rate of the bleeding site is 40% since many cases of bleeding angiodysplasia only intermittently bleed, which decreases its sensitivity for detection(7). The angiodysplasia in our patient was confirmed by histological examination through local enterectomy, but angiodysplasia was not observed via mesentericography several years later. This might be primarily attributed to the fact that the observable suspicious lesions in the gut had been surgically removed or were restricted by thalidomide, and the patient was stable when she underwent mesentericography.

For AVWS, the necessity of gel electrophoresis to confirm the loss of large multimers also makes the biological diagnosis of Heyde's syndrome challenging. Coagulopathy may be absent in patients with aortic gradients below 50 mmHg, and the related testing process is costly and time-consuming(2). The vWFs were not examined in our patient due to the limited capabilities of our laboratory department. Research has shown that the prevalence of abnormal HMWM-vWFs in patients with native AS is

estimated to be 65% to 92%, and the incidence of bleeding angiodysplasia in patients with AVWS is approximately 11.5%. Furthermore, 55.6% to 87.5% of patients with documented angiodysplasia have a deficiency in HMWM-vWFs(8). However, the results of other studies have indicated no increase in the prevalence of AVWS in patients with bleeding angiodysplasia(9). In the context of AS, other mechanisms, such as low perfusion, submucosal ischaemia and hypoxia, or cholesterol embolism, have also been considered to be the cause of the relationship between angiodysplasia, GIB and AS(10).

We searched for case reports of Heyde's syndrome that were published since 2000 in PubMed, and we obtained 91 articles. We excluded 13 articles (1) without available relevant information (n=10), (2) inconsistent with the disease (n=1), (3) that described a patient with epistaxis (n=1), and (4) that described an infant case (n=1). The remaining 78 articles involving a total of 83 cases were summarized (5 articles were double-case reports) with special references to the treatment methods, angiodysplasia and HMWM-vWFs (Supplement table 1). Among these case reports, the primary diseases were severe LVOTO in 6 patients, severe aortic regurgitation in 1 patient, and AS in the remaining 76 patients; 17 of the patients (20.5%) were not diagnosed with angiodysplasia, of which 11 (84.6%) of the 13 patients who were undergoing cardiac surgery (including aortic valve replacement and alcohol septal ablation) were cured of GIB. Additionally, 9 patients (10.8%) had no deficiencies in HMWM-vWFs; 46 patients (55.4%) did not get tested for HMWM-vWFs, of which 31 (91.2%) of the 34 patients who had cardiac surgery had GIB remission; and 10 patients were not diagnosed with either angiodysplasia or AVWS, of which 6 (85.7%) of the 7 patients who underwent heart surgery were cured of GIB.

Given the complicated mechanisms, imperfect accuracy, and lack of available relevant diagnostic methods, we should not simply exclude Heyde's syndrome in practice merely due to a lack of evidence for the presence of bleeding angiodysplasia or AVWS. Notably, we should consider both Heyde's syndrome as an exclusionary diagnosis and the feasibility of aortic valve replacement as a diagnostic therapy.

Treatment

Endoscopic therapies are often ineffective, whereas local enterectomy could be a bridging therapy for aortic valve replacement in patients with continuous enterorrhagia or major or life-threatening haemorrhage; nevertheless, the bleeding recurrence rate after intestinal resection is approximately 30%, which is mainly due to angiodysplasia that cannot be cured locally(11). Our patient underwent segmental enterectomy for severe bleeding, which was temporarily alleviated with regular administration of the angiogenesis inhibitor thalidomide.

SAVR or TAVI has been demonstrated to be a radical therapy for Heyde's syndrome. In comparison, TAVI may be an optimal modality for stable patients who are at high risk, such as patients who are elderly, have multiple comorbidities, or have a haemorrhagic predisposition. Desai et al.(1) found no significant differences in all-cause mortality or total expenses during hospitalization between TAVI and SAVR. Moreover, TAVI is superior to SAVR in lessening the duration of hospitalization and the incidence of

periprocedural complications such as stroke, myocardial infarction, or major or life-threatening bleeding. Nevertheless, patients who had TAVI have been shown to be prone to complications with paravalvular regurgitation (26.6% vs. 4.2%, P<0.001), and TAVI has been shown to be associated with a higher incidence of advanced GIB (3.3% vs. 1.5%, P<0.001) than SAVR(12, 13). Our patient, who had an extremely high risk of bleeding during the operation, consequently received TAVI to avoid surgical complications and to increase the benefit of valve replacement.

Although some cases of Heyde's syndrome are caused primarily by LVOTO, we are not aware of any prognostic reports concerning the complication of LVOTO after TAVI in patients with Heyde's syndrome. One study indicated that 89% of patients with baseline or latent obstructive HCM suffered abnormalities in HMWM-vWFs when the peak gradient of the obstructive LVOT was >15 mmHg (at rest) or >35 mmHg (during exercise). Additionally, approximately 30% of those patients developed GIB(14, 15). Our patient, who was verified as having no myocardial hypertrophy or LVOTO by preoperative echocardiography, was found to be complicated with an asymptomatic and simple LVOTO (maximum peak gradient in LVOT of 55 mmHg) at the 1-year follow-up. It is worth further investigating whether and how the complication of LVOTO following TAVI in patients with Heyde's syndrome impacts their prognosis regarding GIB.

Conclusion

Elderly patients suffering from bleeding angiodysplasia and refractory GIB due to unknown aetiologies (and if conventional gastroenterological therapies have been ineffective) should be examined by echocardiography, and Heyde's syndrome should be ruled out. Attention should be given to the two main symptoms of Heyde’s syndrome during its diagnosis: severe AS and refractory GIB. The possibility of this disease should not simply be ruled out on the sole basis of the absence of evidence of angiodysplasia or AVWS, but other disorders leading to GIB should also be excluded during diagnostic testing. Local enterectomy could be a bridging therapy for aortic valve replacement in severe haemorrhagic patients, and high-risk patients in a stable condition may benefit from TAVI.

Abbreviations

AS: Aortic valve stenosis

GIB: Gastrointestinal bleeding

HMWM-vWFs: High-molecular-weight multimers of vWFs

AVWS: Acquired von Willebrand syndrome

LVOTO: Left ventricular outflow tract obstruction

TAVI: Transcatheter aortic valve implantation

Hb: Hemoglobin

TTE: Transthoracic echocardiography

HCM: Hypertrophic cardiomyopathy

SAVR: Surgical aortic valve replacement

LVOT: Left ventricular outflow tract

PPIs: Proton pump inhibitors

Declarations

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Authors' contributions

The authors' responsibilities were as follows: WW and RL contributed to the conception or design of the case report as well as to the acquisition, analysis, or interpretation of the patient's manifestations; RL drafted the manuscript; LJQ assisted with the treatment of the patient; JCZ, SLJ and JXS critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work to ensure the integrity and accuracy of the case.

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Availability of data and materials

The datasets of the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was conducted with approval from the Ethics Committee of The

First Affiliated Hospital of Guangzhou University of Chinese Medicine. The patient in this study signed an informed written consent form. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

Consent for publication was obtained from the patient.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figures

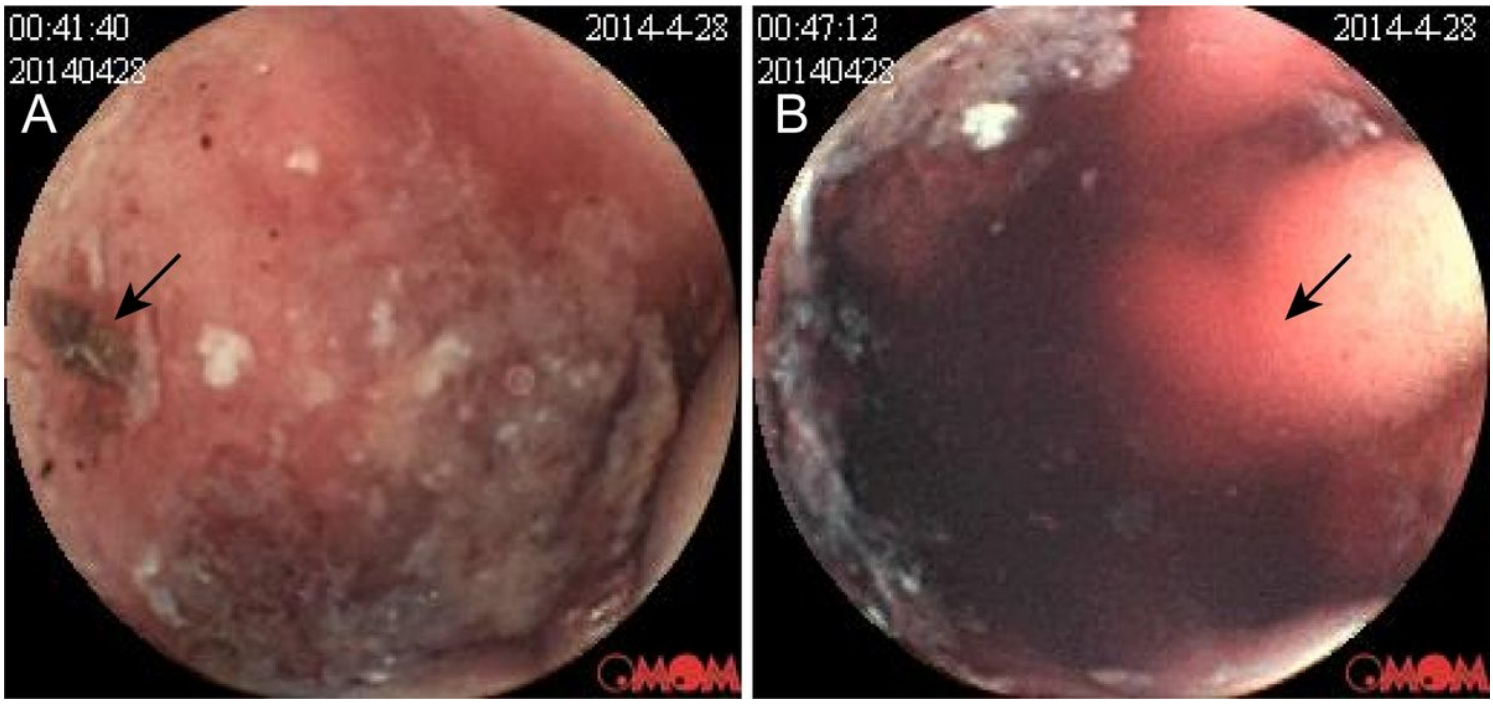

Figure 1

Pictures of patient's capsule endoscopy before laparotomy. Capsule endoscopy pictures show blood scabs(A), active bleeding(B), and hematoma formation(B) in the jejunum (indicated by black arrows).

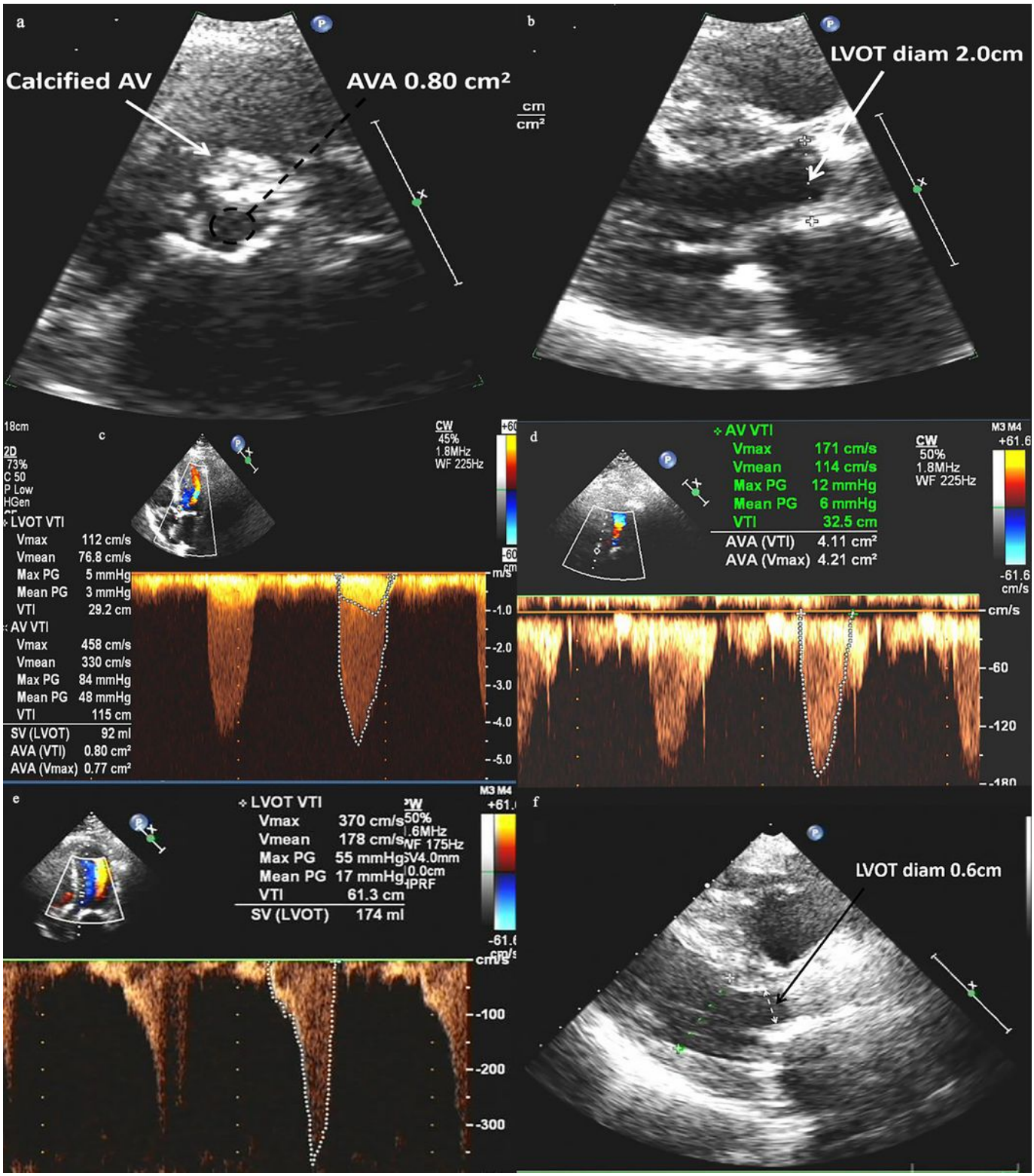

Figure 2

Pictures of patient's Ultrasound Cardiogram. Preprocedural TTE shows (a) severe AS with a calcified aortic valve (AV) and an aortic valve area (AVA) of 0.80 cm2; (b) the left ventricular outflow tract (LVOT) diameter was 2.0 cm; and (c) the maximum peak gradients in the LVOT and AV were 5 mmHg and 84 mmHg, respectively; the maximum systolic flow velocities of the LVOT and AV were 1.12 m/s and 4.58 m/s, respectively. TTE at the one-year follow-up shows (d, e) that the maximum peak gradients in the

LVOT and AV were 55 mmHg and 12 mmHg, respectively; the maximum systolic flow velocities in the LVOT and AV were 3.70 m/s and 1.71 m/s, respectively; the AVA was 4.11 cm2; and (f) the LVOT diameter was 0.60 cm.

Supplementary Files

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- Supplementarytable1.doc