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Mobile Mitral and Aortic Valvular Masses in Patients With Hereditary Hemorrhagic Telangiectasia Receiving Intravenous Bevacizumab

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Abstract

Bevacizumab is now an emerging treatment option for severe hereditary hemorrhagic telangiectasia—related bleeding including epistaxis and gastrointestinal tract bleeding. The impact of long-term intravenous bevacizumab therapy on cardiac structure and function is unknown. We describe 3 patients receiving intravenous bevacizumab therapy for severe hereditary hemorrhagic telangiectasia—related bleeding who were found to have abnormal mobile masses on the mitral valve (n=2) and aortic valve (n=1). The clinical impact of these findings is unknown and requires further study.

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Hereditary hemorrhagic telangiectasia (HHT) is a rare genetic disorder with autosomal dominant inheritance that leads to disorganized angiogenesis in multiple vascular beds.[1] This process results in the formation of the characteristic telangiectasias and arteriovenous malformations.[1] Mucocutaneous telangiectasias can lead to gastrointestinal tract (GI) bleeding and severe epistaxis,[2] and diffuse hepatic vascular involvement with arteriovenous malformations can result in high-output cardiac failure (HOCF).[3] Intravenous (IV) bevacizumab is a recombinant humanized antibody that binds to and inhibits vascular endothelial growth factor and is an emerging treatment option for HHT-related bleeding and HOCF.[1,3,4]

Although IV bevacizumab has proved to be safe in patients with HHT,[1,4,5] its use with cancer chemotherapy is associated with several adverse effects including proteinuria,[6] hypertension,[7] bleeding,[7] GI visceral perforation,[8] and postoperative wound complications.[9] From a cardiovascular perspective, IV bevacizumab has been found to increase the risk of arterial thrombosis (including myocardial infarction and stroke) and venous thromboembolic events in patients with underlying malignancy.[10] However, to our knowledge, no previous studies have reported cardiac valvular complications following the use of systemic bevacizumab. We describe 3 patients who were found to have abnormal mobile masses on the mitral (n=2) and aortic (n=1) valves following prolonged treatment with IV bevacizumab.

REPORT OF CASES

Case 1

A 74-year-old woman had been receiving IV bevacizumab for HHT-related bleeding from GI angioectasia and epistaxis and HOCF for 2 years. Baseline transthoracic echocardiography (TTE) before initiation of IV bevacizumab revealed a cardiac index (CI) of 6.32 L/min per m^2 (normal range, 2.5-4.2 L/min per m^2) and mildly thickened aortic valve without severe stenosis or regurgitation. Serial TTE every 6 months during treatment revealed reduction in CI with no significant change in the aortic valve anatomy. Two years after initiation of IV bevacizumab (1 week after the 15th bevacizumab dose), the patient was scheduled to

undergo surgical left atrial appendage closure (LAAC). Intraoperative transesophageal echocardiography revealed multiple new round, mobile echodensities measuring about 6 mm in diameter attached to the cuspal edges of the left and noncoronary cusps of the aortic valve via a stalk (Figure 1).

On physical examination, the patient was afebrile and had no new murmurs. Laboratory work-up revealed a normal white blood cell count and erythrocyte sedimentation rate, and results of serial blood cultures were negative. C-reactive protein was mildly elevated at 8.6 mg/L (normal, <8 mg/L; to convert to nmol/L, multiply by 9.524) in the setting of recent nonpurulent lower extremity cellulitis treated with oral antibiotics. No antibiotics were administered because the suspicion for infective endocarditis was low. The patient eventually underwent LAAC 4 months later, with no changes noted in the rounded aortic echodensities on intraoperative transesophageal echocardiography. No thromboembolic complications were noted on follow-up. The patient died 2 months after the LAAC procedure of acute hypoxemic respiratory failure in the setting of community-acquired pneumonia. An autopsy was not performed.

Case 2

A 58-year-old woman was receiving IV bevacizumab for HHT-related severe epistaxis and HOCF. Baseline TTE before initiation of IV bevacizumab revealed a mildly calcified mitral annulus and mild mitral regurgitation in addition to a CI of 4.37 L/min per m^2. Cardiac index normalized on subsequent TTE over the course of 2 years of bevacizumab therapy without any change in the structure or functioning of the mitral valve. Routine follow-up TTE 2 years after initiation of therapy (1 week after the 27th bevacizumab dose) revealed a new highly mobile echodensity arising from the posterior lateral mitral annulus measuring 11×4 mm (Figure 2). On physical examination, the patient was afebrile, and a new systolic ejection murmur was heard over the left parasternal area. Laboratory evaluation findings were unremarkable with the exception of normocytic anemia. No specific

intervention was pursued, and the patient continued IV bevacizumab with no changes on follow-up TTE after 3 months. She remained asymptomatic without thromboembolic or infectious complications at the time of last follow-up 8.7 months after initial detection of the mitral valve abnormality.

Case 3

An 88-year-old woman with history of HHT was receiving IV bevacizumab for HHT-related bleeding from GI angioectasia and epistaxis and HOCF. Baseline TTE revealed moderate mitral annular calcification with mild regurgitation. Repeated TTE 1 year after initiation of IV bevacizumab treatment revealed no changes. However, 32 months after initiation of therapy (2 weeks after the 65th bevacizumab dose), routine follow-up TTE revealed a new mobile echodensity attached to the atrial side of the posterior mitral leaflet with severely calcified mitral annulus and moderate mitral regurgitation. Transesophageal echocardiography confirmed the presence of a calcified, mobile echodensity attached to the atrial side of the posterior mitral annulus measuring 12×4 mm (Figure 3). Physical examination revealed a holosystolic murmur on the left sternal border. Laboratory work-up yielded no remarkable findings. The patient was managed conservatively without surgical intervention and continued IV bevacizumab treatment. She remained asymptomatic without thromboembolic or infectious
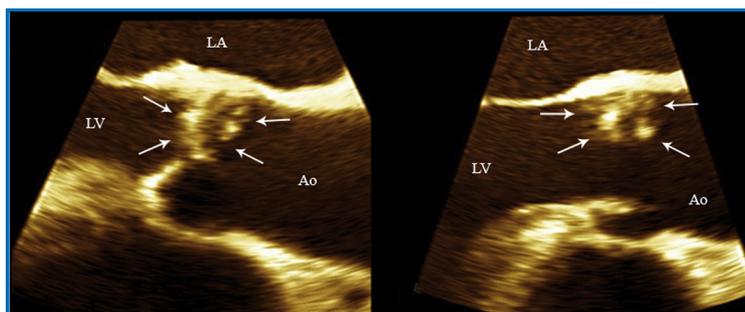
FIGURE 1. Transesophageal images from a modified long-axis view showing an echo-dense mobile round mass (arrows) attached to the aortic valve during diastole (left) and systole (right). Ao= aorta; LA = left atrium; LV = left ventricle.

FIGURE 2. Transthoracic echocardiographic images from a modified 4-chamber view showing a serpiginous mobile echodensity (arrows) attached to a calcified mitral annulus during systole (left) and diastole (right). LA = left atrium; LV= left ventricle.

complications at the time of last follow-up 23.4 months after initial detection of the mitral valve abnormality.

DISCUSSION

We present a case series of 3 patients with HHT who had a novel finding of abnormal mobile valvular masses involving the mitral and aortic valves after treatment with systemic bevacizumab.

Cardiac valvular masses and nonbacterial thrombotic endocarditis (also known as Libman-Sacks endocarditis or marantic endocarditis) are rare disorders that appear as echodensities on the affected valves.[11] The diagnosis requires a high index of suspicion because most cases are asymptomatic until thromboembolic complications such as stroke occur.[11] The differential diagnosis for masslike echodensities includes primary cardiac tumors such as papillary fibroelastoma and myxoma,[12] calcified amorphous tumors or extension of annular valvular calcification,[13] Lambl excrescences (filamentous fibrin echodensities),[14] and valvular thrombi.[15] Other disorders that can present similarly include vegetation from infective endocarditis; valvular abscesses and nonbacterial thrombotic endocarditis, which are associated with a variety of disorders including malignancy; collagen vascular disease; and antiphospholipid syndrome.[11]

Interestingly, all 3 of our patients had multiple previous echocardiograms that did not demonstrate these abnormalities. Although none of the patients received anticoagulation because of the substantially elevated bleeding risk from their underlying HHT, no thromboembolic complications were encountered during follow-up (median, 8.7 months; range, 2-23.4 months). The temporal relationship with IV bevacizumab administration raises the suspicion of association between its use and valvulopathy, although causality cannot be established with the current study design. The exact composition of these masslike structures was not established because autopsy was not performed in the deceased patient and no surgical intervention was pursued in the other 2 patients because of their comorbidities, lack of symptoms, and the considerable risk for perioperative complications. The clinical importance and evolution of these lesions are not clear and deserve further study. These novel findings suggest the possibility of endocardial injury and/or delayed repair due to inhibition of vascular endothelial growth factor—mediated angiogenesis. Serial echocardiography may be warranted for patients receiving prolonged systemic bevacizumab for HHT-related bleeding and/or HOCF.

CONCLUSION

We describe 3 patients with a novel cardiac valvular pathology temporally associated with the use of IV bevacizumab for severe HHT-related bleeding. The exact etiology, clinical importance, and risk of progression are unknown and require further study. Serial echocardiography should be considered in patients with HHT receiving IV bevacizumab for prolonged periods.

FIGURE 3. Transesophageal images from the 4-chamber view showing an echo-dense mobile linear mass (arrow) attached to a calcified mitral annulus during diastole (left) and systole (right). LA = left atrium; LV= left ventricle.

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