

CASE REPORT

Obstructive mechanical mitral valve thrombosis and gastric adenocarcinoma: A therapeutic dilemma

Obstrüktif mekanik mitral kapak trombozu ve gastrik adenokarsinom: Tedavideki zorluklar

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Summary– Fibrinolysis is an option for the management of mechanical prosthetic valve thrombosis when surgery has prohibitive risks. Current guidelines suggest recombinant tissue plasminogen activator (not to exceed 100 mg) with unfractionated heparin. A low-dose (25 mg) alteplase regimen as treatment in patients with a high risk of bleeding warrants further research. This report describes the case of a 65-year-old woman with a history of mechanical prosthetic mitral valve replacement who was diagnosed with signet ring cell adenocarcinoma of the stomach and obstructive mechanical prosthetic thrombosis on echocardiogram. Details of challenging aspects of this case and the use of modified fibrinolytic therapy are provided.

Özet– Cerrahinin riskli olduğu durumlarda fibrinolitik, mekanik protez kapak trombozunun tedavisinde seçilecek bir yöntemdir. Güncel klavuzlar, heparin ile birlikte rekombinant doku plazminojen aktivatörü (toplam 100 mg) önermektedir. Kanama riski yüksek olan hastalarda düşük doz alteplaz protokolünün (25 mg) kullanılabilirliği ileri araştırmalar gerektirir. Bu yazıda, geçirilmiş mitral kapak replasmanı öyküsü olan, midenin taşlı yüzük hücreli adenokarsinomu tanısı alan ve ekokardiyografisinde obstrüktif mekanik protezi olan 65 yaşında bir kadın hasta sunuldu. Olgunun zorlayıcı yanları ve kullanılan modifiye fibrinolitik protokolü açıklandı.

Valve thrombosis can occur in mechanical prosthetic valves, and management is high-risk, regardless of the option pursued. Since surgery is a re-intervention in such a case and signifies substantial risk, fibrinolytic therapy is an alternative, despite a risk of bleeding. Current guidelines suggest the use of recombinant tissue plasminogen activator (tPA) (10 mg bolus+90 mg in 90 min with unfractionated heparin).^[1] In contrast, Özkan et al.^[2] reported that low-dose (25 mg) and ultra-slow infusion (25 hours) of tPA without bolus was associated with low non-fatal complications and mortality for patients with mechanical valve thrombosis. Presently described is the successful resolution of a therapeutic dilemma in the case of a 65-year-old woman with a history of mechanical prosthetic mitral valve replacement who was then diagnosed with signet ring cell adenocarcinoma of the stomach and obstructive mechanical prosthetic thrombosis on echocardiogram.

CASE REPORT

A 65-year-old female with known arterial hypertension and type-2 diabetes mellitus had a myocardial infarction in 2017. In 2018, she underwent coronary artery bypass graft surgery, mechanical mitral valve replacement, and tricuspid valve annuloplasty. In 2018, an intracardiac cardioverter defibrillator was implanted due to a low ejection fraction in the left ventricle (primary prevention). In 2019, she was admitted to the department of general surgery with a history of weight loss and was diagnosed with signet ring cell adenocarcinoma of the stomach (T1N1). The patient was referred to the department of cardiology for a preoperative assessment.

The patient had no orthopnea or exertional dyspnea. She had a temperature of 37°C, a pulse rate of 84

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beats/min, a respiratory rate of 12 breaths/min, and a blood pressure of 96/60 mmHg. A physical examination revealed grade 2 (++) pretibial edema and positive sign of Godet on both legs, a metallic valve sound, and a 2/6 systolic murmur on all cardiac auscultation sites. Electrocardiogram results were consistent with the ventricular pacemaker rhythm. A complete blood count demonstrated mild anemia with a hemoglobin level of 12 g/dL. The white blood cell count and platelet count were normal. The C-reactive protein level was elevated at 44.9 mg/L. Liver and kidney function test findings were within the normal range. Her international normalized ratio was 1.97 at admission and she stated that she was not using warfarin regularly. The pro brain natriuretic peptide (proBNP) measurement was 8589 pg/mL. Transthoracic echocardiogram results demonstrated severe left ventricular systolic dysfunction and hypokinesis of the anterior wall. A left ventricular ejection fraction of 33% was calculated with the Simpson method. Other findings were biatrial dilatation, mild

aortic regurgitation (pressure half-time of 744 ms), severe tricuspid regurgitation, and moderate

systolic pulmonary hypertension (estimated systolic pulmonary artery pressure of 45 mmHg). There was a St. Jude bileaflet prosthesis (St. Jude Medical, Inc., St. Paul, MN, USA) in the mitral position. Color Doppler imaging of the mechanical mitral valve suggested severe stenosis. Continuous-wave Doppler imaging showed an elevated mean pressure gradient of 15 mmHg and the effective orifice area was calculated at 0.8 cm² (Fig. 1). Transesophageal echocardiography (TEE) was performed in order to get better views of the valve. The mobility of the medial leaflet of the mechanical mitral valve was restricted due to an immobile, hypoechogenic mass (1.4x0.8 cm), which was consistent with a thrombus. The mobility of the lateral leaflet was within normal limits. A round, immo-

Abbreviations:

proBNP	Pro brain natriuretic peptide
TEE	Transesophageal echocardiography
tPA	Tissue plasminogen activator

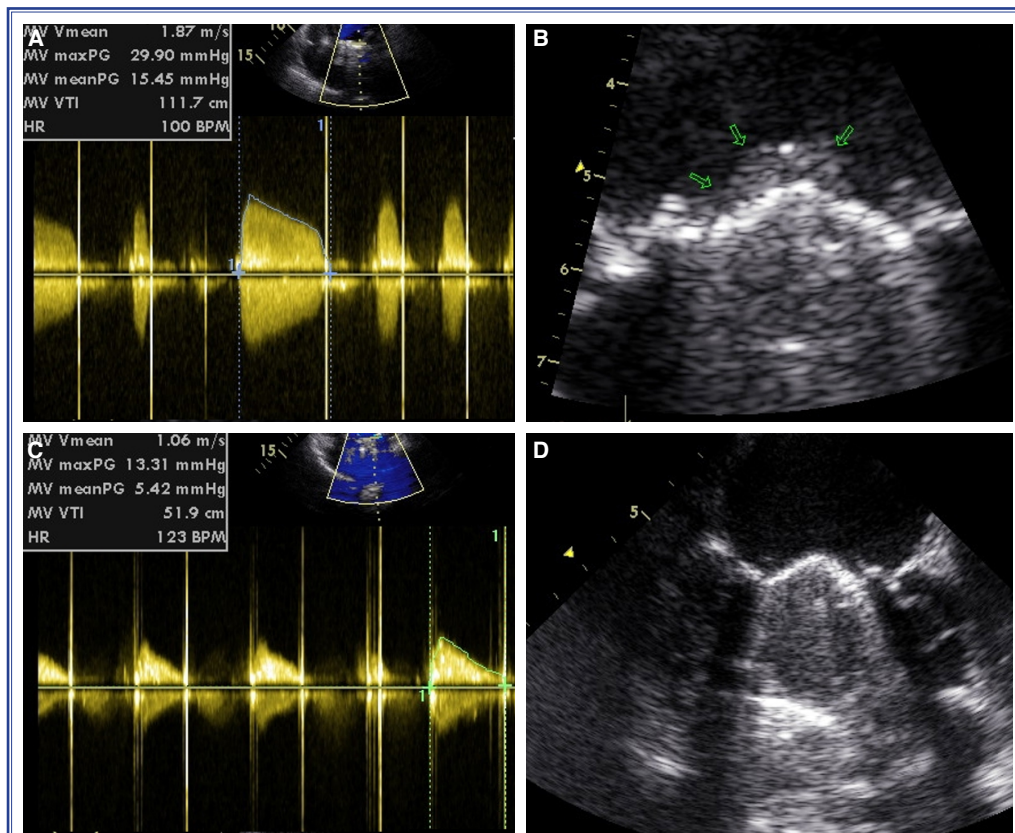


Figure 1. (A) Continuous-wave Doppler imaging of the prosthetic mitral valve demonstrating an increased gradient; (B) Image of the thrombus on the prosthetic mitral valve (arrows); (C) Continuous-wave Doppler imaging of the prosthetic mitral valve demonstrating a decreased pressure gradient after treatment; (D) No thrombus was detected on the prosthetic mitral valve after treatment.

bile, hypoechogenic mass consistent with a thrombus was observed in the left atrial appendage. Since redo surgery included a high risk of mortality for the patient, a choice was made to pursue fibrinolytic therapy. There was no absolute contraindication for fibrinolytic treatment; however, as a result of the active stomach malignancy, there was a substantial risk of gastrointestinal bleeding. The gastroenterology department was consulted for a bleeding risk evaluation and the response was that if the carcinoma began to bleed after the fibrinolytic infusion it would likely be unmanageable. The patient was informed about the risk of gastrointestinal bleeding and the state of the life-threatening, obstructive mechanical prosthetic valve thrombosis. After a thorough evaluation of all of the considerations, the patient decided to proceed with the fibrinolytic treatment. Informed consent for the treatment and to be a subject for this manuscript was provided.

While alteplase is produced in vials of various sizes for different uses (10 mg, 20 mg, 50 mg), in our case, unfortunately, only a 50 mg vial was available. Once alteplase is unsealed and diluted, the reconstituted solution will remain stable for only 8 hours at room temperature and 24 hours if refrigerated (2–8°C). Therefore, a modified regimen of 25 mg total alteplase was planned. A quarter of 1 vial (12.5 mg) was administered for 7 hours followed by another quarter for an additional 7 hours. Subsequently, a 6-hour heparin infusion was administered. No adverse reactions occurred and the hemoglobin level remained stable during the infusion period.

A control TEE was performed after the first infusion, and no thrombus was observed on the mechanical mitral valve (Fig. 1). The mean pressure gradient had decreased to 5 mmHg. The mobility of the leaflet was restored. The patient was discharged with a prescription for an optimized dose of warfarin and 100 mg acetylsalicylic acid. One-and-a-half months after the treatment, the patient underwent a radical distal subtotal gastrectomy and Roux-en-Y gastrojejunostomy in our hospital to treat the adenocarcinoma. There were no adverse events in the perioperative period, and she was later discharged.

DISCUSSION

This case demonstrates some of the difficulties of treating patients with obstructive mechanical valve thrombosis and malignancy. Fibrinolytic therapy is a

treatment option, but it can be hazardous in cases such as active gastric adenocarcinoma.

Cancer generally increases thrombotic events because it causes hypercoagulability. At the same time, it increases bleeding events by causing other disease-related mechanisms, such as thrombocytopenia or altered vascularization. The use of anticoagulants decreases the risk of thrombotic events in cancer patients, but bleeding events may increase, particularly after surgical procedures.^[3] Deep vein thrombosis is commonly seen after gastric cancer surgery, and a case report in the literature has described using fibrinolytic treatment in such a patient.^[4]

Fibrinolytic therapy has been reported to be safe in cancer patients in some studies. The incidence of bleeding was found to be higher in solid tumors than liquid tumors.^[5] Although this treatment is safe with close patient monitoring, some authors still consider it to be contraindicated in cancer patients.^[6] In the present case, despite an active stomach malignancy, there was no history of gastrointestinal bleeding or other absolute contraindication for fibrinolytic therapy. We administered tPA under close clinical monitoring in the intensive care unit, and our patient did not experience any major bleeding complication.

The risk of prosthetic valve thrombosis is higher in right-sided valves than left-sided valves, and it is higher in mitral valves than aortic valves. The incidence of prosthetic mitral valve thrombosis is between 0.1% and 5.7%.^[7] The clinical presentation of valve thrombosis may vary from an incidental finding during a routine echocardiographic evaluation to cardiogenic shock. If the patient is unstable, emergent surgery to treat obstructive left-sided mechanical prosthetic valve thrombosis should be considered. If the patient is hemodynamically stable and thrombosis occurred while anticoagulation was effective, the risk of redo surgery should be assessed. When the risk is high, fibrinolytic therapy is the treatment of choice.^[1,8] Our patient had obstructive mechanical mitral valve thrombosis and was hemodynamically stable. She had a low left ventricular ejection fraction, moderate pulmonary arterial hypertension, and a significantly elevated pro-BNP level that was consistent with the increased transmitral pressure gradient and left ventricular systolic dysfunction. Therefore, a decision was made to administer fibrinolytic therapy. We could have simply optimized the anticoagulant therapy and

waited for resolution of the thrombus; however, semi-urgent surgery to treat the signet ring cell adenocarcinoma of the stomach was considered crucial, as it was regarded to be an aggressive tumor. The treatment plan was to use fibrinolytic therapy to alleviate the prohibitive risks of abdominal surgery in the presence of obstructive mechanical valve thrombosis.

There are several considerations related to the dosage of fibrinolytic therapy in cases of mechanical valve thrombosis. The 2017 European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease suggest tPA (10 mg bolus + 90 mg in 90 min with unfractionated heparin).^[1] However, an ultra-slow dose regimen of 25 mg alteplase infused over 25 hours without bolus was recently reported to be effective and safe. This can be repeated up to 8 times with 6 hours of heparin infusion between doses. Larger doses are also used, but they have higher rates of complications and mortality.^[2]

In the study reported by Özkan et al.,^[9] the authors compared 5 regimens, 2 of which included streptokinase, which is no longer widely used. A third group received 90 mg tPA in a 6-hour infusion, a fourth group was treated with 50 mg tPA for 6 hours, and 25 mg tPA was administered for 6 hours in the fifth group. The safest fibrinolytic regimen was found to be the ultra-slow dose regimen of 25 mg alteplase given in a 6-hour infusion. It had a similar effectiveness with less mortality and fewer complications. In our case, we decided on a modified infusion protocol with a total of 25 mg alteplase infused over 14 hours without bolus. Our patient did not experience any bleeding complications. Her transmitral pressure gradient decreased substantially, and she was able to undergo the needed major abdominal surgery without any compromise.

Conclusion

The decision to use fibrinolytic therapy is difficult in malignancy patients, but obstructive mechanical valve thrombosis is also a life-threatening situation. Our patient with active gastric adenocarcinoma benefited from slow, low-dose fibrinolytic therapy and successfully underwent abdominal surgery. Low-dose or modified-dose regimens may be administered under close clinical monitoring, but the effectiveness and bleeding risk of such protocols in cancer patients is an area that warrants further research.

*Supplementary video file associated with this article can be found in the online version of the journal.

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Anahtar sözcükler: Ekokardiyografi; fibrinolitik; malignite; obstrüktif mekanik protez kapak trombozu.