


CASE REPORT

Open Access



Three cases of diagnostic delay of type A acute aortic dissection

Takeshi Shimamoto^{1*} , Sanae Tomotsuka¹, Makoto Takehara¹ and Shinichi Tsumaru¹

Abstract

Background Diagnostic delay (DD) can be lethal when patients with type A acute aortic dissection (TAAAD). We report 3 cases of DD associated with TAAAD.

Case presentation Case 1 is a female in her sixties presenting with severe back pain. A CT scan was taken, and TAAAD with a thrombosed false lumen was suspected by the radiology technician. He did not successfully transfer his concern to the physicians and the patient was sent home. The next day, she was transferred to another hospital with a recurrence of the symptom, and the diagnosis of TAAAD was made with a CT scan there. Case 2 was an 87-year-old female who was transferred to our hospital because of a loss of consciousness and bruises on the forehead. CT scan was taken and the displaced intimal flap in her aortic arch was overlooked by the part-time physician almost at the end of his shift. The diagnosis of TAAAD was made by the radiologist. Case 3 was the 44-year-old male who did not have health insurance and experienced severe back pain a few days before the visit to our clinic. On that day, he went to the nearby hospital's emergency room, and only pain medication was prescribed. A few days later, a CT scan was taken at our hospital to investigate the cause of pyuria and the diagnosis of TAAAD was made.

Conclusion DD may be common and multifactorial in our practice. Physicians need to take every step to improve diagnostic accuracy.

Keywords Type A aortic dissection, Diagnostic delay, Diagnostic error

Background

Aortic dissections are associated with significant mortality and morbidity. They are caused by a tear in the intima of the aorta that extends into the media of the aortic wall. Blood flow through this tear leads to the formation of a false lumen bordered by the inner and outer layers of the media. Aortic dissections are classified by location and chronicity, with management strategies depending on the nature of the dissection. The Stanford method splits aortic dissections into type A and B, with type A dissections involving the ascending aorta [1].

Type A acute aortic dissection (TAAAD) is the most lethal vascular emergency. If left untreated, approximately 50% of patients die in the first 48 h. The mortality rate increases by 1–3% per hour [2]. Despite recent advances in diagnostic methods, misdiagnosis frequently occurs on initial evaluation in patients with symptoms mimicking those of acute myocardial infarction and other cardiovascular disorders [3]. However, with prompt diagnosis and treatment, the clinical outcome has been steadily improving, and the survival rate in 1 year has been reported as high as 90% [4]. Therefore, it is critical that the physician maintains a high clinical index of suspicion and utilizes a standardized algorithm to establish a prompt and accurate diagnosis of aortic dissection. We describe our experience of 3 cases of diagnostic delay (DD) with TAAAD.

*Correspondence:

Takeshi Shimamoto

takeshishimamoto@hamamatsuh.johas.go.jp

¹ Department of Cardiovascular Surgery, Hamamatsu Rosai Hospital, 25 Shogen-cho, Hamamatsu, Shizuoka 430-8525, Japan

Case presentation

Case 1

At 7 pm one day, a female in her sixties was transferred to our hospital by ambulance because of the sudden onset of back pain. Her systolic blood pressure was over 150. The past history was unremarkable except for hypertension. The electrocardiogram showed no abnormality, and serum troponin was negative. Her white blood cell count was 15,600/ μ L, and her C reactive protein (CRP) was negative. Her renal function was normal with an estimated glomerular filtration rate of 61. Coagulation and fibrinolysis tests were ordered for ruling out aortic dissection and pulmonary embolism. However, the results were not available because of the sample shortage. On that day, the resident doctor was supposed to examine the patient first, and then report to the senior doctor who was not specialized in the cardiovascular field. Computed tomography (CT) scan without contrast material was taken (Fig. 1). In our hospital, the images were taken 5-mm axial view, 5-mm sagittal view, 3-mm coronal view by 64-row, and 0.5-mm multidetector CT (Aquilion 64, Canon Medical Systems Corporation, Tochigi, Japan). Although there was no immediate CT report interpreted by radiologists during the night shift in our hospital, the radiology technician suspected the presence of aortic dissection with a thrombosed false lumen in ascending aorta, and kindly conveyed his suspicion to the resident doctor, not the senior doctor, modestly with words that there was the “thickened wall in the ascending aorta,” hoping that the resident would realize this is potentially the sign of aortic dissection. The technician prepared coronal and sagittal images of the ascending aorta as well so that they could deny the artifact. The resident doctor and his senior doctor knew the disease of TAAAD. However, neither the resident nor the senior doctors knew the typical CT image of TAAAD of the thrombosed false lumen and ruled out the diagnosis of the dissection because the false lumen did not displace the true lumen, which was the typical sign of TAAAD with the patent false lumen. At 9 pm, 2 h after the onset of the symptom, the doctors permitted her to go home without any medication and asked her to see the cardiologist the next morning. At 6 am of the next morning, she was taken to the other hospital in the same city emergently with a recurrence of the symptom, and a CT scan there confirmed the diagnosis of TAAAD.

Case 2

At 11 am of one day, an 87-year-old female was transferred to our hospital by ambulance with a bruise on the forehead. She told us that she was fallen on the floor of the bathroom for some hours. She was not able to tell us



Fig. 1 The axial, coronal, and sagittal views of the plain CT scan of case 1 from the top to the bottom. Note that difference in the contrast persisted throughout the ascending aorta (red arrows), indicating the presence of TAAAD with the thrombosed false lumen

how long she was left on the floor, presumably because of her age or because of true syncope she suffered from the event. Her white blood cell count was elevated as high as 15,800/ μ L, and C reactive protein was 5.02 mg/dL. Her history was remarkable with multiple admission of aspiration pneumonia. The CT scan showed no cerebral bleeding, small pericardial effusion, dilated ascending aorta twice as large as descending aorta at the level of bronchial bifurcation, and mild bilateral pneumonia of the dorsal lower lobe. The physician in charge was a part-time doctor, and he was supposed to leave soon. He examined the images of the CT scan by himself and permitted her to go back to the nursing care house because the only abnormality he recognized was mild pneumonia and its degree was not severe enough for admission. While she prepared herself to leave the hospital, the radiologist noticed the slightly calcified and displaced intimal flap in the aortic arch in the CT scan and took the patient back for the CT scan with contrast material, which revealed the presence of TAAAD with a patent

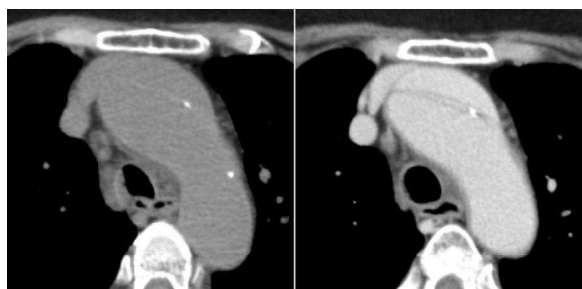


Fig. 2 The axial view of the plain (left) and contrasted (right) CT scan of case 2. Note the presence of a displaced and slightly calcified intimal flap in the plain CT scan, which was confirmed with contrast

false lumen (Fig. 2). At 1 pm, she underwent emergency replacement of ascending aorta with the Dacron graft.

Case 3

At 4 pm one day, a 44-year-old male with a body mass index of 45.7 experienced severe back pain a week before he visited our clinic. His history was remarkable with diabetes, hypertension, and dilatation of the ascending aorta as large as 4 cm. Soon after the onset of back pain, he visited the emergency room of a nearby general hospital, however, the in-charge physician only prescribed him analgesics. He did not order a CT scan presumably because he did not have insurance. The next day, he visited the nearby urologic clinic and found out that he had pyuria, proteinuria, elevated white blood cell count as high as 10,200/ μ L, and uncontrolled hypertension as high as 180/110. A few days later, because his back pain had not resolved, he was referred to our urology clinic with a tentative diagnosis of pyelonephritis refractory to antibiotics. The urologist in our clinic took a CT scan without contrast material, and our radiologist suspected the presence of TAAAD with the patent false lumen (Fig. 3). We confirmed his diagnosis of TAAAD with the CT scan with contrast material at 5 pm of the same day. We underwent semi-emergency total arch replacement.

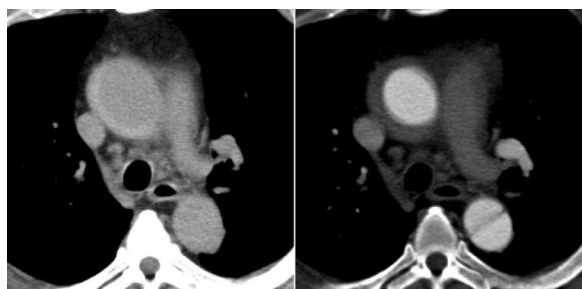


Fig. 3 The axial view of the plain (left) and contrasted (right) CT scan of case 3. Note the difference in the contrast in the ascending aorta, which was confirmed with contrast

Discussion

Every disease is associated with misdiagnosis and diagnostic delay with significant variances of frequency and interval until reaching the correct diagnosis [5]. In the setting of the emergency department, aortic dissection is rare, and misdiagnosis and DD of aortic dissection are common, occurring in 14.1–39.4% of TAAAD patients [6] and are associated with worse outcomes [7]. In IRAD, DD was reported to be associated with a history of previous cardiac surgery, presentation without abrupt or any pain, and initial presentation to a nontertiary care hospital [8].

The diagnosis of TAAAD can be made by transthoracic or transesophageal echocardiography, CT, or magnetic resonance imaging (MRI). Although the transthoracic echocardiography is very useful in diagnosing aortic regurgitation, pericardial tamponade and cardiac wall motion abnormalities associated with coronary malperfusion caused by TAAAD, the value of transthoracic echocardiography is limited in patients with abnormal chest wall configuration, narrow intercostal spaces, obesity, pulmonary emphysema, and in patients on mechanical ventilation [9]. The transesophageal echocardiography is highly accurate for the detection of TAAAD; however it requires esophageal intubation, thus highly invasive. MRI is highly accurate imaging modality with a sensitivity of 95–98% and specificity of 94–98% for detecting aortic dissection [10]. However, its use in the emergency setting is very limited because of the limited access and cost. Moreover, it is time-consuming. Therefore, CT scan with contrast material is of paramount use because of relatively good access, acceptable cost, and good diagnostic accuracy. Although most of the diagnosis of aortic dissection was made based on the images of CT scan with contrast material, and the diagnosis was more likely to be missed or delayed when patients presented with atypical symptoms and physicians were not willing to infuse contrast material for potential renal damage and radiation.

The visualization of an intimal flap is the characteristic feature of TAAAD. If there is flow within both lumina, typical imaging features are probably present in the images of CT scan with contrast material. If the false lumen is thrombosed or there is no intimal tear to permit flow through the false lumen, a visible intimal flap may not be present. Secondary signs of TAAAD include an intramural or periaortic acute thrombus, which manifests as a high-attenuation cuff or crescent on the images of CT scan without contrast material as in our case 1. Other conditions that can reduce the diagnostic accuracy of the intimal flap include atypical configurations of the flap, such as seen with short dissections or with multiple false channels, in which the flaps are complex [11]. It is very important to pay attention to the small calcified masses,

if any, located on the displaced flap, which renders physician accurate diagnosis of TAAAD with patent false lumen, even with CT scan without contrast material.

Every error in medical decision-making reportedly can be classified into three types: non-fault errors, system errors, and cognitive errors [12]. Non-fault errors include cases where the illness is silent, masked, or presented in such as an atypical fashion that divines the correct diagnosis. System errors reflect latent flaws in the health care system, including weak policies, poor coordination of care, inadequate training or supervision, defective communication, and the many system factors that detract from optimal working conditions such as stress, fatigue, and distraction. Cognitive errors are those in which the problem is inadequate knowledge faulty data gathering, inaccurate clinical reasoning, or faulty verification.

All the cases in this article were with diagnostic delay, not misdiagnosis. In our cases of diagnostic delay, every case has a component of non-fault error because the illness presentation is less severe compared with typical tearing pain of TAAAD or unstable hemodynamics. System error was more evident in case 1 where the radiology technician was almost confident about the presence of TAD, and poor communication between the radiology technician and doctors hampered the re-CT scan with contrast material or at least hospital admission for observation. The lack of knowledge of TAD with thrombosed false lumen is also attributable to system error as well. Case 3 was the case in which the definitive diagnostic step was delayed. According to the history the patient had given, the fact that he did not have health insurance might be a sufficient excuse for the physician not to take a CT scan during the emergency visit to the first hospital. Even in this circumstance, when the patient presented with severe back pain, the physician should have paid attention to the history of 4 cm ascending aorta dilatation since normal proximal ascending aorta was reported as 3.0 ± 0.4 cm [13].

Cognitive error was evident in case 2 in which the physician noticed the presence of aspiration pneumonia, but not the difference of contrast in the ascending aorta and size between ascending and descending aorta. This overlook might be influenced by the fact that the physician in charge was a part-time doctor and the timing of CT scan was the end of his working hour.

There might be several solutions to improve the diagnostic accuracy of TAAAD; careful medical examination including the characteristics of pain that patients experienced, improvement of communication within the medical team, timely and adequate education and training of TAAAD management, mutual assisting system between full-time and part-time physician, and so on to reduce diagnostic errors. The use of aortic dissection detection

risk score [14] and echocardiography [15, 16] might be helpful to prevent misdiagnosis and DD. Either way, every single step should be taken to reduce diagnostic errors to save the lives of patients with TAAAD.

Conclusions

TAAAD remains the life-threatening cardiovascular disorder facing physicians in the current era. A high clinical suspicion is crucial for accurate and prompt diagnosis. Aortic dissection is often misdiagnosed or diagnosed with significant delay, particularly when accompanied by less severe symptoms. A multidisciplinary and systematic approach with optimal teamwork and good communication is crucial to the diagnosis and treatment of TAAAD to improve the clinical outcome.

Abbreviations

TAAAD	Type A acute aortic dissection
DD	Diagnostic delay
CT	Computed tomography
MRI	Magnetic resonance imaging

Acknowledgements

Not applicable

Author contributions

TS and ST conceptualized the ideas of the manuscript. TS, ST, and MT collected the data. TS, ST, MT, and ST wrote the manuscript.

Funding

Not applicable.

Availability of data and materials

The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

The need for ethics approval was waived due to the retrospective case report. Consent for publication was taken from cases 2 and 3. Consent of publication was not able to be taken from case 1, and the committee of ethics and clinical research of Hamamatsu Rosai hospital waived the consent under the condition of concealing the personal information including the patient's age and timing of hospitalization.

Competing interests

The authors declare that they have no competing interests.

Received: 31 July 2023 Accepted: 19 January 2024

Published online: 29 January 2024

References

1. Flower L, Arrowsmith JE, Bewley J, Cook S, Cooper G, Flower J et al (2023) Management of acute aortic dissection in critical care. *J Intensive Care Soc* 24:409–418
2. Jassar AS, Sundt TM 3rd (2019) How should we manage type A aortic dissection? *Gen Thorac Cardiovasc Surg* 67:137–145
3. Dixon M (2011) Misdiagnosing aortic dissection: a fatal mistake. *J Vasc Nurs* 29:139–146

4. Nienaber CA, Eagle KA (2003) Aortic dissection: new frontiers in diagnosis and management: Part II: therapeutic management and follow-up. *Circulation* 108:772–778
5. Miller AC, Cavanaugh JE, Arakkal AT, Koeneman SH, Polgreen PM (2023) A comprehensive framework to estimate the frequency, duration, and risk factors for diagnostic delays using bootstrapping-based simulation methods. *BMC Med Inform Decis Mak* 23:68
6. Lovatt S, Wong CW, Schwarz K, Borovac JA, Lo T, Gunning M et al (2022) Misdiagnosis of aortic dissection: a systematic review of the literature. *Am J Emerg Med* 53:16–22
7. Pourafkari L, Tajili A, Ghaffari S, Parvizi R, Chavoshi M, Kolahdouzan K et al (2017) The frequency of initial misdiagnosis of acute aortic dissection in the emergency department and its impact on outcome. *Intern Emerg Med* 12:1185–1195
8. Harris KM, Strauss CE, Eagle KA, Hirsch AT, Isselbacher EM, Tsai TT et al (2011) Correlates of delayed recognition and treatment of acute type A aortic dissection: the International registry of acute aortic dissection (IRAD). *Circulation* 124:1911–1918
9. Cigarroa JE, Isselbacher EM, DeSanctis RW, Eagle KA (1993) Diagnostic imaging in the evaluation of suspected aortic dissection. Old standards and new directions. *N Engl J Med* 328:35–43
10. Shiga T, Wajima ZI, Apfel CC, Inoue T, Ohe Y (2006) Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: systematic review and meta-analysis. *Arch Intern Med* 166(13):1350–1356
11. Fisher ER, Fau SE, Godwin 2nd JD, Otto CMF (1994) Acute aortic dissection: typical and atypical imaging features. *Radiographics* 14(6):1263–1271
12. Graber M, Gordon R, Franklin N (2002) Reducing diagnostic errors in medicine: what's the goal? *Acad Med* 77:981–992
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 16:233–270
14. Nazerian P, Mueller C, Soeiro AM, Leidel BA, Salvadeo SAT, Giachino F et al (2018) Diagnostic accuracy of the aortic dissection detection risk score plus D-dimer for acute aortic syndromes: the ADVISED prospective multicenter study. *Circulation* 137:250–258
15. Evangelista A, Maldonado G, Gruosso D, Gutierrez L, Granato C, Villalva N et al (2019) The current role of echocardiography in acute aortic syndrome. *Echo Res Pract* 6:R53–R63
16. Kaeley N, Gangdev A, Galagali SS, Kabi A, Shukla K (2022) Atypical presentation of aortic dissection in a young female and the utility of point-of-care ultrasound in identifying aortic dissection in the emergency department. *Cureus* 14:e27236

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Parietal pleural hematoma: plausible aortic dissection in an octogenarian on multiple antiplatelets, coumadin and oral steroids

Hideyuki Katayama · Takeshi Shimamoto ·
Genichi Sakaguchi · Shinichi Ijuin ·
Tatsuhiko Komiya

Received: 9 January 2013 / Accepted: 19 April 2013 / Published online: 1 May 2013
© The Japanese Association for Thoracic Surgery 2013

Abstract An 84-year-old male on oral steroids, coumadin and multiple antiplatelets for stented superficial femoral artery presented to our hospital with chest oppression. His CT scan showed cardiac tamponade with periaortic hematoma. At first, sealed rupture of aortic dissection with thrombosed false lumen was suspected. However, delayed enhancement view revealed extravasation of contrast agent, which appeared to drain into the pericardium or pericardial space. Emergency thoracotomy revealed normal aorta with several small spurting vessels of pulmonary side of the pericardium. To the best of our knowledge, this is the first reported case in the literature of a parietal pleural hematoma without known cause such as malignancy or hematologic disorders.

Keywords Parietal pleural hematoma · Aortic dissection · Steroid · Antiplatelet

Introduction

Parietal pleural hematoma is a rare pathology, except for hemopericardium concomitant with hemophilia [1]. We report a case of parietal pleural hematoma in an octogenarian, which might have resulted from multiple antiplatelets, coumadin and oral steroids.

Case

A slightly demented 84-year-old man living in a nursing home presented at our emergency room with chest oppression. He had no past history or clinical signs of hematological disease, including hemophilia. He was on 5 mg of steroids for rheumatoid arthritis, 1 mg of coumadin for atrial fibrillation, three kinds of antiplatelets (25 mg clopidogrel, 200 mg sarpogrelate, and 40 mg cilostazol) because of frequently repeated restenosis following percutaneous transluminal angioplasty for arteriosclerosis obliterans. At the time of presentation, his blood pressure was 77/55 mmHg; heart rate 96 beats/min (irregular); SpO₂ 93 % (room air); and body temperature 36.7 °C. His physical examination showed coldness of the extremities along with sweating. Auscultation findings were normal and his transthoracic echocardiogram showed normal function of left ventricular. Chest radiograph showed an apparently enlarged mediastinum. His hemoglobin level was 116 g/L; white blood cell count, $7.7 \times 10^9/L$; and platelet count, $12.4 \times 10^9/L$. Although his activated partial thromboplastin time was normal at 32.2 s, his prothrombin time was slightly prolonged at 17.1 s (normal prothrombin time <14.0), and his international normalized ratio (INR) was 1.44. D-dimer was slightly increased at 4.8 µg/mL. Enhanced computed tomography revealed cardiac tamponade and hematoma located in the periaortic arch. At first, sealed rupture of aortic dissection (Stanford type A) with thrombosed false lumen was suspected (Fig. 1). However, delayed enhancement view revealed extravasation of contrast agent, which appeared to drain near the left atrial appendage into the pericardium or pericardial space (Fig. 2). Moreover, no evidence of increase in the aortic diameter was found; this strange occurrence made us doubt our initial diagnosis. Because the hemodynamic state was unstable with clinical features of

H. Katayama · T. Shimamoto (✉) · G. Sakaguchi · S. Ijuin ·
T. Komiya
Department of Cardiovascular Surgery,
Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki,
Okayama 710-8602, Japan
e-mail: ts12295@kchnet.or.jp

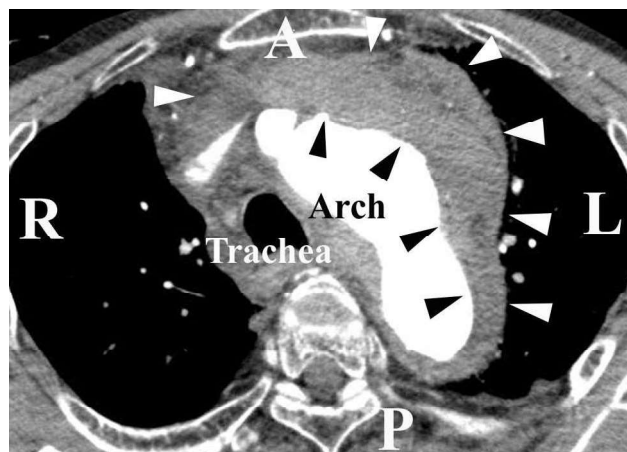


Fig. 1 Enhanced computed tomography scan of the chest (axial view). Periaortic hematoma (surrounded by *arrows*) and clinical symptoms misled us to the tentative diagnosis of aortic dissection classified as Stanford A with thrombosed false lumen. *A* anterior, *P* posterior, *L* left, *R* right, *Arch* aortic arch

cardiac tamponade, emergency operation was performed via median sternotomy. A large periaortic and pericardial hematoma was observed, but pericardial effusion was serous and approximately 100 mL, which indicated that the pathology of the case is different from a hemopericardium. The aorta itself was normal, and apparently not dissected. On detailed observation of the pericardium as well as the heart and aorta, no bleeders were found except several small spurting vessels of pulmonary side of the pericardium, which were controlled with small hemostasis clips and electrocautery. Postoperatively, the patient's anticoagulants were discontinued, and he became stable without any bleeding complication. Unfortunately, he died 46 days after the operation due to sepsis from enterocolitis.

Discussion

Parietal pleural hematoma is a rare pathology, and to the best of our knowledge, this is the first case without known cause such as malignancy or hematologic disorders in the literature. As a consequence of increasing number of atherosclerotic diseases and dramatic technical improvements in catheter intervention, more and more antiplatelet drugs are prescribed for patients who receive intraluminal stenting. In fact, guidelines of TASC II [2] recommend use of multiple antiplatelets as adjuvant pharmacotherapy for maintaining patency. However, there is so far no reliable method for the therapeutic monitoring for their effectiveness, and the use of dual antiplatelets was reported to increase the frequency of bleeding complications compared with single [3]. Although the risks of triple antiplatelet

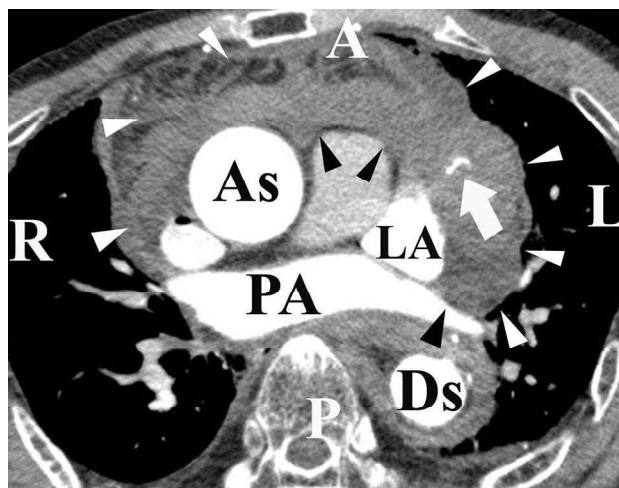


Fig. 2 Enhanced computed tomography scan of the chest (axial view). The *arrow* shows an extravasation of contrast agent near the left atrial appendage. *As* ascending aorta, *LA* left atrial, *PA* pulmonary artery, *Ds* descending aorta

therapy and coumadin, as in the presented case, have never been estimated in the literature, it has been reported with significant size of patient cohort in randomized controlled study that compared with dual, triple antiplatelet therapy shows no significant difference in major adverse events including bleeding [4, 5]. Based on these studies, the interventionist might have prescribed triple antiplatelets. However, a meta-analysis evaluating the use of dual antiplatelet with or without coumadin [6] shows the increasing risk of bleeding was associated with use of coumadin compared with dual antiplatelet alone. Considering this analysis, although INR of the present case was below the therapeutic level, the risk of bleeding should be estimated as high.

In addition, several factors may have contributed to the pathogenesis of parietal pleural hematoma in this case: old age, which, in general, is frequently associated with tissue fragility and enhanced adverse effect of any medical agent or steroids. With regard to the steroids, although no large-scale study has shown a direct connection between steroids and bleeding complications, a strong association between purpura, subdermal bleeding, and corticosteroids has been reported [7], indicating that steroids might cause soft tissue fragility leading to a certain degree of bleeding.

Conclusions

Physicians are facing a dilemma between the patency of stented vessels and bleeding complication. It is necessary to take both risks and benefits of the drugs into consideration, and risk optimization is needed for individual cases.

References

1. Ghosh N, Teefy P, Laudenbach L, Rivard GE. Cardiac tamponade in a patient with moderate hemophilia A and factor VIII inhibitors. *Can J Cardiol*. 2006;22:73–5.
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg*. 2007;33(Suppl 1):S1–75 Epub 2006 Nov 29.
3. Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. *Stroke*. 2008;39:1740–5 Epub 2008 Apr 3.
4. Sakurai R, Koo BK, Kaneda H, Bonneau HN, Nagai R. Cilostazol added to aspirin and clopidogrel reduces revascularization without increases in major adverse events in patients with drug-eluting stents: a meta-analysis of randomized controlled trials. *Int J Cardiol*. 2012 Jun 22. [Epub ahead of print].
5. Choi YH, Suh SH, Choi JS, Kim CS, Sim DS, Bae EH, et al. Triple vs. dual antiplatelet therapy in patients with acute myocardial infarction and renal dysfunction. *Circ J*. 2012;76(10):2405–11.
6. Andrade JG, Deyell MW, Khoo C, Lee M, Humphries K, Cairns JA. Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/stenting: a systematic review and meta-analysis. *Can J Cardiol*. 2013;29(2):204–12.
7. Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY. Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ*. 1990;300:1548–51.