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Abdominal aortic aneurysm complicated by descending thoracic aortic dissection in a patient with TGFBR1 mutation

Chen Huang[1] and Wenwen Zhang[2*]

Abstract

Background We described a case of abdominal aortic aneurysm complicated by type B thoracic aortic dissection, in whom molecular analysis revealed a pathogenic *TGFBR1* missense mutation.

Case presentation A 36-year-old woman was admitted to our hospital with sudden onset of back pain. Computed tomography angiogram demonstrated descending aortic dissection extending into the abdominal aorta aneurysm. Whole-exome sequencing and subsequent Sanger sequencing confirmed a pathogenic mutation in the *TGFBRI* gene (NM_004612.4: c.605C > T; p.Ala202Val). She refused to receive surgery and died one month later.

Conclusion To our knowledge, this is the first documented case of the *TGFBR1* gene mutation who suffered from abdominal aortic aneurysm complicated by descending thoracic aortic dissection. Her rapid death underscores the importance of timely intervention in *TGFBR1* mutation-positive patients.

Keywords Whole-exome sequencing, *TGFBR1*, Mutation, Descending aortic dissection, Abdominal aortic aneurysm

Introduction

Thoracic aortic dissection represents a potentially life-threatening condition characterized by medial layer degeneration of the thoracic aorta. There is a growing understanding that genetic factors predispose to aortic dissection [1]. To date, more than a dozen of genes have been identified to account for hereditary aortic dissection, due to in large part to the advancement of high-throughput sequencing and family screening [2]. However, clinical manifestations and disease severity vary significantly in patients harboring distinct genetic mutations [3].

TGFBR1 is among the first widely recognized aortic dissection causal genes [4]. Mutations in *TGFBR1* have been described to affect the transforming growth factor beta (TGF-β) signaling, leading to a range of clinical manifestations, known as Loeys-Dietz syndrome (LDS) [5]. LDS is typically characterized by the triad of bifid uvula or cleft palate, hypertelorism, and arterial aneurysms or tortuosity. LDS is further divided into six subtypes based on distinct mutated genes of TGF-β signaling, including type 1 (*TGFBR1*), type 2(*TGFBR2*), type 3 (*SMAD3*), type 4 (*TGFB2*), type 5(*TGFB3*), and type 6 (*SMAD2*). Aortic phenotypes of individuals affected by *TGFBR1* mutation are mainly thoracic aortic aneurysms and type A aortic dissections, whereas other forms are relatively scarce [6]. Here we described a rare case of abdominal aortic aneurysm complicated by type B thoracic aortic dissection, in whom molecular analysis revealed a pathogenic *TGFBR1* missense mutation.

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Case presentation

A 36-year-old woman presented to our hospital with sudden onset of back pain. The patient had no significant past medical history. She denied any history of smoking or high blood pressure. Physical examination revealed that blood pressure was 122/71 mmHg and pulse 69 beats/min. Evaluation with computed tomography angiogram (CTA) demonstrated descending aortic dissection originating distal to the origin of the left subclavian artery and extending into the abdominal aorta aneurysm measuring up to 62 mm x 58 mm, accompanied by pleural effusion (Fig. 1). Echocardiography examination revealed no cardiac defects. Laboratory findings included the following: hemoglobin, 74 g/L; white blood cell count, 8.5×10^9/L; platelet count, 287×10^9/L; C-reactive protein, 147 mg/L; and percentage of neutrophil, 83.1%. She had no remarkable family history of aortic aneurysm or dissection or sudden death. Apart from bifid uvula, dysmorphic features of connective tissue disorder were not notable. Screening brain magnetic resonance imaging and angiography excluded intracranial aneurysm and arterial tortuosity.

After admission, she developed fever to a maximum of 39.6C. She was given analgesic pump analgesia and intravenous antibiotics therapy. Her symptoms of pain and fever gradually subsided. CTA reexamination demonstrated no progression of aortic lesions. The patient was advised to receive surgical operation. She preferred to wait, and was discharged from hospital several days later. Unfortunately, a phone follow-up at one month revealed sudden death of the patient.

In light of early-onset age and pronounced aortic pathology, underlying genetic defect of the patient was suspected. Due to high genetic heterogeneity of inherited aortopathy, whole-exome sequencing of the patient was conducted as per previously reported procedural [7]. Sequence data generated by WES had an average coverage of 152-fold, with 98% of target bases covered by 20 or more independent reads. The stepwise filtering process conducted revealed an uncommon pathogenic heterozygous missense mutation of the *TGFBR1* gene (NM_004612.4: c.605C > T; p.Ala202Val), which was validated in the Sanger sequencing (Fig. 2). The mutation was absent in common databases (1000G, ESP, ExAC) and predicted pathogenic by bioinformatic softwares SIFT, PolyPhen_2 and MutationTaster. Besides, it had been reported in a 26-year-old patient with thoracic aortic aneurysm and was included in the HGMD database [8]. Taken together, the identified mutation was responsible for the severe aortic phenotype of our patient. The

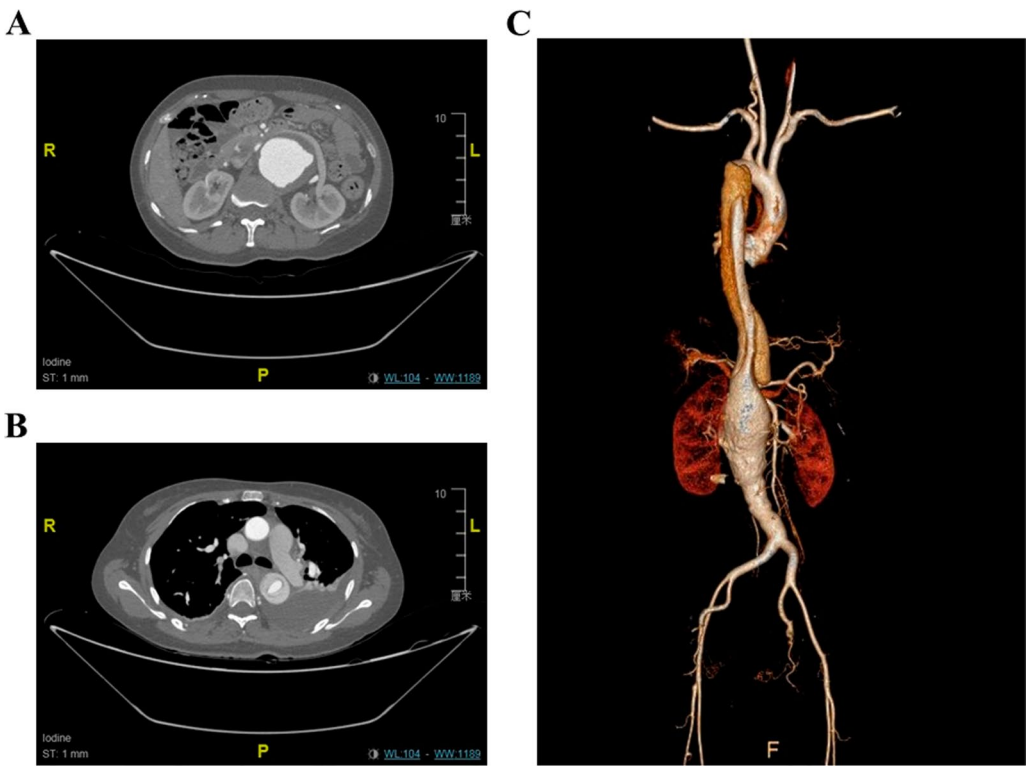

Fig. 1 (**A**) Computed tomography angiography of aneurysmal abdominal aorta and (**B**) Type B thoracic aortic dissection with pleural effusion. (**C**) Three-dimensional reconstruction of aorta demonstrating coexistence of thoracic aortic dissection and abdominal aortic aneurysm

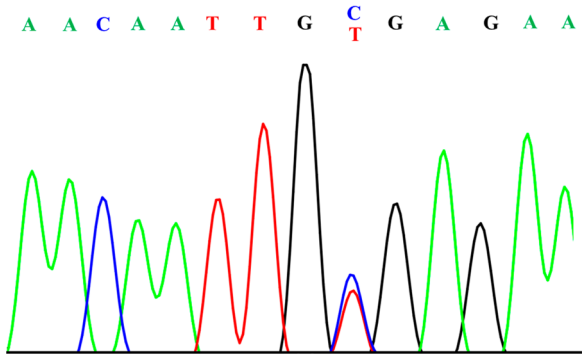

Fig. 2 Sequence sequencing confirmed the *TGFBR1* mutation (c.605C > T; p.Ala202Val)

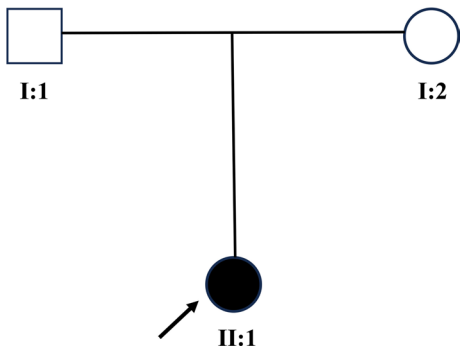

Fig. 3 Pedigree; Proband is indicated with an arrow. Square symbols, males; round symbols, females; filled symbols, affected; unfilled symbols, unaffected

mutation was not found in any of her unaffected parents, showing it is a de novo mutation (Fig. 3).

Discussion

LDS is an autosomal dominant genetic disorder associated with thoracic aortic aneurysm and dissection. It is secondary to aberrations in the TGF-β signaling pathway [5]. Previous studies have revealed that some specific gene mutation-carriers have characterized clinical manifestations. For example, *SMAD3* mutations are often associated with early-onset osteoarthritis [9]. However, considerable inter- and intra-genetic variability of phenotypes are observed among LDS patients. Dysmorphic facial features (hypertelorism, bifid uvula, cleft palate) may be present or absent. Abnormal vascular features include aneurysms and dissections throughout the arterial tree and arterial tortuosity [5]. Accurate diagnosis of LDS is therefore challenging solely based on clinical traits, whereas molecular analysis could provide unparalleled diagnostic information. Due to its unbiased assessment of all coding genes, WES emerges a valuable tool in the diagnosis of LDS with multiple disease-causing genes. In this study, early onset of marked aortic pathologies accompanied by minor facial features prompted us to raise the suspicion of hereditary aorta-related syndrome, even in the absence of a family history. WES identified a pathogenic *TGFBR1* mutation and thus final diagnosis of LDS was confirmed.

TGFBR1 encodes a transmembrane serine/threonine kinase, which is comprised of a cysteine-rich extracellular domain, a single transmembrane region, and a cytoplasmic juxtamembrane region, including a conserved glycine-serine-rich (GS) domain adjacent to the kinase domain. The p.Ala202Val mutation results in the substitution of a alanine with valine in the conserved GS domain of *TGFBR1*, which might hamper phosphorylation of the GS domain and inhibit signal transduction. This alanine is highly evolutionarily conserved from humans down to zebrafish. The same mutation was once reported in a 26-year-old male presented with thoracic aortic aneurysm and some systemic features indicative of Marfan syndrome [8]. His father died of acute aortic dissection at the age of 40. He underwent David's procedure at the age of 18. Apart from thoracic aorta, dilation of the coronary arteries, brachiocephalic trunk, and pulmonary artery were also observed. These findings add to the evidence that the p.Ala202Val mutation of *TGFBR1* is pathogenic and accounts for the aortic lesions in both cases. This also highlights the clinical heterogeneity of *TGFBR1* mutations, even within the same mutation.

Documented abdominal aortic aneurysm in LDS is relatively rare. In a large cohort of TAAD caused by genetic alterations, the first aortic event included an acute thoracic aortic dissection (214 type A, 66 type B, and 25 unspecified) or elective surgical repair of an aortic aneurysm (n = 151) with median age of 36 years. Only two of the first elective aortic aneurysm repairs involved the abdominal aorta and the underlying genetic defects were not specified. Of the type B thoracic aortic dissection, only three were found to harbor *TGFBR1* mutations [6]. This is the first clinical report of a patient with a *TGFBR1* mutation presenting with concurrent abdominal aortic aneurysm and type B thoracic dissection. Aneurysms in LDS patients have a higher propensity for dissection or rupture than those in Marfan syndrome [1]. A recent study revealed that freedom from all causes of mortality rate was similar between the LDS and Marfan patients [10]. Given its more malignant natural history, early surgical repair and close monitoring are recommended. The patient in our report hesitated to receive operation and soon passed away suddenly, further emphasizing the importance of timely intervention.

Conclusion

In this case, genetic screening for our patient led to the diagnosis of LDS syndrome. To our knowledge, this is the first documented case of the *TGFBR1* gene mutation who suffered from abdominal aortic aneurysm complicated by descending thoracic aortic dissection. Our case underscores the importance of timely intervention in *TGFBR1* mutation-positive patients.

Author contributions

WWZ conceived the manuscript, collected patient data, and made the final edits of the report. CH performed the genetic testing and wrote the first draft of the report.

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Availability of data and materials

The data and materials that support the findings of this study are available on request from the corresponding author [WWZ]. The data are not publicly available due to them containing information that could compromise research participant privacy/consent.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the institutional review board, the Second Affiliated Hospital of Nanchang University. After explanation of the possible consequences of the study, written informed consent was obtained from all study participants.

Consent for publication

The husband of the patient gave full permission for the publication of his wife's case details and radiologic information.

Competing interests

None declared.

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References

1. Pinard A, Jones GT, Milewicz DM (2019) Genetics of Thoracic and Abdominal Aortic Diseases. Circ Res 124(4):588–606
2. Milewicz DM et al (2014) Successes and challenges of using whole exome sequencing to identify novel genes underlying an inherited predisposition for thoracic aortic aneurysms and acute aortic dissections. Trends Cardiovasc Med 24(2):53–60
3. Ostberg, N.P., et al., The Genetics of Thoracic Aortic Aneurysms and Dissection: A Clinical Perspective. Biomolecules, 2020. 10(2).
4. Loeys BL et al (2005) A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 37(3):275–281
5. Gouda P et al (2022) Clinical features and complications of Loeys-Dietz syndrome: A systematic review. Int J Cardiol 362:158–167
6. Regalado ES et al (2022) Comparative Risks of Initial Aortic Events Associated With Genetic Thoracic Aortic Disease. J Am Coll Cardiol 80(9):857–869
7. Zhang W, Huang C, Zhou W (2021) Rapid identification of a pathogenic variant of PROS1 in a thrombophilic family by whole exome sequencing: A case report. Medicine (Baltimore) 100(52):e28436
8. Poninska JK et al (2016) Next-generation sequencing for diagnosis of thoracic aortic aneurysms and dissections: diagnostic yield, novel mutations and genotype phenotype correlations. J Transl Med 14(1):115
9. Zhang W et al (2015) A Novel Mutation of SMAD3 Identified in a Chinese Family with Aneurysms-Osteoarthritis Syndrome. Biomed Res Int 2015:968135
10. Seike, Y., et al., The differences in surgical long-term outcomes between Marfan syndrome and Loeys-Dietz syndrome. J Thorac Cardiovasc Surg, 2022. 164(1): p. 16–25 e2.

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