Cerebral Hemorrhage following Aspirin Administration in a Patient with Delayed Diagnosis of Kawasaki Disease

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Research Article

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Abstract

Background: Kawasaki disease (KD) is an acute vasculitis of childhood, which has a typical coronary artery aneurysm complication. Cerebral arteries are usually spared from the disease process. Intracranial aneurysms and hemorrhage strokes are rarely reported.

Case presentation: A 12-year-old boy presented with a sudden disturbance of consciousness caused by an intracranial aneurysm's rupture. Through later clinical manifestations and echocardiography, we found that he had been in Kawasaki disease 20 days before the hospitalization.

Conclusions: This case shows a close link between Kawasaki disease and cerebral aneurysm complication. It arouses more attention to applying aspirin appropriately in the perioperative intracranial surgery period of KD patients. For febrile patients with high-risk factors for KD, echocardiograms may be performed before day 5 of fever.

Introduction

Kawasaki disease is a systemic vasculitis of unknown etiology, predominantly affecting infants and young children. The coronary aneurysm is the significant sequela of KD. Patients with severe coronary artery involvement may also develop aneurysms of other medium-sized arteries. Common sites include the axillary, subclavian, brachial, femoral, and iliac arteries.[1] Arterial strokes are rarely reported. Only 5 cases have been reported on hemorrhagic stroke as a possible complication of KD to date.[2–6] Here, we report a case of Kawasaki disease with an intracranial aneurysm. In our case, the intracranial aneurysm developed more rapidly than the coronary aneurysm. The consequence of intracranial aneurysm in this patient is more severe than that in the patients described in the previous reports.

Case Presentation

A 12-year-old boy presented to the emergency department with a chief complaint of a sudden disturbance of consciousness for eight hours. Upon admission, he was in a coma. The vital signs were body temperature 37.3°C, heart rate 120/min, respiratory rate 30/min, and blood pressure 104/78 mmHg. The light reflexes of both pupils were prompt, and his pediatric Glasgow Coma Scale score was 7. The blood test showed no anemia or thrombocytopenia. Coagulation spectrum examination showed no abnormal clotting function. He had normal electrolyte levels. Blood biochemistry revealed normal liver and kidney function. Emergency head CT revealed the brainstem occupying, supratentorial ventricle dilatation, bilateral lateral ventricle hemorrhage cast. The head MRI findings suggested that the right vertebral artery aneurysm should be considered first (Fig. 1).

After an urgent lateral ventriculoperitoneal shunt, the patient recovered consciousness, and his condition kept stable. To make a definite diagnosis, a cerebrovascular MRI was performed on day 3, which showed the right vertebral artery V5 segment aneurysm (Fig. 2). After anti-infection, the patient kept having high fever repeatedly, with a peak temperature of up to 39.8 ℃. Kawasaki disease was suspected, and a transthoracic echocardiography examination was performed on day 5. It showed the diameter of the left coronary artery was 0.44 cm (Z score[7], 3.10) (Fig. 3a), and the right coronary artery was 0.40 cm (Z score, 2.77). The diameter at the beginning of the circumflex coronary artery was 1.07 cm (Z score, 17.36) (Fig. 3b), and the anterior descending artery was 0.52 cm (Z score, 6.89) (Fig. 3c). We found a hyperechoic mass at the intersection of the anterior descending branch and the circumflex branch, and the size was about 0.81 cm ×0.50 cm (Fig. 3d). Venous ultrasound revealed right iliac vein thrombosis. There were no abnormal findings on B-mode ultrasonography of the liver, gallbladder, pancreas, spleen, and kidney. No abnormal findings on vascular ultrasound of vessels of the neck and abdomen. Ferritin level was 151.9 μg/L.

We inquired about the patient's medical history again. He had a history of fever about 20 days before admission. After repeated inquiries, his parents recalled that he had fingers' desquamation but could not remember when exactly it appeared. There was no other clinical manifestation consistent with KD, also no personal or family history of KD. So, he didn't get a KD diagnosis at that time and hadn't received aspirin or immunoglobulin. After we found his vascular lesions, we retrospectively analyzed his medical history 20 days ago and believed that he had KD at that time. Then low-molecular-weight heparin (LMWH) and oral aspirin (3mg/kg/day) were administered, with intravenous immunoglobulin (IVIG) at a dose of 2g/kg/day. Methylprednisolone was also used for the anti-inflammatory effect.

The patient developed a disturbance of consciousness on day 8. Emergency head CT showed a new intracranial hemorrhage. We stopped LMWH and aspirin then. Coagulation spectrum examination showed that activate partial thromboplastin time was 30.6 s, plasma D-dimer 0.70 mg/L, Fibrinogen 3.75 g/L, International standardization ratio 1.15, and prothrombin time 13.8 s.

A second surgery named "posterior cranial fossa aneurysm clamping + intracranial hematoma removal + bilateral partial tonsillectomy decompression + extraventricular drainage" was performed. During the operation, a giant aneurysm originated from the right vertebral artery was found, but the distal end of the aneurysm cannot be clipped. Eventually, despite the emergency rescue efforts, the patient died three days after the second surgery. Figure 4 describes the timeline of clinical features, investigation, and treatment of the case report.

Discussion

Intracranial aneurysms are rare in the pediatric population. The natural history of pediatric aneurysms is quite different from that of the adult population. In children, there are some factors to consider, including (1) cerebral arteriovenous malformations, (2) extracellular matrix and connective tissue disorders, and (3) other associated medical conditions such as sickle cell anemia, tuberous sclerosis, and polycystic kidney disease.[8] Few case reports of coronary and intracranial aneurysms coexisting in the same patient have been previously reported.[9, 10] In our patient, the intracranial aneurysm progressed during his

hospitalization. We found no other organ damage, and he had no other specific diseases or family medical history. Our patient's intracranial aneurysm seems to be more closely linked to KD.

Kawasaki disease is a systemic vasculitis of childhood. A few studies have suggested that asymptomatic cerebral vasculitis might be more common than initially thought.[11] Some cerebrospinal fluid parameters such as TNF-α, IL-6, PTX3, and sTNFR1 are likely to help distinguish cerebral involvement in KD children.[12, 13] The combination of cerebral aneurysm and KD was first reported in 2007. So far, only 5 cases have been reported on hemorrhagic stroke as a possible complication of KD.[2–6] We summarize cases published in English or Chinese (Table 1). In three cases, cerebral artery aneurysms were observed, and the patients had surgical operations.[3, 4, 6] The rupture of aneurysms occurred from 7 months to 9 years after KD onset.[3, 4] Two of them had a good recovery, and one had left hemiparesis. In two cases, no cerebral artery aneurysm was observed. Still, the clinical manifestations of intracranial hemorrhage were quite typical. After sedation, hemostasis, and lowering intracranial pressure, the children recovered quickly. In our patient, the aneurysm rupture developed only about 20 days after the onset of Kawasaki disease, located at the basilar artery and the vertebral artery, indicating a more plausible causal relationship and more severe result than in the patient described in the previous reports.

The diagnosis of KD rests on the identification of principal clinical findings. According to the guidelines of the American Heart Association (AHA)[14], classic KD is diagnosed in the presence of fever for at least 5 days together with at least 4 of the 5 following principal clinical features: (1) changes of lips or oral mucosa (2) conjunctivitis (3) rash (4) changes to extremities (5) cervical lymphadenopathy. The diagnosis of incomplete KD should be considered in any infant or child with prolonged unexplained fever, 2 or 3 of the principal clinical findings, and compatible laboratory or echocardiographic results. If coronary artery abnormalities are detected, the diagnosis of KD is considered confirmed in most cases. In our case, the patient had persistent fever and changes in the peripheral extremities. The patient and his parents couldn't recall any symptoms of rash, conjunctivitis, changes of lips or oral mucosa in the fever history, which increases the difficulty of diagnosis to a certain extent. Not until the echocardiography showed dilatation in both the right coronary and the left coronary artery on day 5, did we make a definite diagnosis of incomplete KD. In European consensus-based recommendations, KD diagnosis and treatment should not be delayed if coronary artery aneurysms or coronary dilation are present.[15] The experts of Single Hub and Access point for pediatric Rheumatology in Europe acknowledge that the requirement for fever ≥ 5 days may lead to delayed treatment. It's acknowledged that diagnosing KD in patients with incomplete clinical criteria relies on a high index of suspicion. In these situations, early echocardiography is recommended.[15] There is no doubt that echocardiography can help early diagnosis and treatment of such patients. The initial echocardiogram should be performed as soon as the diagnosis is suspected.[14] For patients with high suspicion of KD, such as unexplained fever with several or even one principal clinical findings, gender[16], age[14], and previous history or family history of KD[17, 18], we recommend that echocardiograms could be performed earlier, maybe before day 5 of fever. To perform echocardiogram earlier may reveal evidence of coronary vasculitis, confirming the diagnosis of KD. However, the completeness and accuracy of the medical history, the degree of suspicion, and the patient's and parents' attitude should all be considered.

Possible differential diagnoses include polyarteritis nodosa, macrophage activation syndrome, and fibro-muscular dysplasia. The major one is polyarteritis nodosa. The patient had cardiovascular and intracranial vascular lesions. There were no abnormal findings on vascular ultrasound of neck and abdomen vessels, no ischemia symptoms in other organs, and normal blood pressure. Polyarteritis nodosa is a prototypic necrotizing vasculitis that usually affects small and medium vessels in multiple organs.[19] Although the skin, joints, kidneys, gastrointestinal tract and peripheral nerves are most commonly involved, intracranial aneurysms are rare, with 15 reported cases. Gupta et al.[20] found that most reported cases were already diagnosed as polyarteritis nodosa before presenting with cerebral symptomatology. But our patient did not fulfill the criteria for a polyarteritis nodosa diagnosis. He might have polyarteritis nodosa, which may account for the rapid progress of cerebral aneurysm in this KD patient. In terms of other differential diagnoses, macrophage activation syndrome was ruled out as the patient had an average fibrinogen and ferritin level. In fibro-muscular dysplasia, the lesion is segmental, with renal and internal carotid arteries being the most common, often bilaterally symmetrical lesions. The investigations were not suggestive of this differential diagnosis.

After the definitive diagnosis of Kawasaki disease, the patient was treated according to AHA guidelines. KD patients with current large and giant aneurysms (Z Score ≥ 10 or Absolute Dimension ≥ 8 mm) should be treated with low-dose aspirin for thromboprophylaxis. They are at exceptionally high risk for coronary artery thrombosis. The use of LMWH is reasonable. IVIG should be administered to children presenting after the tenth day of illness if they have coronary artery aneurysms.[14] Our patient had thromboses in the body and had anticoagulation indications. Recent intracranial surgery is a relative contraindication to anticoagulant therapy, as anticoagulant treatment will increase the risk of intracranial hemorrhage. However, if the underlying disease KD is not treated, thrombocytosis, increased platelet adhesion, inflammation, and endothelial dysfunction, together with abnormal flow conditions in severely expanded areas, will contribute to thrombotic occlusion aneurysms and even the rupture of a cerebral aneurysm or coronary aneurysm. Therefore, the patient underwent anticoagulant therapy as the guidelines suggest. Unfortunately, the patient suffered an intracranial hemorrhage 1 day later.

The case also provoked more significant thinking about applying aspirin and anticoagulant correctly in the perioperative period of intracranial surgery in KD patients who currently have intracranial aneurysms, giant coronary aneurysms, and thrombosis. Administration of antiplatelet agents (aspirin and nonsteroidal anti-inflammatory drugs) was the most commonly associated risk factor for a perioperative bleeding disorder.[21] In a meta-analysis of 41 studies, Burger et al.[22] demonstrated that aspirin therapy was associated with a 1.5-fold increase in postoperative bleeding events but no increase in the severity of bleeds, so concluded that low dose aspirin could be continued through most surgical procedures except neurosurgery and prostatectomy. When being used for secondary prevention of cardiovascular disease, David Keeling et al.[23] recommended that if the perceived bleeding risk is high, aspirin can be omitted from day − 3 to day + 7 with no net detriment. The guidelines of the American College of Surgeons [24] suggest that if deemed safe by the operating surgeon, LMWH can be resumed 48–72 hours after high-risk bleeding surgery. They recommend holding aspirin (low/high dose) for 7–10 days before a high bleeding risk procedure in patients without a history of percutaneous coronary intervention, and aspirin should not be restarted until the operative bleeding risk is minimal.[24] Given this, the applying of LMWH to our patient seems no problem. But it's quite challenging to decide how to apply aspirin at the moment.

From the result, it appears that aspirin should not be used in the perioperative period of intracranial surgery in KD patients. We recommend that a consensus view on aspirin's usage in KD patients under intracranial surgery or other high bleeding risks would be required.

Ultimately, the reason for the rapid progress of the aneurysms of the presented patient is unclear. We think it may be due to a delay in diagnosis and treatment. This case's limitation is that KD had not been fully recognized and treated in the early stage. The patient's previous fever improved without KD treatment, resulting in KD not being identified. His parents did not take it seriously, making the patient's preceding fever history and other symptoms unspecific. We need to pay attention to the problem that the condition of these patients who will get better on their own is often covered up. Kawasaki disease is often taken seriously because of coronary artery disease. Still, the complications of other medium-sized arteries are often unconsidered, which may delay the condition and make it worse. Our case shows a close link between KD and the complication of a cerebral aneurysm. Considering the fatal consequences of cerebral vascular involvement in KD patients, increased attention is required.

Abbreviations

KD
Kawasaki disease
LMWH
low-molecular-weight heparin
IVIG
intravenous immunoglobulin
AHA
American Heart Association

Declarations

Ethics statement

Ethics Committee approval was obtained from the Institutional Ethics Committee of Children's Hospital, Zhejiang University School of Medicine to the commencement of the study. Written informed consent was obtained from the parents of the participant for the publication of this case report.

Availability of data and materials:

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

YT provided medical care for this patient, drafted the initial manuscript, and approved the final manuscript as submitted. FG reviewed and revised the manuscript, confirmed revisions, and approved the final manuscript as submitted. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

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Tables

Table 1
Literature review of studies of hemorrhagic stroke associated with Kawasaki disease

Study	Gender	Age of KD	Symptoms of stroke	Lesion	Onset of stroke[a)]	Other arterial lesions	Fever duration	KD treatment	Stroke treatment	Prognosis
Du et al. (2005)	Female	16 mo	Vomiting, dipyridamole	Meningeal hemorrhage (No aneurysm)	14 days	Small aneurysms[b)] in left and right coronary artery	5 days	IVIG, dipyridamole, aspirin (stopped when diagnosed with stroke)	Vit K, Etamsylate, Haemocoagulase	Good prognosis
Du et al. (2005)	Male	8 mo	Vomiting, dipyridamole	Meningeal hemorrhage	21 days	Small aneurysm in left and medium aneurysm in right coronary artery	5 days	IVIG & aspirin	Vit K, Etamsylate, Haemocoagulase	Good prognosis
Tanaka et al. (2007)	Male	3 yr	Headache	Meningeal hemorrhage by rupture of right PCA aneurysm	9 yr	A mild dilation[c)] of the coronary artery	3 days	Unknown	Surgery	A left hemipares
Ahn et al. (2010)	Male	6 mo	Seizure	Intracerebral & meningeal hemorrhage by rupture of left MCA aneurysm	7 mo	None	5 days	IVIG & aspirin	Surgery	Good prognosis (except fo delayed expressio of langua for his ag
Ishida et al. (2014)	Male	Unknown	Headache, Vomiting	Meningeal hemorrhage by rupture of right MCA aneurysm	Unknown	Unknown	Unknown	Unknown	Surgery	Good prognosis
Our case	Male	12 yr	Coma, Decline GCS	Meningeal hemorrhage by rupture of right vertebral artery aneurysm	20 days	Large and medium coronary artery aneurysms[d)]	Unknown	No treatment before stroke; IVIG & aspirin later	Surgery	Death

KD, Kawasaki disease; MCA, middle cerebral artery; PCA, posterior cerebral artery; IVIG, intravenous immunoglobulin; MRA, magnetic resonance angiography; GCS, Glasgow Coma Scale.

[a)] Stroke after KD symptom onset; [b)] Small aneurysms: Z Score ≥ 2.5 to < 5; [c)] Dilation: Z Score ≥ 2 but < 2.5; [d)] Large aneurysms (Z Score ≥ 10), medium aneurysms (Z Score ≥ 5 to < 10)

Figures

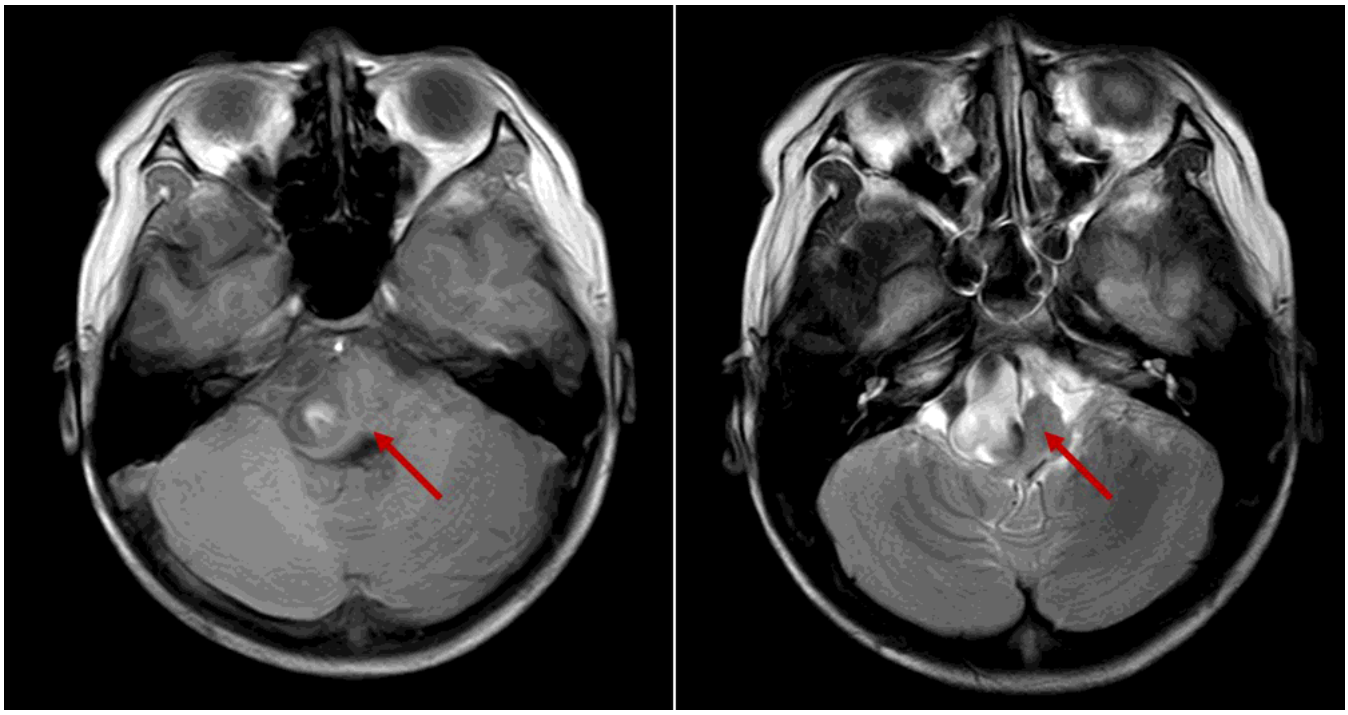

Figure 1

Cerebral MR on admission: (T1W, T2W) The right vertebral artery aneurysm was considered first; there was hemorrhage in the lateral ventricles on both sides with interstitial edema around.

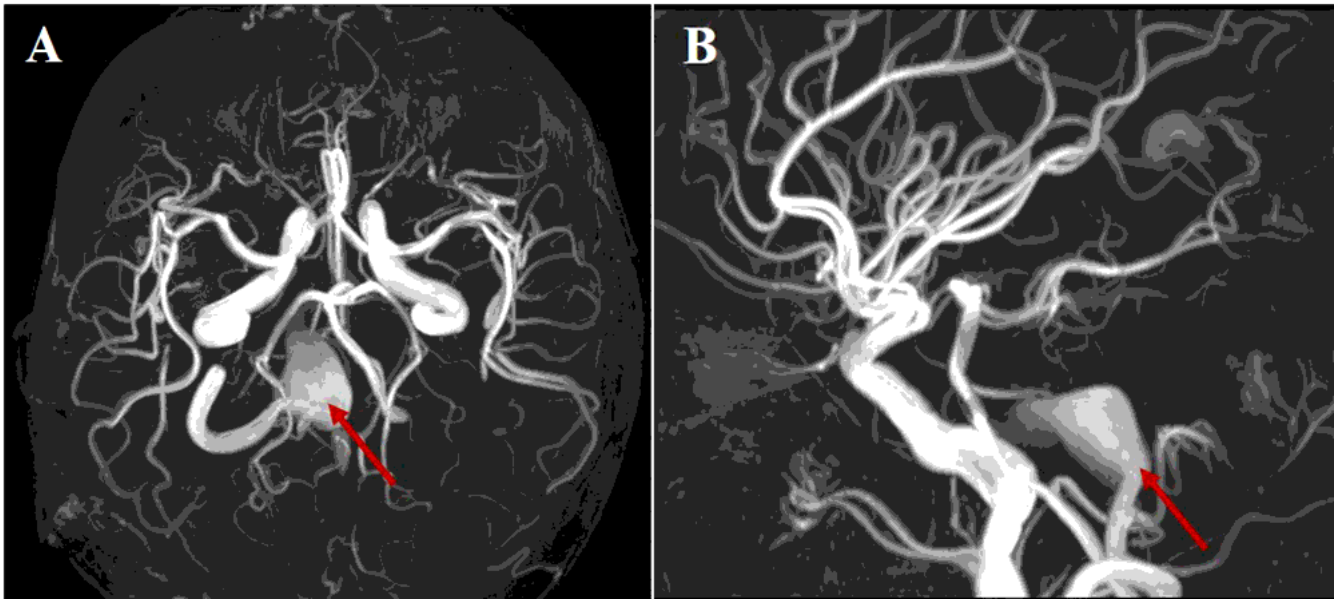

Figure 2

A: coronal position; B: sagittal position of cerebrovascular MRI: the right vertebral artery V5 segment aneurysm.

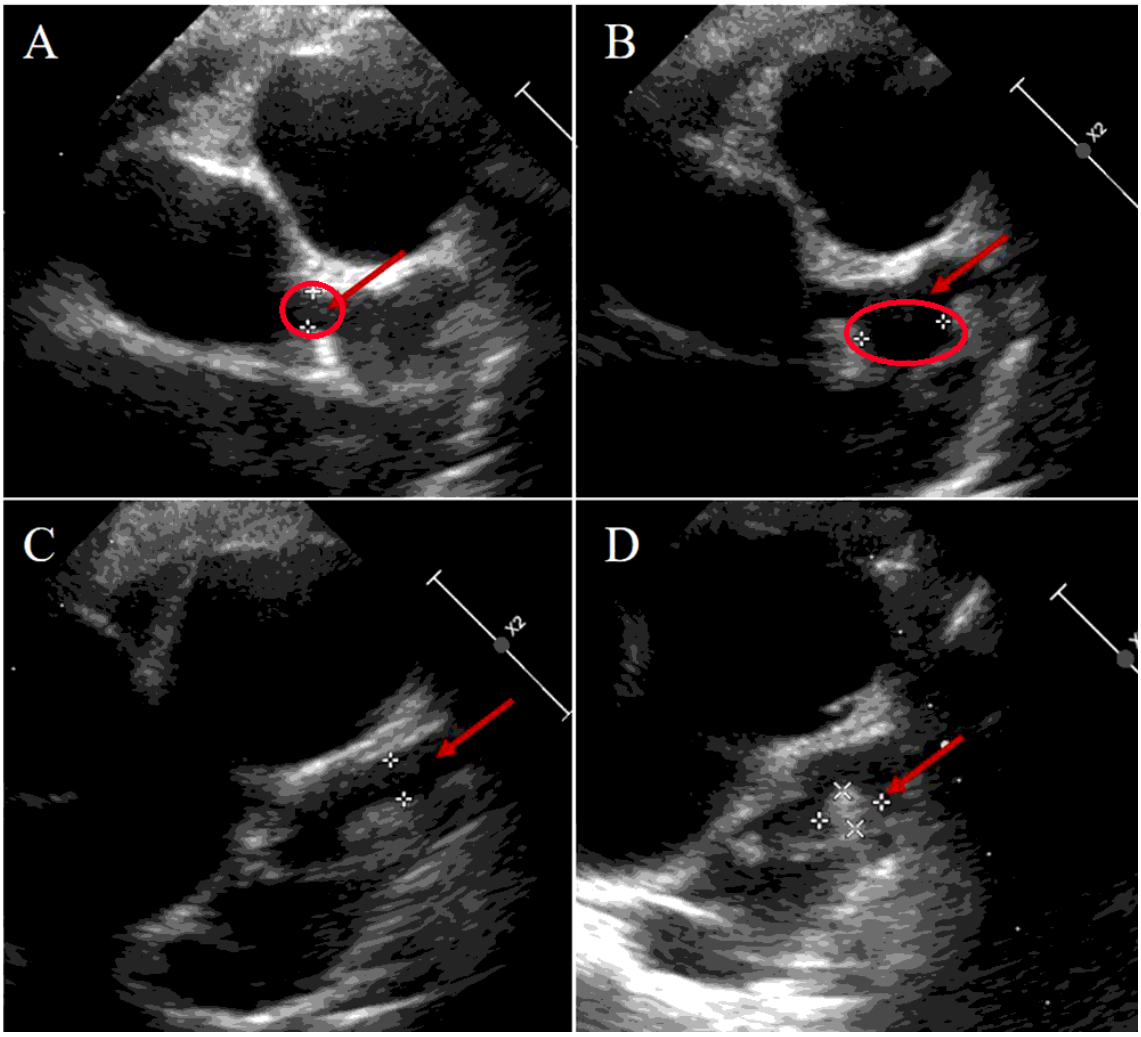

Figure 3

Transthoracic echocardiography examination: A: Diameter of the left coronary artery was 0.44 cm; B: Diameter at the beginning of the circumflex coronary artery was 1.07 cm; C: Diameter of the anterior descending artery was 0.52 cm; D: A strong echo group could be seen at the intersection of the anterior descending branch and the circumflex branch, and the size was about 0.81 cm ×0.50 cm.

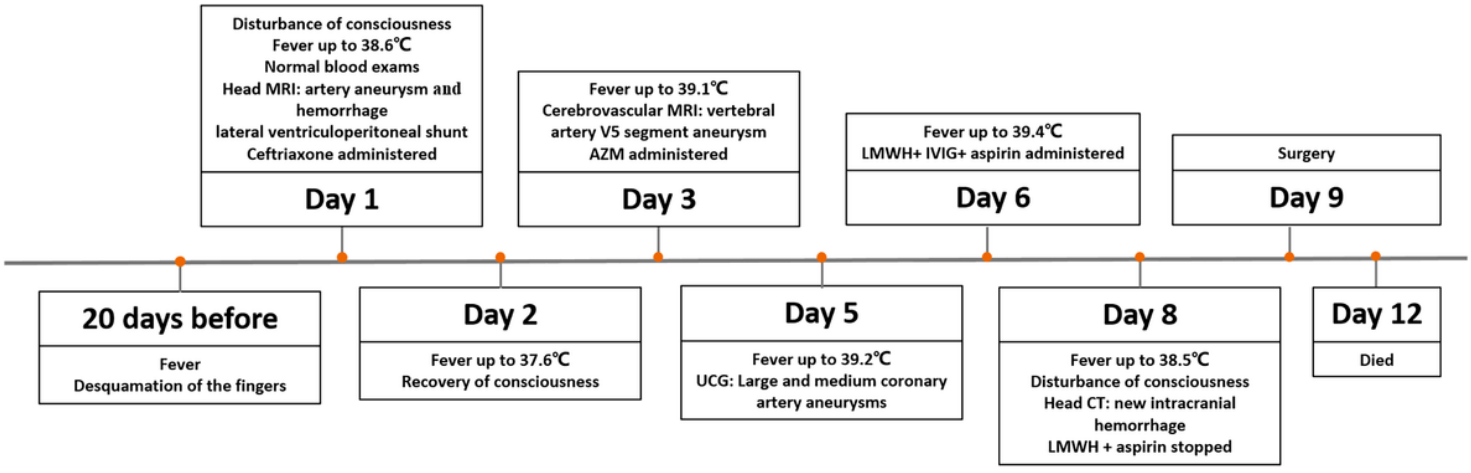

Figure 4

Timeline of clinical features, investigation and treatment of the case report. MRI, Magnetic resonance imaging; AZM, Azithromycin; LMWH, low-molecular-weight heparin; IVIG, Intravenous immunoglobulin.