Dural sinus thrombosis and giant pulmonary artery aneurysm in paediatric Behçet's disease

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Abstract

Paediatric Behçet's disease (BD) accounts for only 2–5% of all patients with BD. Neurological and vascular involvement account for only 3.6% and 1.8% of paediatric BD in China, but both are lethal complications. We report the case of a 12-year-old Chinese boy presenting with recurrent oral ulcers, extensive thrombosis, cerebral sinus vein thrombosis and bilateral inferior pulmonary artery aneurysm. With treatment that included oral prednisone, a monthly pulse of cyclophosphamide followed by mycophenolate mofetil, and anticoagulant therapy, the patient became symptom free, his C-reactive protein and erythrocyte sedimentation rate remained normal, and the right inferior pulmonary artery aneurysm was reduced to normal. However, the left inferior pulmonary artery aneurysm progressively expanded to 64.9 mm×36.2 mm×44 mm. Eventually, the patient underwent left pulmonary aneurysm resection and a left inferior lobectomy. The post-operative maintenance treatment included oral prednisone, mycophenolate mofetil and low-dose aspirin, and the patient was followed for 2 years without recurrence. Additionally, we retrospectively analysed the clinical characteristics of 23 paediatric BD patients from our medical centre and briefly reviewed the literature on paediatric BD.

Key words

paediatric Behçet's disease, dural sinus thrombosis, pulmonary artery aneurysm

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Introduction

Behçet's disease (BD) is a chronic, multisystemic, recurrent, inflammatory vasculitis with protean clinical manifestations including recurrent oral and genital aphthous ulcers as well as cutaneous, ocular, articular, gastrointestinal and central nervous system inflammatory lesions. Recurrent oral ulcers, genital ulcers and uveitis are the most characteristic triad symptoms but may be absent at the time of medical evaluation. Neurological and vascular involvement in BD are uncommon, but represent serious complications. The diagnosis of BD is mainly clinical with no specific laboratory tests, which can result in diagnosis delay and irreversible damages. BD shows the highest prevalence of onset in the third decade of life, and Turkey has the highest prevalence rate at up to 42/10000 (1). Paediatric BD is defined as the onset of BD in children (≤16 years old); it is relatively rare, accounting for 2–5% of all patients with BD (2-4).

Here, we describe a boy with the features of BD presenting with recurrent oral ulcers, extensive thrombosis, cerebral sinus vein thrombosis and bilateral inferior pulmonary artery aneurysm. Additionally, we retrospectively analysed the clinical characteristics of 23 paediatric BD patients from our medical centre and briefly reviewed the literature on paediatric BD.

Case description

A 12-year-old boy presented in August 2016 with intermittent fever and headache for more than 5 months and serious chest pain for 10 days. In March 2016 the patient had been hospitalised in the local hospital for fever and headache. Anti-infection and symptomatic treatment were given but were ineffective. On April 13, 2016, the boy was admitted to a children's hospital with high medical standards. Physical examination revealed no other positive signs, except for multiple oral mucosal ulcers. Blood tests showed a significant increase in the white blood cell count, the neutrophil count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Central nervous system infection was considered, but no positive signs were observed on neurophysical examination and the cerebrospinal fluid examination revealed no specific findings. Cervical vascular ultrasound indicated bilateral internal jugular vein thrombosis. Cranial enhanced MRI showed multiple strip-like and nodular unenhanced areas in the bilateral transverse sinus, internal cerebral vein, great cerebral vein and superior sagittal sinus, which indicated sinus suppository. Ophthalmology examination showed a high degree of papillary oedema in both eyes, the right one being more serious. Anticoagulation and anti-infection therapies were performed, and the boy's headache symptom eased but his fever persisted. There was no hypercoagulation or infection that could explain the cerebral sinus vein thrombosis. BD was suspected, but there was no uveitis, no genital ulcers, and no gastrointestinal symptoms. More detailed medical tests were requested prior to making the diagnosis, but the boy's parents asked for him to be discharged to the local hospital for economic reasons. The details of the treatment at the local hospital were unclear, and the boy's parents recalled that he had recurrent fever.

On August 4, 2016, the boy was referred to the emergency room of the local hospital for fever and serious chest pain. Computed tomography indicated extensive thrombosis of the superior vena cava, left brachiocephalic vein, left subclavian vein and left internal jugular vein as well as bilateral inferior pulmonary artery thrombosis with aneurysm formation. Anti-infection and anticoagulant therapies were given, but there was no improvement.

On August 14, 2016, the boy was transferred to our hospital.

Past history and family history included oral mucosal ulcer attacks that recurred almost every month for the past year. His sister died of "abdominal distention" at the age of 2, but no medical details were available. His brother, who was five years older, was in good health. There was no other contributory past medical history or family history.

Physical examination revealed body temperature at 37.1ºC, pressure 96 bpm/min, R 26 pm/min, B.P. left up-

per limb 88/51 mmHg, B.P. right upper limb 98/61 mmHg, B.P. left lower limb 102/52 mmHg, and B.P. right lower limb 103/56 mmHg. The pulses of the right carotid artery, right femoral artery and dorsal foot artery were weak. Mucosal ulcers were seen on the tip of the tongue. Ophthalmologic examination revealed *oculus dexter* (OD) pupil diameter 3.5 mm, *oculus sinister* (OS) pupil diameter 3 mm; OD pupil reflex insensitive, OS pupil reflex sensitive; OD vision CF/BE (counting fingers/before eye), OS vision 0.5; and bilateral papilloedema. Pathergy reaction test was not carried out, but during the hospital stay, multiple venipunctures did not cause skin allergies. No other remarkable finding was observed on physical examination.

Laboratory tests (Table I) showed elevated ESR (60 mm/h) and CRP (55 mg/L) levels. Extensive microbiological investigation found no evidence of infection. Immunological tests were negative. There was no deficiency in protein C or S, activated protein C resistance, antithrombin, or factor V. No abnormality in amino acid analysis was observed in the blood or urine. No pathogenic mutations that could clearly explain the phenotype of the patient were detected by target sequence capture high-throughput sequencing technology. Human leukocyte antigen B51 (HLA-B51) was not tested.

Table I. Relevant laboratory results.

	Test results at transfer	Normal range
White cell count	8.7	(4-10) × 10^9 cells/L
Neutrophil %	81.5	45-75%
Haemoglobin	97	120-160 g/L
Platelets	326	(100-300) × 10^9 cells /L
C-reactive protein	55	<8 mg/L
Erythrocyte sedimentation rate	60	<10 mm/h
Procalcitonin	0.05	<0.05 ng/ml
Interleukin-6	210.30	<7 pg/ml
T-Spot	negative	negative
HIV	negative	negative
Syphilis	negative	negative
Mycoplasma IgM	negative	negative
Hepatitis virus antibody	negative	negative
TORCH	negative	negative
EB virus	negative	negative
Widal reaction	negative	negative
Blood culture	negative	negative
Urine culture	negative	negative
Antistreptolysin "O"	12.6	<200 IU/ml
Rheumatoid factor	11.4	<20 IU/ml
Anti-nuclear antibodies	negative	negative
Anti-ENA antibodies	negative	negative
Anti-neutrophil cytoplasmic antibodies	negative	negative
Anticardiolipin	negative	negative
Lupus anticoagulant	negative	negative
Anti-β2-glycoprotein I	negative	negative
Prothrombin time	13.2	12-14.8 s
Activation of partial thrombin time	29.6	28-44.5 s
D-Dimer	2.46	0-0.3 mg/L
Fibrinogen	4.72	2-4 g/L
Fibrin degradation products	8.99	0-5 ug/ml
Thromboelastogram (TEG) α angle	66.7	53-72 degrees
(TEG) Coagulation index	1.9	-3- 3
(TEG) Estimated percentage of lysis	0.0	0-15%
(TEG) Kinetics time	1.8	1-3 min
(TEG) Percent lysis 30 min after MA (%)	0	0-8%
(TEG) maximum amplitude	62.1	50-70 mm
(TEG) Reaction time	3.6	5-10 min
Blood amino acid analysis	normal	
Urine tandem mass spectrometry	normal	
Panel sequencing	normal	

Colour Doppler ultrasonography showed thrombosis of the bilateral internal jugular veins, the right common femoral vein and the right superficial femoral vein. Computed tomography angiography (CTA) of the aorta illustrated that the bilateral inferior pulmonary arteries had partly nodular dilatation and were surrounded by a soft tissue density shadow (Fig. 1A). No significant abnormalities were observed in the abdominal aorta. Cephalic magnetic resonance venography demonstrated uneven thickness of the superior sagittal sinus and multiple collateral vessels formation (Fig. 2). No significant lesion was found on head magnetic resonance angiography (MRA).

BD was diagnosed based on the occurrence of recurrent oral ulcers, neurological involvement (headaches, bilateral papilloedema and cerebral venous thrombosis) and vascular involvement (venous thrombosis and arterial aneurysm) according to the 2015 paediatric criteria for BD (PEDBD) (5) and the 2013 International Criteria for BD (ICBD) (6). This case did not fulfill the 1990 International Study Group criteria for BD (ISGBD) (7).

The patient's medical treatment is summarised in Fig. 3. In August 2016, prednisolone (30 mg bid, 1 mg/kg/d), low molecular weight heparin, and diclofenac (25 mg tid) were given. Low molecular heparin calcium was subcutaneously injected for 2 weeks and then switched to oral warfarin. With these treatments, the patient's body temperature returned to normal, his chest pain was relieved, and his ESR and CRP levels were normal. However, two months later (on October 16, 2016), MRA indicated that the bilateral inferior pulmonary arterial aneurysm expanded further compared with the previous CTA on August 15, 2016, with diameters of 21 mm (left) and 16 mm (right) (Fig. 4A). Then, monthly pulses of cyclophosphamide 500 mg/m^2 were given 7 times. On December 25, 2016, MRA showed that the diameters of the inferior pulmonary arterial aneurysms were 20.6 mm (left) and 8.9 mm (right), without further expansion (Fig. 4B). The oral glucocorticoids were gradually reduced to 15 mg per day. On January 19, 2017, the boy again developed fever; CRP was 82 mg/L and ESR was 42 mm/h. BD recurrence was diagnosed and prednisolone 2 mg/kg per day was add-

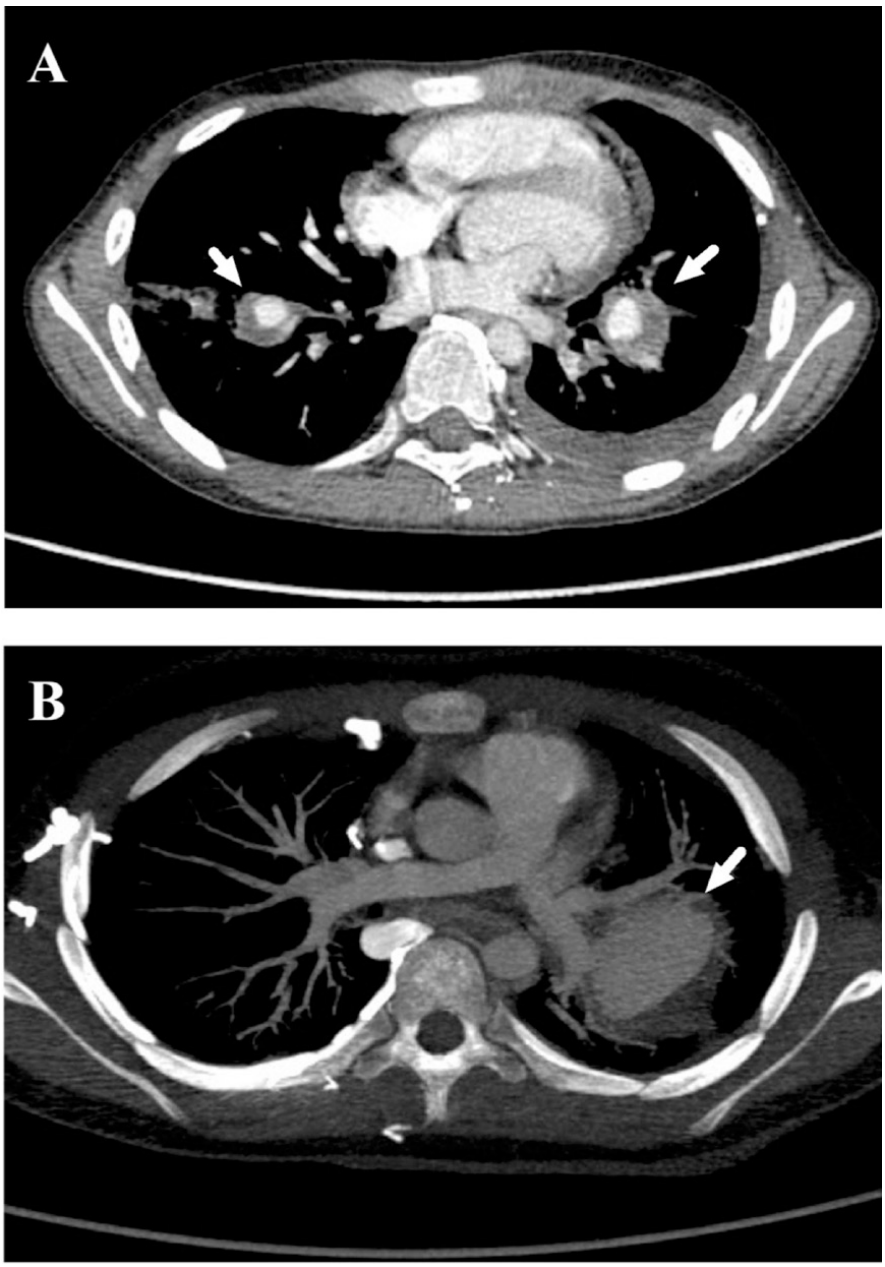

Fig. 1. **A**: CT angiography on August 15, 2016 disclosed severe inflammatory wall thickening and dilation in bilateral inferior pulmonary arteries (white arrows). The diameters at the widest point of the left and right inferior pulmonary arteries were 18.2 mm and 7.4 mm, respectively.
B: CT angiography on July 24, 2017, indicated a left inferior pulmonary arterial aneurysm measuring approximately 64.9 mm×36.2 mm×44 mm; the right pulmonary artery was normal.

ed. On March 17, 2017, MRA revealed that the left inferior pulmonary aneurysm expanded to 41 mm×39 mm×44 mm without symptoms, but the right inferior pulmonary aneurysm disappeared (Fig. 4C). In June 2017, the cyclophosphamide treatment course was completed, with a cumulative dose of 5g (150 mg/kg) and was followed by mycophenolate mofetil (MMF, 0.625 g q12 h, weight 48.5 kg) and oral prednisolone tapering. The patient had no clinical symptoms other than decreased vision in the right eye. CRP and ESR were normal. In July 2017, haemoptysis appeared without fever; there was no elevation of CRP or ESR. CTA showed a 64.9 mm×36.2 mm×44 mm left inferior pulmonary aneurysm and a normal right inferior pulmonary artery (Fig. 1B). On September 27, 2017, surgical repair (left pulmonary aneurysm resection and left inferior lobectomy) was carried out. With the support of extracorporeal circulation, the pulmonary artery, pulmonary vein and bronchus of the lower lobe of the left lung were dissociated, and the aneurysm and the lower lobe of the left lung were successfully removed (Fig. 5). Histologic examination showed that the vascular wall had an uneven thickness, endothelial cells were shed, inflammatory cells had infiltrated, a thrombus formed in the lumen, most of the surrounding tissue had alveolar congestion and bleeding, a large number of foam cells and phagocytic monocytes containing hemosiderin and scattered inflammatory cells had infiltrated, and some of the peribranchial lymphatic follicles were formed (Fig. 5). After surgery, an oral maintenance regimen of prednisolone (20 mg qd) and MMF (0.75 g q12 h) was given until the patient experienced more than 1 year without recurrence of the disease; then, in December 2018, MMF was reduced to 0.625 g q12 h, and the prednisolone was gradually reduced. Currently, low-dose prednisolone (3.75 mg qd), MMF (0.625 g q12 h) and aspirin (100 mg qd) are given for maintenance therapy. On a recent 2-year medical follow-up, the boy remained symptom-free. Repeated chest MRA demonstrated radiological regression (Fig. 4D). Unfortunately, the optic nerves in both eyes were atrophied, leaving irreversible visual loss in the right eye (VOD <0.05, VOS 0.9)

Retrospective cohort analysis and literature review

We retrospectively analysed the clinical manifestations of 23 children (13 females, 10 males) diagnosed with BD at the Children's Hospital of Fudan University from January 2007 to August 2019 (Table II). Eleven patients (47.8%) fulfilled the 2015 PEDBD criteria, 19 (82.6%) fulfilled the 2013 ICBD criteria, 12 (52.2%) fulfilled the 1990 ISGBD criteria and 4 (17.4%) did not fulfill any of them. The median age of disease onset was 6.90 (0-15.17) years; the median time to diagnosis was 1.93 (0.04–6) years. All patients had oral ulcers, but only 2 (8.7%) had the oral aphthosis-genital aphthosis-ocular manifestations triad; 1 (4.3%, male) had neurological manifestations

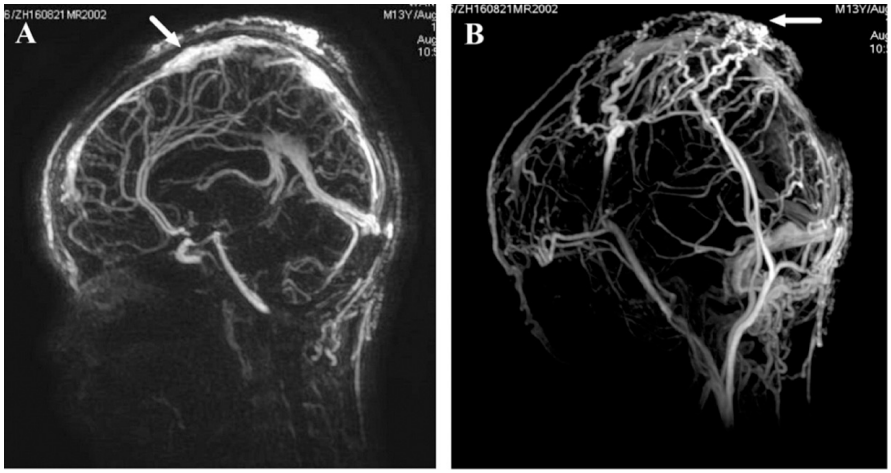

Fig. 2. Cephalic magnetic resonance venography showed uneven thickness of the superior sagittal sinus (**A**), and multiple collateral vessels were seen around them (**B**).

and 2 (8.7%, male) had vascular manifestations. The initial symptoms were recurrent oral ulceration (OU 78.2%), gastrointestinal symptoms (GI 13.0%), genital ulceration (GU 4.3%), and skin lesions (SL 4.3%).

We searched the PubMed database using the keywords or MeSH terms "pediatric Behçet's disease", "juvenile Behçet's disease", "Behçet's disease" AND "children" to identify English language articles published from January 2000 to June 2019. There were few epidemiological data on paediatric BD, mostly limited to case series (Table III) (3, 4, 8-16). According to these reports, the typical BD symptom triad is very rare. Oral ulcers were the most frequent clinical manifestation, with an incidence of 91.7–100%; ocular involvement was not common in China, with a frequency of 20–27.3% (8, 11). Only in France the incidence rates of oral ulcers, genital ulcers and ocular involvement, the typical clinical symptom triad, were relatively high (74%, 79% and 87%, respectively) (16). Neurological BD was reported with a minimum incidence of 3.6% in China (8), 4.9–10.3% in Iran (3, 13), and 3.6-12.9% in Turkey (4, 14, 15); however, the incidence of neurological BD was higher in other studies with a rate of 28.3–44% (9, 10, 11, 12, 16). Vascular involvement was rare in the Chinese population, with a rate of 1.8% (8), and it had a low frequency in most other studies (3.610%) (3, 4, 9, 10, 13, 14), with a slightly higher rate in France (21%) (16).

Discussion

Neurological BD is one of the most severe and life-threatening manifestations of BD; it includes the parenchymal type (usually in the form of mesodiencephalic meningoencephalitis) and the nonparenchymal type with involvement of dural sinus thrombosis (superior sagittal and transverse sinuses are affected most of the time) (1). In a study of 728 neurological BD patients, paediatric neurological BD comprised 3.6% of the whole cohort, with a male predominance (male/female ratio 5.5/1), mainly in the form of dural venous sinus thrombosis, whereas in the adult neurological BD population, the dominant form of neurologic involvement is parenchymal (17). The prevalence of cerebral thrombosis in the paediatric age group ranged between 0.4/100000 and 0.7/100000 children (18). Cerebral venous sinus thrombosis is strongly associated with vascular involvement elsewhere in the body and most of the time precedes its development (1). Screening is needed to assess vascular disease at extracranial sites at the first episode.

Thrombosis is a multifactorial event that usually develops as a result of he-

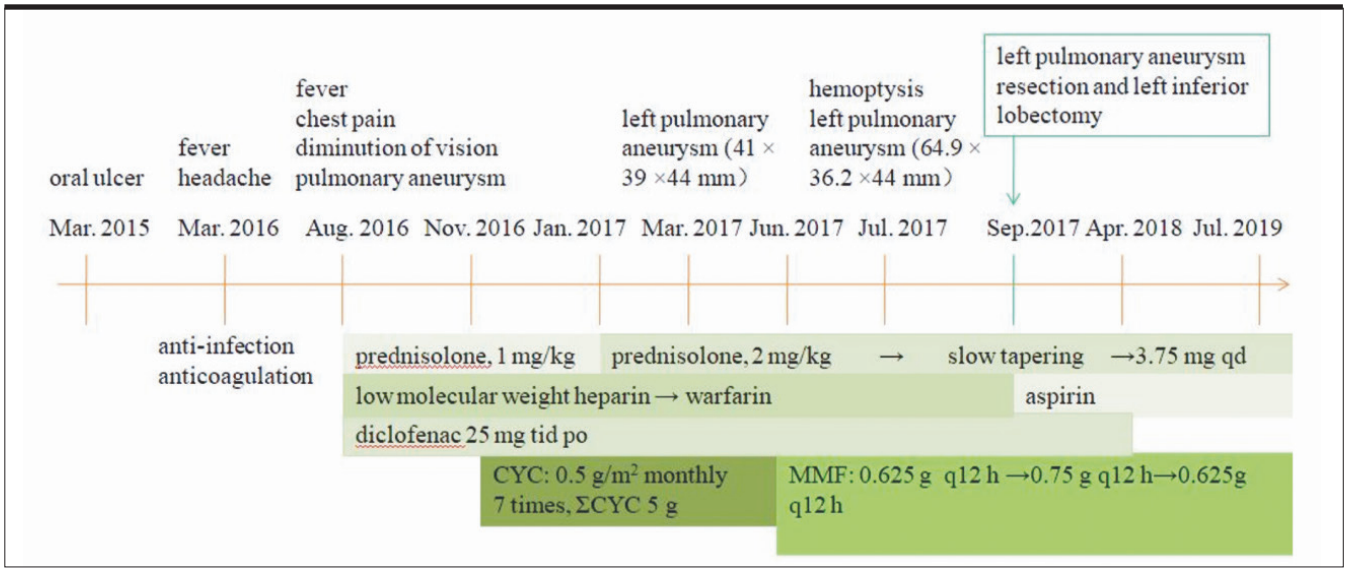

Fig. 3. The patient's treatment history.
CYC: cyclophosphamide; MMF: mycophenolate mofetil.

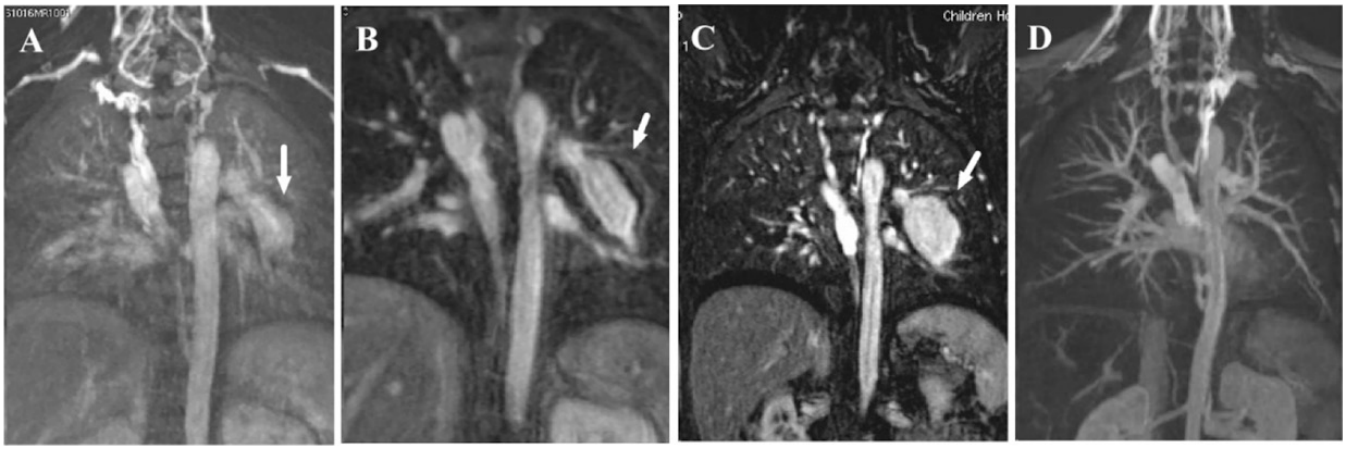

Fig. 4. MR angiography follow-up.
A: On October 16, 2016, the diameter of the left inferior pulmonary arterial aneurysm was 21 mm, and that of the right inferior pulmonary arterial aneurysm was 16 mm.
B: On December 25, 2016, the diameter of the left inferior pulmonary arterial aneurysm was 20.6 mm, and that of the right inferior pulmonary arterial aneurysm was 8.9 mm.
C: On March 17, 2017, the left inferior pulmonary aneurysm expanded to 41 mm×39 mm×44 mm, and the right inferior pulmonary artery was normal.
D: On July 11, 2019, approximately 2 years after the left pulmonary aneurysm resection. There was no obvious expansion of the main thoracic aorta.

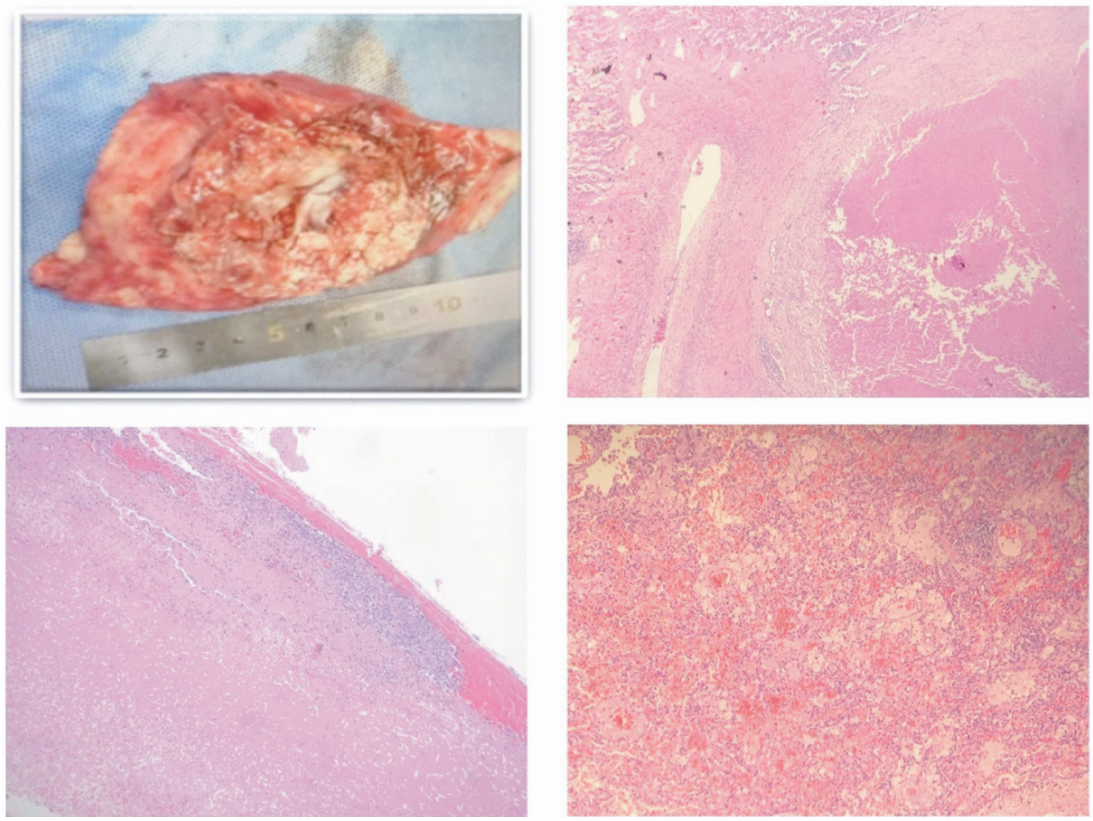

Fig. 5. Left lobe specimen and histologic examination. Histologic examination showed that the vascular wall had an uneven thickness, endothelial cells were shed, inflammatory cells had infiltrated, a thrombus formed in the lumen, most of the surrounding tissue had alveolar congestion and bleeding, a large number of foam cells and phagocytic monocytes containing haemosiderin and scattered inflammatory cells had infiltrated, and some of the peribranchial lymphatic follicles were formed.

reditary and acquired risk factors (Table IV) (19). Local or systemic infections, vascular trauma, cancer, acute lymphoblastic leukemia, drugtoxicity, systemic lupus erythematosus, nephrotic syndrome, dehydration, asphyxia, BD and metabolic disorders have been described as predisposing factors (19, 20). In addition, congenital abnormal coagulation factors, including protein C or S, activated protein C resistance, antithrombin, factor V Leiden, and prothrombin mutations, can also result in thrombophilia. In this case, infection and thrombophilia were ruled out. No abnormalities were found in the blood and urine with mass spectrometry or panel sequencing. Non-specific fever

Table II. Clinical data of 23 children with BD in our medical centre.

NO.	Gender	Age(year)		Initial symptom	Clinical manifestations								
		Onset	Diagnosis		OU	GU	OI	SL	A	GI	NS	V	Pt
1	Female	5	6.25	OU	*	*		*					p
2	Male	11	11.42	OU	*	*		*		*			
3	Male	1	2.08	OU	*	*				*			p
4	Male	13	13.92	GI	*	*		*		*		*	
5	Female	1	3	OU	*	*			*				
6	Male	11	12	OU	*						*	*	
7	Female	5	9	OU	*	*				*			
8	Male	12.33	13.33	SL	*		*	*					
9	Male	6.75	7	OU	*			*		*			
10	Female	3.17	3.21	GI	*	*		*		*			
11	Female	3	4.92	OU	*	*		*		*			
12	Female	15.17	15.75	OU	*		*		*				
13	Male	12.67	14.25	OU	*			*		*			
14	Male	0 (10 days)	5.25	GU	*	*	*	*		*			n
15	Female	12.92	13.17	OU	*	*		*	*	*			
16	Female	1.83	2.42	GI	*	*				*			
17	Male	3	9	OU	*	*				*			
18	Female	1.08	1.25	OU	*	*							
19	Female	8.42	8.5	OU	*	*	*		*				
20	Male	0.25	6.25	OU	*					*			
21	Female	14.17	14.25	OU	*			*	*				p
22	Female	4	10	OU	*	*		*					
23	Female	13	15	OU	*			*					

OU: oral ulcers; GU: genital ulcers; OI: ocular involvement; SL: skin lesions; A: arthritis; GI: gastrointestinal; NS: nervous system; V: vascular; Pt: pathergy test; p: positive; n: negative.
*indicates that the child has this clinical symptom. Pathergy test was performed in 4 patients and was positive in 3/4.

Table III. Comparison of clinical features of paediatric BD in different geographical regions**.**

Study (reference, country, published time)	Time span (year)	Cases no.	M/F ratio	Age of onset (year)	Percentage of patients in the series with each clinical features (%)							
					OU	GU	OI	SL	A	GI	NS	V
Our medical centre	2007- 2019	23	0.77/1	7	100	65.2	17.4	56.5	26.1	56.5	4.3	8.7
Hu (8) China, 2019	n.r.	55	0.67/1	11	100	69.1	27.3	36.4	27.3	29.1	3.6	1.8
Shahram (3) Iran, 2018	n.r.	204	1.02/1	10.5±3.4	91.7	42.2	66.2	51.5	30.9	5.9	4.9	6.4
Gallizzi (9) Italy, 2017	n.r.	110	1.29/1	8.3±4.1	94.5	33.6	43.6	39.6	42.7	42.7	30.9	10
Nanthapisal (10) UK, 2016	1987- 2012	46	0.92/1	4.9	97.8	73.9	8.7	23.9	21.7	56.5	28.3	6.5
Hung (11) China, 2013	1990- 2010	20	1/1	13	100	70	20	65	30	50	n.r.	n.r.
Zakiya (12) Bahrain, 2012	2002- 2010	9	2/1	7	100	55	77	88	77	55	44	n.r.
Atmaca (4) Turkey, 2011	1986- 2005	110	0.6/1	11.6±3.4	100	82.7	30.9	76	22.7	n.r.	3.6	3.6
Davatchi (13) Iran, 2010	1975- 2010	1973	1/1	n.r.	97.8	64.7	56.1	65.3	37.1	7.6	10.3	6.5
Sungur (14) Turkey, 2009	1990- 2005	62	1.14/1	n.r.	100	54.8	80.7	58.1	41.9	n.r.	12.9	6.4
Karincaoglu (15) Turkey, 2007	n.r.	83	0.84/1	12.3±3.4	100	81.9	34.9	n.r.	39.8	4.8	7.2	n.r.
Koné-Paut (16) France, 2002	n.r.	55	0.89/1	8±4.3	74	79	87	78	17	40	35	21

M/F ratio: male/female ratio; Age of onset: median age of disease onset; OU: oral ulcers; GU: genital ulcers; OI: ocular involvement; SL: skin lesions; A: arthritis; GI: gastrointestinal involement; NS: nervous system; V: vascular; n.r.: not reported.

and headache at early onset without genital ulcer, uveitis or skin lesions make the differential diagnosis difficult. Delayed diagnosis and the consequently delayed immunosuppressive treatment favoured optic atrophy in this case.

The vascular BD incidence in adult BD patients in China was 17.4% (21). Vascular involvement in BD is seen mainly among men and is unique from other types vasculitis since it usually affects both the vein and artery. The majority of the patients (75%) experience their first vascular event within 5 years of disease onset (1). BD has a significant thrombotic tendency associated with vascular inflammation, which cannot be explained by thrombophilic factors. Venous thrombosis and arterial involvement affect 15–40% and 3–5% of BD patients, respectively (22). Yong *et al.* reported 923 Chinese patients with BD, of whom 166 (17.98%) had vascular involvement and 17 (1.84%) had aneurysms or pseudoaneurysms (23).

Pulmonary system involvement occurs in 1–8% of paediatric BD (24) and is the leading reason for mortality. In children, males are more frequently affected than females (M/F; 6/1) (25). Pulmonary artery aneurysms are uncommon, and most are asymptomatic

at diagnosis, but fatal aneurysm rupture occurs in one-third and dissection occurs in one-fifth of patients (26). Arteriovenous aneurysm is defined as a threefold expansion or an absolute expansion of approximately 18 mm (27). Various origins of pulmonary artery aneurysms have been described that allow us to differentiate among congenital causes, acquired causes, anti-idiopathic causes (Table IV) (26). Congenital causes include congenital heart disease and connective tissue abnormalities (Ehlers-Danlos syndrome, Marfan syndrome, cystic medial necrosis, etc.) and have been recognised as the major reason for pulmonary artery aneurysm. Acquired causes include infection (*e.g.* TB, syphilis, bacterial infection, viral infection or fungal infection), vasculitis (*e.g.* Hughes-Stovin syndrome, Takayasu's arteritis), pulmonary arterial hypertension, chronic pulmonary embolism, neoplasm, and iatrogenic syndrome (26).

Table IV. The differential diagnosis.

Cerebral venous thrombosis risk factors (20)	Causes of Pulmonary artery aneurysms (27)
Acquired	Acquired
Local or systemic infections	Infections including syphilis, tuberculosis, pyogenic bacteria, septic embolisms, bacterial and fungal pneumonia.
Cancer	Vasculitis including Hughes-Stovin syndrome, Takayasu's arteritis, Behçet's disease.
Vascular trauma	Pulmonary arterial hypertension.
Drug toxicity	Chronic pulmonary embolism.
Nephrotic syndrome	Neoplasm including primary lung cancer, Pulmonary metastasis.
Behçet's disease	Iatrogenic including cardiac surgery, catheters, chest tubes, angiography, surgical resection, etc.
Inflammatory bowel disease	
Thyroid disorders	
Systemic lupus erythematosus	
Antiphospholipid antibodies	
Sarcoidosis	
Wegener granulomatosis	
Asphyxia	
Paroxysmal nocturnal haemoglobinuria, etc.	
Hereditary thrombophilia	Congenital
Protein C or S deficiency, activated protein C resistance, antithrombin deficiency, factor V Leiden, prothrombin mutation, etc.	Heart defects including persistent ductus arteriosus, ventricular septal defects, atrial septal defescts, pulmonary valve stenosis, etc.
	Connective tissue abnormalities including Ehlers-Danlos syndrome, Marfan syndrome and cystic medial necrosis, etc.
	Idopathic

Hughes-Stovin syndrome (HSS), a rare autoimmune disorder of unknown origin, is also characterised by pulmonary artery aneurysm formation and recurrent thrombophlebitis (28). Aneurysm-thrombosis complexes with negative microbiology/mycology testing and without pulmonary hypertension or features of trauma/iatrogenic injury, congenital abnormalities or connective tissue disorder, suggest HSS or BD (29). HSS may also have diagnostic features of BD, such as recurrent oral ulcers and vascular manifestations, but no arthritis or gastrointestinal manifestations. There are no formally described diagnostic criteria or pathognomonic laboratory investigations for HSS. The current consensus is that HSS results from vasculitis similar to that in BD, and the medical treatment of both diseases involves a combination of immunosuppressive agents. Several investigators have suggested that HSS is actually a variant of BD rather than a discrete clinical entity. In this case, intracranial venous sinus thrombosis was considered a manifestation of non-parenchymal involvement of neurological BD. Therefore, this patient, with recurrent oral ulcers, vascular involvement and central nervous system involvement, fulfilled the diagnostic criteria of the 2015 PEDBD and the 2013 ICBD.

For the treatment of vascular BD, aneurysms or thrombosis may disappear or regress in approximately 70% of patients with the use immunosuppressive agents (30). However, in this case, glucocorticoids combined with immunosuppressive therapy induced the disappearance of the right lower pulmonary artery aneurysm, but the left lower pulmonary artery aneurysm continued to expand. The aneurysm was so giant that endovascular embolisation and surgical resection may not have been successful and may have caused several complications. Lobectomy was performed, but massive bleeding occurred when isolating the pulmonary aneurysm, and external cardiopulmonary circulation support was urgently established. EULAR established the following recommendations in 2018 for the management of vascular BD (31): 1) for the first episode of cerebral venous thrombosis, patients should be treated with high-dose glucocorticoids followed by tapering. Anticoagulants may be added for a short duration; 2) for the management of acute deep vein thrombosis, which is thought to result from inflammation of the vessel wall rather than hypercoagulation, glucocorticoids and immunosuppressive agents are recommended; 3) for the management of pulmonary artery aneurysms, the use of cyclophosphamide in association to high-dose corticosteroids is strongly suggested, while the use of anti-TNF-α should be considered for refractory cases; 4) for patients who have or are at high risk for major bleeding, embolisation should be preferred to open surgery; 5) for both aortic and peripheral artery aneurysms, surgery or stenting should not be delayed if the patient is symptomatic, and medical treatment with cyclophosphamide and corticosteroids is necessary before intervention to repair.

In this case, BD was not initially recognised, and glucocorticoids were delayed five months from the first episode of cerebral venous thrombosis, which resulted in irreversible visual impairment of the right eye.

Conclusion

Although recurrent oral ulcers, genital ulcers and uveitis are considered to be the three most characteristic symptoms of BD, only a very small percentage of patients have this symptom triad. For early diagnosis and to reduce irreversible damage, clinicians should be alert to patients with both arteritis and phlebitis.

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