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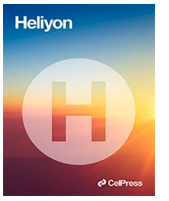

Coronary artery dilation in children with febrile illnesses other than Kawasaki disease: A case report and literature review

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ABSTRACT

Background: Coronary artery dilation (CAD) had rarely been described as a cardiac complication of febrile disease other than Kawasaki disease (KD). There are rare cases complicated by CAD reported in patients with Mycoplasma pneumoniae (MP) infection.

Case presentation: A 6-year-old boy with severe Mycoplasma pneumoniae pneumonia (MPP) was transferred to our hospital due to significant respiratory distress on the 11th day from disease onset. Nadroparin, levofloxacin, and methylprednisolone followed by oral prednisone were aggressively prescribed. His clinical condition gradually achieved remission, and the drugs were withdrawn on the 27th day. Regrettably, the recurrent fever attacked him again in the absence of infection-toxic manifestations. Necrotizing pneumonia (NP) was found on chest CT. And echocardiography revealed right CAD (diameter, 3.40mm; z-score, 3.8), however, his clinical and laboratory findings did not meet the diagnostic criteria of KD. CAD was proposed to result from MP infection, and aspirin was prescribed. Encouragingly, the CAD regressed one week later (diameter, 2.50mm; z-score, 1.4). Additionally, the child defervesced seven days after the initiation of prednisone and Nadroparin treatment. The patient was ultimately discharged home on the 50th day. During follow-up, the child was uneventful with normal echocardiography and fully resolved chest CT lung lesions.

Conclusions: CAD can develop in patients with severe MP infection. Pediatricians should be alert to the possibility of CAD in patients with severe MP infection and recognize that CAD might also develop in febrile disease rather than KD.

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1. Introduction

Coronary artery aneurysm (CAD) is a rare disease, occurs in 0.3–4.9 % of patients undergoing coronary angiography. It may lead to fatal complications such as rupture, compression of adjacent cardiopulmonary structures, thrombosis, and distal embolism. The pathophysiological mechanism of CAD in children is still unknown and may be related to proteolytic imbalance, abnormal immune and inflammatory response [1]. Kawasaki disease (KD), the leading cause of acquired heart disease in children in developed countries, is known as a form of vasculitis with unknown causes, can lead to CAD formation commonly [2,3]. In addition, CAD also can occur in various inflammatory and infectious diseases, including systemic-onset juvenile idiopathic arthritis (SJIA) [4,5] polyarteritis nodosa

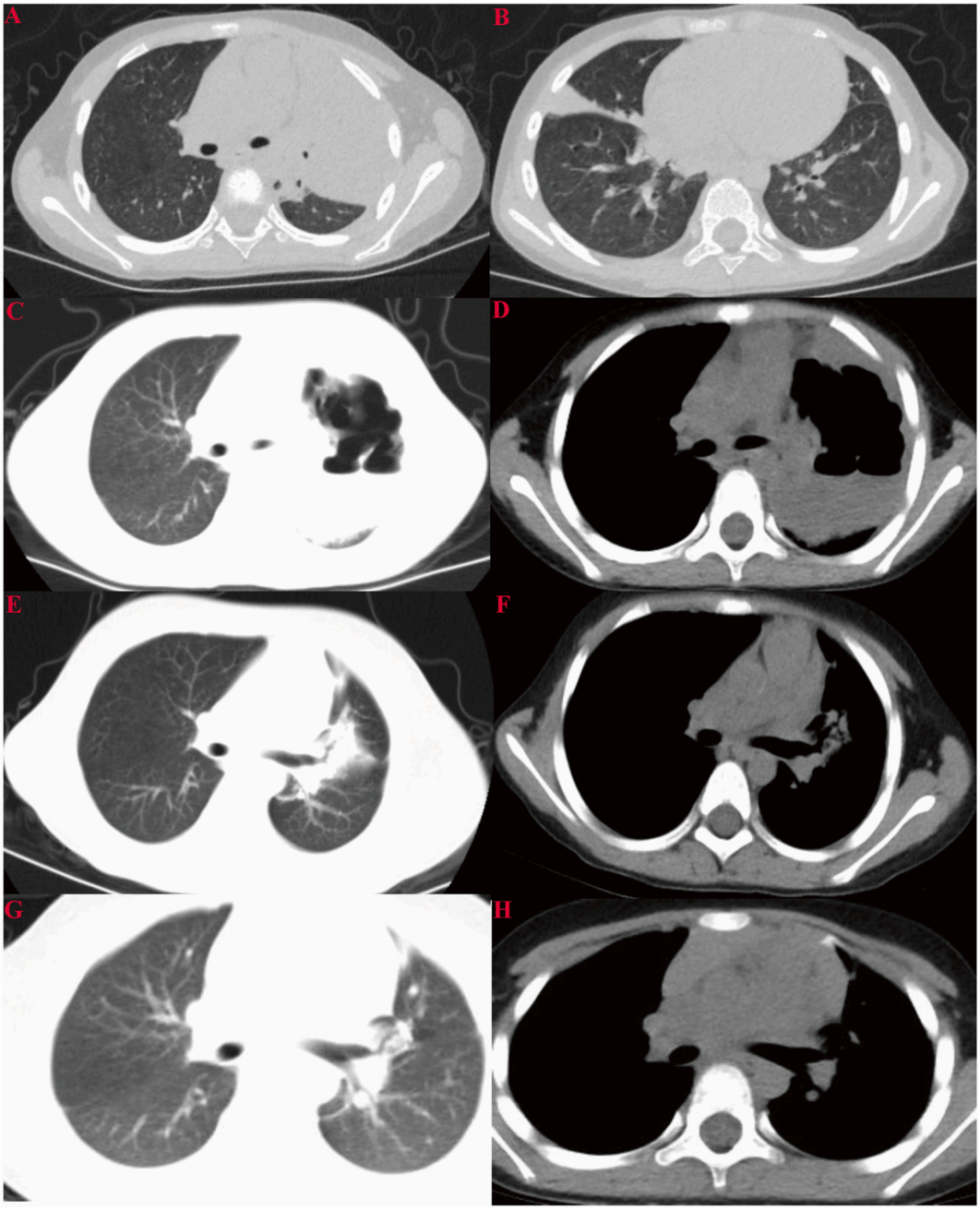


Fig. 1. A–B, Chest computed tomography (CT) identified bilateral diffuse parenchymal infiltration, lobar consolidation in the middle and lower lobes of the right lung and the upper lobe of the left lung, and bilateral pleural effusions. **C-D**, Chest CT was repeated, revealing worsened lung damage. **E–F**, On the 50th day after admission, chest CT showed lung lesions had partly resolved. **G–H**, Chest CT lung lesions completely resolved during follow-up.

(PAN) [6–9], systemic lupus erythematosus (SLE) [10–13], Epstein-Barr virus (EBV) infections [14–20], and Rickettsial infections [21]. These illnesses may have similar clinical features to KD; thus, enhancing awareness of other febrile diseases which may induce CAD is of great clinical significance to avoid misdiagnosis and thereby improve patient prognosis.

Mycoplasma pneumoniae (*M. pneumoniae*) is a common pathogen of the respiratory tract and is responsible for community-acquired pneumonia in school-aged children and adults [22]. *M. pneumoniae* infection is generally a self-limited and mild illness; however, clinical presentations vary from asymptomatic to severe complicated pneumonia with extrapulmonary manifestations. Some patients with *M. pneumoniae* pneumonia (MPP) are resistant to macrolide antibiotic therapy (refractory MPP [RMPP]). RMPP is characterized by prolonged fever and deteriorating radiological findings [23]. RMPP can involve extrapulmonary organs and tissues, including the neurological, dermatological, digestive, hematopoietic, and musculoskeletal systems; sensory organs; and the urogenital tract [24]. Notably, although cardiac involvement in patients with MPP is well documented [23,25], coronary artery damage is rare. To date, only two case of coronary artery lesions has been reported in MP infection [26,27].

In this study, we report the case of a 6-year-old boy with severe *M. pneumoniae* infection who developed CAD during the acute phase of MPP. This report highlights that clinicians should pay attention to the cardiovascular system especially for the CAD. Additionally, we performed a literature review on the presence of CAD in patients with febrile illnesses other than KD, aiming to increase understanding of the disease spectrum of pediatric CAD and avoid misdiagnosis of KD.

1.1. Case presentation

A 6-year-old male (height: 107.5cm, weight: 18.5kg), with no remarkable medical and family history, was admitted to the local hospital due to fever, cough, dyspnea, nasal flaring, and grunting lasting four days. Physical examination showed body temperature was 39.6 °C, respiratory rate was 48 breaths per minute, and oxygen saturation was 96 % undergoing mask oxygen inhalation (FiO_2 40 %). He had the presence of nasal flaring, accessory respiratory muscle exertion (three depressions sign), scattered crackles, dullness to percussion, decreased breath sounds, and grunting in the lung. No other positive findings, such as bilateral bulbar conjunctival injection without exudates, rash, edema or erythema of the extremities, erythema of oral and pharyngeal mucosa, erythema of palms or soles, and cervical lymphadenopathy, were identified by physical examination. Laboratory tests showed elevated levels of white blood cells (17.23×10^9/L, normal range: 4.03–11.09×10^9/L) with neutrophil dominance (89.9 %, normal range: 21.9%–68.5 %), C-reactive protein (CRP) (211.66 mg/L, normal range: 0–8 mg/L), procalcitonin (1.69 ng/ml, normal range: <0.05 ng/ml), and serum *M. pneumoniae*-immunoglobulin M (MP-IgM titer: 1:320, normal range: <1:160). Chest X-ray and computed tomography (CT) identified bilateral diffuse parenchymal infiltration, lobar consolidation in the middle and lower lobes of the right lung and the upper lobe of the left lung, and bilateral pleural effusions (Fig. 1A and B). Based on the presence of dyspnea, nasal flaring, grunting, bilateral pleural effusions, and multilobar infiltrates of the lungs, the diagnosis of severe MPP was established. Oral azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–7), intravenous cefotaxime (150 mg/kg/day for seven days), and noninvasive assisted ventilation were initiated.

On the 11th day following disease onset, the patient was transferred to the pediatric intensive care unit due to a deteriorating clinical condition (persistent fever, severe cough, and significant respiratory distress). On arrival, his body temperature was 38.0 °C, blood pressure was 106/74 mmHg, pulse was 140 beats per minute, respiratory rate was 60 breaths per minute, and oxygen saturation was 95 % undergoing mask oxygen inhalation (FiO_2 50 %). Physical examination revealed the presence of nasal flaring, accessory respiratory muscle exertion (three depressions sign), scattered crackles, dullness to percussion, decreased breath sounds, and grunting in the lung. Lung examination revealed scattered crackles, dullness to percussion, and decreased breath sounds in the upper lobe of the left lung. The presence of bilateral bulbar conjunctival injection without exudates, rash, edema or erythema of the extremities, erythema of oral and pharyngeal mucosa, erythema of palms or soles, periungual peeling of fingers and toes, or cervical lymphadenopathy, and other positive findings, were also not identified by physical examination. The liver function test showed elevated alanine transaminase (115 U/L) and aspartate transaminase (263 U/L) levels and decreased serum albumin (27.6 g/L) and lactate dehydrogenase (1376 U/L) levels. The repeated inflammatory indicators showed increased white blood cells (18.2×10^9/L) with dominant neutrophils (93.0 %), CRP (175.6 mg/L), and procalcitonin (0.7 ng/ml) levels. With normal erythrocyte sedimentation rate (ESR) (12mm/h, normal range: 0–20mm/h) level and mormal interleukin-6 level (2.03pg/ml, normal range: <5.9pg/ml). And the level of brain natriuretic peptide (BNP) was slight elevation (123.77pg/ml, normal range:0–100pg/ml). The coagulation function test showed an increased D dimer index (9.12 mg/l, normal range: <0.55 ml/l) and fibrin degradation products (28.8 μg/ml, normal range: <5 μg/ml). The level of total IgE was 72.4IU/ml (normal range: < 60IU/ml) by humoral immune test, and the level of other indicators like IgG, IgA, C3, C4, C1q were normal. The MP-IgM titer increased to >1:1280. On the 12th day following disease onset, fiber bronchoscopy with bronchoalveolar lavage revealed plastic bronchitis with increased cell count (neutrophil dominance). The polymerase chain reaction (PCR) assay was positive for *M. pneumoniae* and the bacterial culture and gram stain and fungal culture were negative in the bronchoalveolar lavage fluid and sputum. Microbial environmental genome demonstrated the positive for MP infection and negative for other microbiological pathogens. Tuberculosis and parasitic infection were not considered because the patient had a negative history of probable contact and negative bacille Calmette-Guerin, purified protein derivative test, T-SPOT.*TB* (Oxford Immunotec, Abbingdon, UK), and specific parasite antibody results. CMV-IgM, HSV-IgM, RV-IgM, EBV-IgM, JEV-IgM, EV71 antigen, coxsackie virus antigen were all negative. We also tested the common respiratory virus pathogens, including influenza virus, adenovirus, and respiratory syncytial virus, which were all negative by PCR assay in the bronchoalveolar lavage fluid and sputum. Chest X-ray showed no changes in pulmonary imaging. Electrocardiography and echocardiography were normal. Based on the increased MP-IgM titer, the patient's deteriorated respiratory distress, persistent fever, and no changes in pulmonary imaging after oral azithromycin administration for seven days, RMPP was proposed. Levofloxacin (8 mg/kg every 12 hours) and methylprednisolone (2 mg/kg/day for seven

days) followed by oral prednisone (2mg/kg/d × 7days, 1mg/kg/d × 4 days, 0.5mg/kg/d × 3 days) were prescribed for 21 days. With normal inflammatory mediator levels, the patient defervesced with resolved cough and respiratory distress three days after RMPP treatment initiation. On the 27th day after admission, the patient achieved remission, and drugs were withdrawn.

Fever returned on the 28th day but without manifestations of infection. The signs of lung examination remained without accessory respiratory muscle exertion, and other physical examinations, including bilateral bulbar conjunctival injection without exudates, rash, edema & erythema of the extremities, erythema of oral and pharyngeal mucosa, erythema of palms or soles, periungual peeling of fingers and toes, and cervical lymphadenopathy, were negative. Clinical history was re-evaluated, and further complementary tests were done. Only increased CRP levels (41.1 mg/l) and erythrocyte sedimentation rate (ESR; 47 mm/h) were found. Tests for other causative organisms, autoimmune disease, and immunocompromised host were negative. Chest CT was repeated, revealing worsened lung damage (Fig. 1C and D). The imaging findings and the patient's clinical manifestation strongly suggested necrotizing pneumonia (NP). Echocardiography was routinely repeated to exclude KD because of the recurrent fever, elevated CRP levels, and ESR. A right CAD with a z-score of 3.8 (diameter, 3.40 mm) was found (Fig. 2A), with a normal diameter of the left main coronary artery (LMCA, 2.55 mm (Fig. 2B),), proximal left anterior descending artery (LAD, 1.90 mm), and left proximal circumflex artery (LCX, 1.20 mm). Atypical KD was initially suspected. A pediatric cardiologist was consulted; despite the positive findings of echocardiography, the patient's clinical (no physical signs of KD) and laboratory findings (only elevated level of CRP and ESR) did not meet the diagnostic criteria for atypical KD according to the 2017 American Heart Association Recommendations for KD [1](If the patients have fever $\geq$ five days and two or three compatible clinical criteria with increased C-reactive protein (CRP)$\geq$30mg/l and/or erythrocyte sedimentation rate (ESR)$\geq$40mm/h, while there are more than three supplemental laboratory criteria including albumin$\leq$30g/l, elevated alanine aminotransferase (ALT) level, urine$\geq$10 WBC/hpf, white blood cell (WBC) count$\geq 15 \times 10^9$/l, platelet count after seven days $\geq 450 \times 10^9$/l, anemia for age, or less than three supplemental laboratory criteria but with positive echocardiogram, the diagnosis of incomplete KD is established).

Therefore, CAD was thought to develop due to the *M. pneumoniae* infection other than KD, and aspirin (5 mg/kg per day) was prescribed to treat the CAD. CAD regressed after one week, and aspirin was withdrawn. Echocardiography was thereafter performed weekly, with no presence of coronary artery lesions during the remaining hospitalization time.

We speculated the recurrent fever might be attributed to NP-related pyrogenic products of inflammation and tissue destruction because of the patient's negative presentation of infection. Thus, conservative treatment for NP was initiated, including oral prednisone (2 mg/kg/day) and nadroparin (75 U/kg/day). The patient defervesced seven days after NP treatment initiation. The prednisone dose tapered to 1 mg/kg on days 8–14 and 0.5 mg/kg/day on days 15–21 (Fig. 3). On the 50th day, prednisone and nadroparin were withdrawn because of his resolved clinical condition, and chest CT showed the lung lesions had partly resolved (Fig. 1E and F).

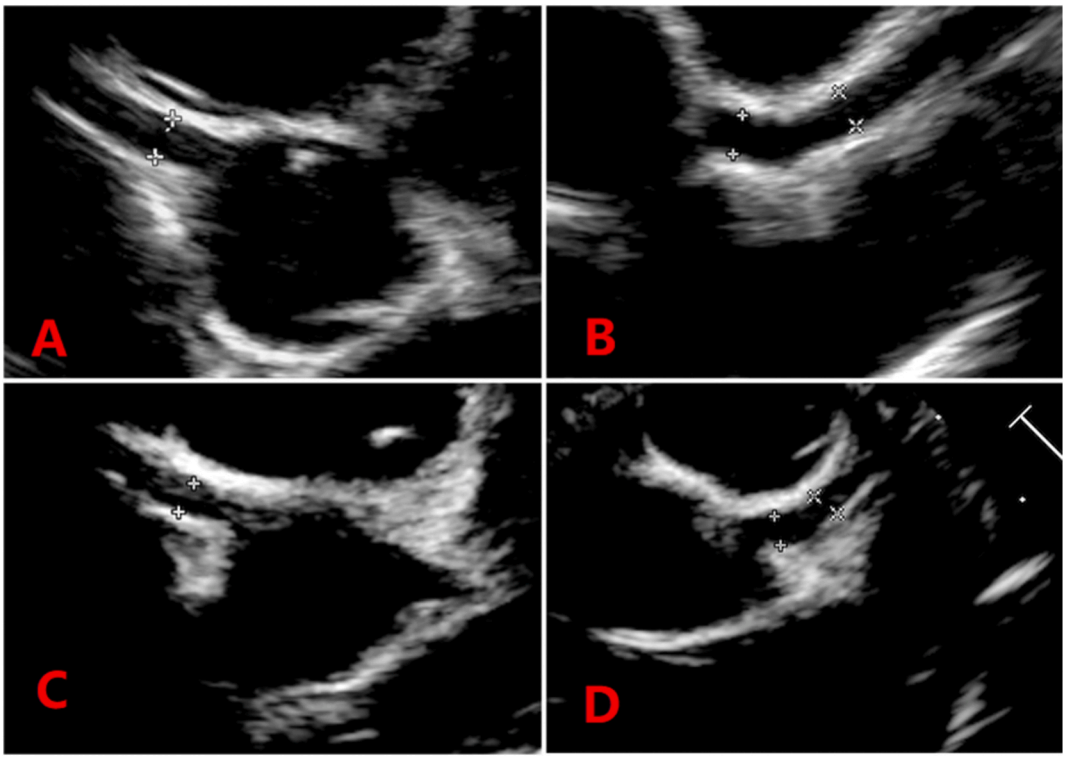


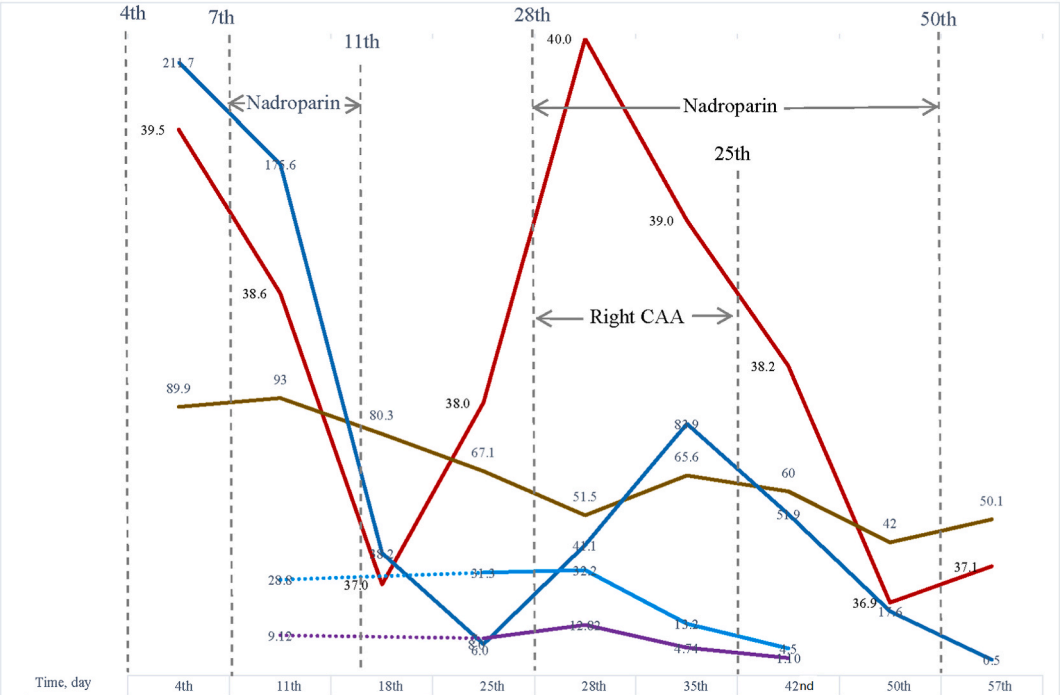
Fig. 2. A, right coronary artery aneurysm (CAD) with a z-score of 3.8 (diameter, 3.40 mm) was found on cardiac echocardiography at the 28th day. **B,** left main coronary artery (2.55 mm) and left descending artery (1.90mm) with normal diameter at the 28th day. **C,** diameter of right coronary artery aneurysm came to normal level (2.50 mm; z-score, 1.4) at the 42nd day, and with normal LCA (2.50 mm) in picture **D**.

The patient's clinical condition was ultimately controlled, and he was discharged home with normal inflammatory indicators and blood coagulation function. During follow-up, the child was uneventful with normal echocardiography (Fig. 2C and D) and fully resolved chest CT lung lesions. (Fig. 1G and H).

2. Discussion

A previous study demonstrated that children with *M. pneumoniae* infection can develop coronary artery lesions [26,27]; however, to our knowledge, this is the second case to report CAD due to *M. pneumoniae* infection. In this study, we identified CAD as a cardiac complication of *M. pneumoniae* infection after excluding the possibility of KD due to the absence of clinical and typical features of KD during the disease course. The present case suggested CAD may develop in febrile illnesses other than KD. Moreover, the study reviewed and summarized febrile illness (excluding KD) that can result in CAD development, which will benefit pediatricians in clinical practice.

The underlying mechanisms regarding CAD development in a patient with MP infection remain elusive. First, patients with fever and tachycardia had a greater myocardial demand for oxygen. Consequently, coronary blood flow may increase through the compensatory dilation of coronary arteries [26]. However, previous studies have demonstrated that dimensions of coronary arteries of children with prolonged fever are larger than those of healthy subjects but smaller than those of children suffering from KD [26]. Therefore, this mechanism could not explain the development of CAD in our patient. Second, several studies showed that patients with KD receiving a prolonged course of corticosteroid had a high incidence of coronary artery abnormalities [28,29]. Notably, these patients did not respond to initial IVIG treatment, which were identified as a risk factor for CALs [30]. Moreover, these studies were limited by the small sample size and retrospective nature of the design. On the contrary, recent randomized controlled studies demonstrated that primary IVIG infusion combined with corticosteroid decreased the incidence of coronary artery abnormalities in patients with KD [31–34]. Similar findings were also reported in a Cochrane review [35]. Moreover, both the RAISE and Post-RAISE study (multicenter randomized, open-label blinded-endpoints trail) in 2012 and 2018 further proved that the combination treatment consisting of IVIG and a longer course of prednisolone decreased the incidence of coronary artery abnormalities among high-risk KD patients for initial IVIG resistance predicted by Kobayashi risk-scoring system [33,36]. Thus, methylprednisolone administration might also not be responsible for the development of CAD in our case. Third, emerging evidence indicated that coinfection with MP might be a crucial cofactor for coronary artery disease [37]. MP was often detected in coronary plaques, mainly in the lipid cores of ruptured



Time, day	4th	11th	18th	25th	28th	35th	42nd	50th	57th
Fever,℃	39.5	38.6	37.0	38.0	40.0	39.0	38.2	36.9	37.1
N,%	89.9	93	80.3	67.1	51.5	65.6	60	42	50.1
CRP,mg/L	211.7	175.6	38.2	6.0	41.1	83.9	51.9	17.6	0.5
FDP,ug/ml		28.8		31.3	32.2	13.2	4.5		
DDI,mg/L		9.12		8.07	12.82	4.74	1.10		
RCA,mm					3.4	2.6	2.5	2.1	

Fig. 3. Clinical treatment course of the patient.

			diagnosed	CAA				
Karim, 2019	15/M	anti-synthetase syndrome, IIM	Seven weeks	7th week	Fever, rash, polyarthralgia, bilateral eye, and foot swelling	LMCA5.91mm LAD4.42mm	IVMP, CTX	Regression
Keskindemirci, 2014	2/M	iKD, SJIA	NA	NA	Fever, rash, arthritis, lymphadenopathy	LMCA 3.4	IVIG, aspirin, IV-MP, CSA, anakinra	Regression
Binstadt, 2005	11/F	iKD, SJIA	18 months	Simultaneous	Fever, rash, lymphadenopathy	LCMA4.0mm	MTX, hydroxychloroquine	Normal
Hui Zhang, 2020	13/M	iKD, SLE	10 days	Simultaneous	Fever, rash, rash, non-exudative conjunctivitis, lymphadenopathy, knee and ankle arthralgia	LCA5.5mm RCA6.1mm	IV-MP, prednisone	Unchanged
Agarwal, 2015	9/F	Systemic vasculitis, SLE	Two months	2nd month	Fever, arthralgias, thigh pain, lower extremities, bilateral conjunctival erythema, ulcer under her tongue, extremity changes, positive auto-immune, AIHA, ANA, anti-dsDNA	LAD4mm	IV MP, MTX, hydroxychloroquine, aspirin	Normal
	6/F	iKD, SLE	NA	NA	fever, non-exudative conjunctivitis, cervical adenopathy, rash, and knee and ankle arthralgia, positive ANA, dsDNA, AIHA, and arthritis,	LMCA4.2mm	IVIG, aspirin, IV MP, hydroxychloroquine	Normal
	13/M	SLE	One month		arthritis, AIHA, positive ANA, positive dsDNA and Smith antibodies, oral ulcers, and rash	LMCA5.0mm LAD4.2mm RCA4.4mm	IV MP, Rituximab, enalapril, hydroxychloroquine, aspirin	Regression
	13/F	SLE	Three months		arthritis, AIHA, glomerulonephritis, serositis, positive ANA, dsDNA, and Smith Ab	LMCA4.5mm LAD4.1mm	IV-MP, enalapril, prednisone, furosemide, hydroxychloroquine, mycophenolate mofetil	Normal
Blount, 2017	11/F	iKD, SLE	Three weeks	3rd week	lymphadenopathy, rash, and conjunctivitis	LMCA4.6mm LAD4.6mm LCX5.2mm	IV-MP, IVIG	Regression
Englund JA, 1983	14/M	SLE	14 days	14th day	RASH, ANA+, chest pain	Bilateral coronary artery aneurysms and occlusion	Prednisone, CTX Anticoagulation	Regression
Bloom, 2018	9/M	HSP	Nine days	Simultaneous	Petechiae, abdominal pain without fever	LMCA5.32mm	Infliximab, IVIG, aspirin	Normal
Hwang, 2012	17/F	polyarteritis nodosa	NA	NA	Hypertension, hypertensive retinopathy	Aneurysms in RCA	Prednisolone, CTX, Aspirin, warfarin,	NA
Canares TL, 2012	16/F	SJIA/Atypical KD/systemic vasculitis, juvenile PAN	11 years	11th year	Fever, arthritis, myalgias, rash, hypertension	LMCA9mm LAD8.7mm	Aspirin, warfarin, IV-MP, IVIG prednisone	Unchanged
Glanz, 1976	1/M	PAN	Two months	2nd month	Fever, rash, conjunctivitis	Aneurysms in LAD and LCX	Prednisone, azathioprine	Regression
Holt, 1975	0.3/M	PAN	Eight weeks	8th week	Fever, rash, respiratory distress, and cardiogenic shock	LCA10*12*9mm	Ampicillin	Die
Englund, 1983	14/M	SLE	Six months	6th month	Rash, hematologic disorders, positive ANA	Aneurysms in RCA	Prednisone, azathioprine anticoagulation	Regression
Kikuta, 1988	2/M	CAEBV	Three months	3rd month	Fever, hepatosplenomegaly, lymphadenopathy	RCA 6mm	NA	NA
Jiang S, 2016	16/F	CAEBV	18 months	18th month	Fever, hepatosplenomegaly, extensive lymphadenopathy	Multiple stenoses and dilations in RCA	Leflunomide, Medrol	Progress
Nakagawa, 1996	5/F	CAEBV	Eight months	8th month	Fever, rash, hepatosplenomegaly	RCA8mm LCA5mm	Acyclovir, interferon	Die
Ba HJ, 2019	10/M	CAEBV	Three year	3rd year	Rash	Aneurysms in RCA and LCA	IVIG, CTX, prednisone, ganciclovir, anticoagulation	Regression
Li GM, 2009	1.8/M	EBV	13 days	Simultaneous	Fever, convulsion	RCA3.8mm LCA4.1mm	Acyclovir, Anticoagulation, IVIG	Regression
Shi Yin, 2015	1.7/F	EBV	12 days	Simultaneous	Fever, lymphadenopathy	LCA3mm	Acyclovir, IVIG	Normal
Xie XF, 2016	6/F	CAEBV, MAS	16 months	15th month	Fever, rash, hepatosplenomegaly	RCA8.2mm LCA5.0mm	Corticosteroids, IVIG, CSA	Unchanged
	3/M	CAEBV	Two months	2nd month	Fever, lymphadenopathy	RCA4.0mm LCA4.8mm	Ganciclovir, IVIG, Anticoagulation	Unchanged
	2/M	CAEBV	Five months	5th month	Fever, lymphadenopathy, hepatosplenomegaly	LCA5.1mm	Acyclovir, Anticoagulation	Progress
	4/F	CAEBV	Eight months	8th month	Fever, rash, uveitis, hepatosplenomegaly	RCA6.1mm	Ganciclovir, corticosteroids, cyclosporin, MTX	Progress
Takano, 1990	1.8/F	Measles	NA	NA	Fever, hepatomegaly, lymphadenopathy	RCA4mm	antibiotic and adrenocortical	Die

plaques. Moreover, coronary artery plaque was a potential role of atherogenesis in the evolution of CAD long after KD [38]. Therefore, it suggested the direct vascular injuries might contribute to the development of CAD in patients with MP infection [39]. Lastly, another potential mechanism would involve pathogenic proteins of MP infection. It bind to the endothelial cells and activates immune response pathways, which produce cytokines and promote additional cellular damage [25]. However, the incidence of CAD associated with MP infection may be underestimated. Because echocardiography is not a routine test for patients with MP infection. The detailed pathogenesis of coronary artery damage in febrile illness other than KD and the relationship between MP infection and coronary artery involvement has not yet been identified. Therefore, more studies warrant to be carried out to explore the relationship between MP infection and coronary artery involvement.

Although the etiology of KD is not well known, it is speculated that specific infection agents might cause genetic susceptibility in certain children [40–42], which induces an aberrant immune response involving in the pathogenic process of this disease [43]. Notably, previous study found the overall positive rate of viral PCR referred to 50.4 % [42]. Therefore, the relationship between CAD, MP infection, and KD needs to be further clarified since MP infection was supposed to be one of the predisposing factors of KD [30, 44–46] and CAD was considered one of the most common complications of KD [47]. The incidence of MP infection in KD was reported to range from 3.4% to 10.7 % [44–46]. Despite the etiology of KD remains elusive, an abnormal and exaggerated inflammatory response to one or more environmental triggers in genetically predisposed individuals has been implicated [48,49]. As an inflammatory Mycoplasma lipid-associated membrane protein, the M. pneumoniae N602 protein may represent potential superantigens for the occurrence of uncontrolled immune response in KD [25]. In other words, MP infection might be an important causative agent for KD. However, unlike previous studies, our case and Muniz's study [26] provided additional evidence that MP infection could lead to the occurrence of CAD in the absence of typical features of KD. Like myocarditis, pericarditis, and endocarditis, CAD and KD should be regarded as two independent extrapulmonary complications of MP infection. Additionally, the management strategies were also different between patients with CAD and KD after MP infection. The combination of IVIG and aspirin administration is the primary therapy for KD patients with MP infection, while the macrolides and/or anticoagulants treatment is the cornerstone for patients with severe MP infection and CAD.

Clinically, on the basis of the development of CAD in febrile children, pediatricians were more likely to propose the primary diagnosis as atypical or incomplete KD. However, CAD was observed in various inflammatory and infectious diseases (Table 1), including SJIA [4,5,50], PAN [6–9], SLE [10–13], and EBV infections [14–20]. These findings make it clear that the etiology of coronary artery changes is not unique. Therefore, coronary changes should be carefully considered for the diagnosis of KD since patients with SJIA, PAN, and SLE could also share clinical features with KD. For instance, a total of six cases were initially misdiagnosed with incomplete KD due to the development of CAD and ultimately diagnosed with SLE [10–12], SJIA [5,50], and PAN [7]. Additionally, it was found that CAD was one of the cardiovascular complications of EBV infection [14–20]. There were also overlapping clinical features between EBV infection and incomplete/atypical KD. In addition, children with MIS-C resulting from SARS-CoV-2 can also develop CAD with an incidence of 13%–16.5 % [51,52]. These findings may have significant clinical implications that some of the febrile cases with the presence of CAD primarily considered incompatible with KD should be reconsidered. Other febrile diseases, including SJIA, PAN, SLE, EBV infection, and MP infection, should be excluded entirely before diagnosing incomplete/atypical KD since there were significant differences in the treatment strategies and prognosis of these diseases.

3. Conclusion

CAD can develop in patients with severe *M. pneumoniae* infection. Pediatricians should be aware of the possibility of CAD in patients with severe *M. pneumoniae* infection and recognize that CAD may develop in febrile illnesses other than KD. Other febrile diseases, including SJIA, PAN, SLE, EBV infection, and MP infection, should be excluded in patients complicated with CAD before diagnosing incomplete/atypical KD.

4. Ethics approval and consent to participate

Not Applicable.

5. Consent for publication

Informed consent was obtained from the patient(s) (or relative/guardian) for the publication of all images, clinical data and other data included in the main manuscript.

6. Availability of data and material

All data are included in this published article.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Yafei Guo: Writing – original draft. **Lixia Yang:** Writing – original draft. **Shuran Shao:** Resources. **Nanjun Zhang:** Resources. **Yimin Hua:** Resources. **Kaiyu Zhou:** Resources. **Fan Ma:** Writing – review & editing, Supervision. **Xiaoliang Liu:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not Applicable.

References

[1] A.S. Sheikh, A. Hailan, T. Kinnaird, A. Choudhury, D. Smith, Coronary artery aneurysm: evaluation, prognosis, and proposed treatment strategies, Heart Views 20 (3) (2019 Jul-Sep) 101–108, https://doi.org/10.4103/HEARTVIEWS.HEARTVIEWS_1_19. PMID: 31620255; PMCID: PMC6791093.
[2] B.W. McCrindle, A.H. Rowley, J.W. Newburger, J.C. Burns, A.F. Bolger, M. Gewitz, et al., Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American heart association, Circulation (2017), https://doi.org/10.1161/cir.0000000000000484.
[3] K.A. Taubert, A.H. Rowley, S.T. Shulman, Nationwide survey of Kawasaki disease and acute rheumatic fever, J. Pediatr. 119 (2) (1991) 279–282.
[4] S. Kumar, B. Vaidyanathan, S. Gayathri, L. Rajam, Systemic onset juvenile idiopathic arthritis with macrophage activation syndrome misdiagnosed as Kawasaki disease: case report and literature review, Epub 2010/12/07, Rheumatol. Int. 33 (4) (2013) 1065–1069, https://doi.org/10.1007/s00296-010-1650-8. PubMed PMID: 21132551.
[5] B.A. Binstadt, J.C. Levine, P.A. Nigrovic, K. Gauvreau, F. Dedeoglu, R.C. Fuhlbrigge, et al., Coronary artery dilation among patients presenting with systemic-onset juvenile idiopathic arthritis, Pediatrics 116 (1) (2005).
[6] J. Hwang, J.H. Yang, D.K. Kim, H.S. Cha, Polyarteritis nodosa involving renal and coronary arteries, J. Am. Coll. Cardiol. 59 (7) (2012) e13. PubMed PMID: 22322092.
[7] T.L. Canares, D.M. Wahezi, K.M. Farooqi, R.H. Pass, N.T. Ilowite, Giant coronary artery aneurysms in juvenile polyarteritis nodosa: a case report, Pediatric rheumatology online journal 10 (1) (2012) 1. PubMed PMID: 22222048.
[8] S. Glanz, S.J. Bittner, M.A. Berman, T.F. Dolan Jr., N.S. Talner, Regression of coronary-artery aneurysms in infantile polyarteritis nodosa, Epub 1976/04/22, N. Engl. J. Med. 294 (17) (1976) 939–941, https://doi.org/10.1056/nejm197604222941709. PubMed PMID: 3734.
[9] S. Holt, P. Jackson, Ruptured coronary aneurysm and valvulitis in an infant with polyarteritis nodosa, Epub 1975/10/01, J. Pathol. 117 (2) (1975) 83–87, https://doi.org/10.1002/path.1711170204. PubMed PMID: 5583.
[10] H. Zhang, L. Zhang, N. Guo, Pediatric-onset systemic lupus erythematosus with coronary artery dilation: a case report, Medicine 99 (5) (2020), e18946. PubMed PMID: 32000416.
[11] T.J. Blount, S.J. Ferns, Coronary artery dilatation in systemic lupus erythematosus, Prog. Pediatr. Cardiol. 47 (2017) 71–72.
[12] A. Agarwal, S.B.M. Student, S. Limstavros, J.K. Votavasmith, A. Ramanathan, Pediatric systemic lupus erythematosus presenting with coronary arteritis: a case series and review of the literature, Semin. Arthritis Rheum. 45 (1) (2015) 42–47.
[13] J.A. Englund, R.V. Lucas, Cardiac complications in children with systemic lupus erythematosus, Pediatrics 72 (5) (1983) 724–730. PubMed PMID: 6634279.
[14] B.L.X. Hongjun, L. Xuandi, L. Yuese, P. Huimin, W. HuiShen, Chronic active epstein-barr virus infection combined with systemic vasculitis:a case report and literature review, Practical Clinical Medicine 4 (20) (2019).
[15] X.G.L. Xf, P. h, L. Z, L.H. Zp W, Chronic active Epstein-Barr virus infection complicated with coronary aneurysm in four pediatric cases and the literature review, Chinese Journal of Applied Clinical Pediatrics 22 (31) (2016) 1721–1727.
[16] S. Jiang, X. Li, J. Cao, D. Wu, L. Kong, L. Lin, et al., Early diagnosis and follow-up of chronic active Epstein-Barr-virus-associated cardiovascular complica tions with cardiovascular magnetic resonance imaging: a case report, Medicine 95 (31) (2016), e4384. PubMed PMID: 27495050.
[17] Y.S. Xw, Reactivation of Epstein-Barr virus infection with coronary artery dilatation, Chin. J. Med. 12 (2015) 9–11.
[18] G.M.L. Sg, W. Sy, X. Z, H. Xl, L. Yq, Coronary artery dilatation caused by acute Epstein-Ban" virus infection: case report and literature review, JOURNAL OF CLINICAL PEDIATRICS 9 (27) (2009) 853–855.
[19] A. Nakagawa, M. Ito, T. Iwaki, Y. Yatabe, J. Asai, K. Hayashi, Chronic active Epstein-Barr virus infection with giant coronary aneurysms, Am. J. Clin. Pathol. 105 (6) (1996) 733–736. PubMed PMID: 8659448.
[20] H. Kikuta, Y. Taguchi, K. Tomizawa, K. Kojima, N. Kawamura, A. Ishizaka, et al., Epstein-Barr virus genome-positive T lymphocytes in a boy with chronic active EBV infection associated with Kawasaki-like disease, Nature 333 (6172) (1988) 455–457.
[21] J. Reyna, L.M. Reyes, L. Reyes, F.H. Campos, P. Meza, A. Lagunas, et al., Coronary artery dilation in children with febrile exanthematous illness without criteria for Kawasaki disease, Arq. Bras. Cardiol. 113 (6) (2019) 1114–1118.
[22] J.S. Bradley, C.L. Byington, S.S. Shah, B. Alverson, E.R. Carter, C. Harrison, et al., The management of community-acquired pneumonia in infants and children older than 3 months of age: cl inical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America, Clin. Infect. Dis. : an official publication of the Infectious Diseases Society of America 53 (7) (2011) e25–e76. PubMed PMID: 21880587.
[23] K.B. Waites, L. Xiao, Y. Liu, M.F. Balish, T.P. Atkinson, Mycoplasma pneumoniae from the respiratory tract and beyond, Clin. Microbiol. Rev. 30 (3) (2017) 747–809. PubMed PMID: 28539503.
[24] M. Narita, Classification of extrapulmonary manifestations due to mycoplasma pneumoniae infection on the basis o f possible pathogenesis, Front. Microbiol. 7 (2016) 23. PubMed PMID: 26858701.
[25] D. Poddighe, Extra-pulmonary diseases related to mycoplasma pneumoniae in children: recent insights into the pathogenesis, Curr. Opin. Rheumatol. 30 (4) (2018) 380–387.
[26] J.C. Muniz, K. Dummer, K. Gauvreau, S.D. Colan, D.R. Fulton, J.W. Newburger, Coronary artery dimensions in febrile children without Kawasaki disease, Epub 2013/01/30, Circulation Cardiovascular imaging 6 (2) (2013) 239–244, https://doi.org/10.1161/circimaging.112.000159. PubMed PMID: 23357243.

[27] I. Matthys, D. Borsboom, S. Steyaert, D. Vervloet, K. Cornelis, E. Vanderstraeten, et al., A plethora of manifestations following a Mycoplasma pneumoniae infection: a case report, Epub 2019/02/16, Acta Clin. Belg. 75 (3) (2020) 229–234, https://doi.org/10.1080/17843286.2019.1578029. PubMed PMID: 30767713.
[28] H. Kato, S. Koike, T. Yokoyama, Kawasaki disease: effect of treatment on coronary artery involvement, Pediatrics 63 (2) (1979) 175–179. Epub 1979/02/01. PubMed PMID: 440805.
[29] T. Kibata, Y. Suzuki, S. Hasegawa, T. Matsushige, T. Kusuda, M. Hoshide, et al., Coronary artery lesions and the increasing incidence of Kawasaki disease resistant to initial immunoglobulin, Epub 2016/04/14, Int. J. Cardiol. 214 (2016) 209–215, https://doi.org/10.1016/j.ijcard.2016.03.017. PubMed PMID: 27070994.
[30] Y. Tang, X. Gao, J. Shen, L. Sun, W. Yan, Epidemiological and clinical characteristics of Kawasaki disease and factors associated with coronary artery abnormalities in east China: nine years experience, J. Trop. Pediatr. 62 (2) (2016) 86–93. PubMed PMID: 26884440.
[31] Y. Inoue, Y. Okada, M. Shinohara, T. Kobayashi, T. Kobayashi, T. Tomomasa, et al., A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary artery outcome, Epub 2006/08/31, J. Pediatr. 149 (3) (2006) 336–341, https://doi.org/10.1016/j.jpeds.2006.05.025. PubMed PMID: 16939743.
[32] J.W. Newburger, L.A. Sleeper, B.W. McCrindle, L.L. Minich, W. Gersony, V.L. Vetter, et al., Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease, Epub 2007/02/16, N. Engl. J. Med. 356 (7) (2007) 663–675, https://doi.org/10.1056/NEJMoa061235. PubMed PMID: 17301297.
[33] T. Kobayashi, T. Saji, T. Otani, K. Takeuchi, T. Nakamura, H. Arakawa, et al., Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial, Epub 2012/03/13, Lancet 379 (9826) (2012) 1613–1620, https://doi.org/10.1016/s0140-6736(11)61930-2. PubMed PMID: 22405251.
[34] S. Ogata, Y. Ogihara, T. Honda, S. Kon, K. Akiyama, M. Ishii, Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial, Epub 2011/12/07, Pediatrics 129 (1) (2012) e17–e23, https://doi.org/10.1542/peds.2011-0148. PubMed PMID: 22144699.
[35] A.J. Wardle, G.M. Connolly, M.J. Seager, R.M. Tulloh, Corticosteroids for the treatment of Kawasaki disease in children, Cochrane Database Syst. Rev. 1 (2017) Cd011188. PubMed PMID: 28129459.
[36] K. Miyata, T. Kaneko, Y. Morikawa, H. Sakakibara, T. Matsushima, M. Misawa, et al., Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicentre, prospective cohort study, Epub 2018/10/20, Lancet Child Adolesc Health 2 (12) (2018) 855–862, https://doi.org/10.1016/s2352-4642(18)30293-1. PubMed PMID: 30337183.
[37] Y. Momiyama, R. Ohmori, H. Taniguchi, H. Nakamura, F. Ohsuzu, Association of Mycoplasma pneumoniae infection with coronary artery disease and its interaction with chlamydial infection, Atherosclerosis 176 (1) (2004) 139–144. PubMed PMID: 15306186.
[38] Y. Mitani, H. Ohashi, H. Sawada, Y. Ikeyama, H. Hayakawa, S. Takabayashi, et al., In vivo plaque composition and morphology in coronary artery lesions in adolescents and young adults long after Kawasaki disease: a virtual histology-intravascular ultrasound study, Epub 2009/05/20, Circulation 119 (21) (2009) 2829–2836, https://doi.org/10.1161/circulationaha.108.818609. PubMed PMID: 19451352.
[39] M.L. Higuchi, J.A. Ramires, Infectious agents in coronary atheromas: a possible role in the pathogenesis of plaque rupture and ac ute myocardial infarction, Rev. Inst. Med. Trop. Sao Paulo 44 (4) (2002) 217–224. PubMed PMID: 12219114.
[40] C.L. Wang, Y.T. Wu, C.A. Liu, H.C. Kuo, K.D. Yang, Kawasaki disease: infection, immunity and genetics, Epub 2005/11/12, Pediatr. Infect. Dis. J. 24 (11) (2005) 998–1004, https://doi.org/10.1097/01.inf.0000183786.70519.fa. PubMed PMID: 16282937.
[41] K.P. Weng, J. Cheng-Chung Wei, Y.M. Hung, S.H. Huang, K.J. Chien, C.C. Lin, et al., Enterovirus infection and subsequent risk of Kawasaki disease: a population-based cohort study, Epub 2017/08/24, Pediatr. Infect. Dis. J. 37 (4) (2018) 310–315, https://doi.org/10.1097/inf.0000000000001748. PubMed PMID: 28834956.
[42] L.Y. Chang, C.Y. Lu, P.L. Shao, P.I. Lee, M.T. Lin, T.Y. Fan, et al., Viral infections associated with Kawasaki disease, Epub 2014/02/06, Journal of the Formosan Medical Association = Taiwan yi zhi 113 (3) (2014) 148–154, https://doi.org/10.1016/j.jfma.2013.12.008. PubMed PMID: 24495555; PubMed Central PMCID: PMCPMC7125523.
[43] T. Hara, Y. Nakashima, Y. Sakai, H. Nishio, Y. Motomura, S. Yamasaki, Kawasaki disease: a matter of innate immunity, Epub 2016/06/28, Clin. Exp. Immunol. 186 (2) (2016) 134–143, https://doi.org/10.1111/cei.12832. PubMed PMID: 27342882; PubMed Central PMCID: PMCPMC5054572.
[44] Y. Lan, S. Li, D. Yang, J. Zhou, Y. Wang, J. Wang, et al., Clinical characteristics of Kawasaki disease complicated with Mycoplasma pneumoniae pneumonia: a retrospective study, Epub 2020/05/10, Medicine 99 (19) (2020), e19987, https://doi.org/10.1097/md.0000000000019987. PubMed PMID: 32384451; PubMed Central PMCID: PMCPMC7220055.
[45] Y. Tang, W. Yan, L. Sun, J. Huang, W. Qian, M. Hou, et al., Kawasaki disease associated with Mycoplasma pneumoniae, Ital. J. Pediatr. 42 (1) (2016) 83. PubMed PMID: 27609267.
[46] M.N. Lee, J.H. Cha, H.M. Ahn, J.H. Yoo, H.S. Kim, S. Sohn, et al., Mycoplasma pneumoniae infection in patients with Kawasaki disease, Korean journal of pediatrics 54 (3) (2011) 123–127.
[47] R. Fukazawa, J. Kobayashi, M. Ayusawa, H. Hamada, T. Kimura, JCS/JSCS 2020 guideline on diagnosis and management of cardiovascular sequelae in Kawasaki disease, Circ. J. 2020 84 (8) (2020) 1348–1407, https://doi.org/10.1253/circj.CJ-19-1094. Epub 2020 Jul 8. PMID: 32641591.
[48] K.Y. Lee, J.W. Rhim, J.H. Kang, Kawasaki disease: laboratory findings and an immunopathogenesis on the premise of a "protein homeostasis system, Epub 2012/02/10, Yonsei Med. J. 53 (2) (2012) 262–275, https://doi.org/10.3349/ymj.2012.53.2.262. PubMed PMID: 22318812; PubMed Central PMCID: PMCPMC3282974.
[49] J.W. Rhim, H.M. Kang, J.W. Han, K.Y. Lee, A presumed etiology of Kawasaki disease based on epidemiological comparison with infectious or immune-mediated diseases, Epub 2019/06/06, Frontiers in pediatrics 7 (2019) 202, https://doi.org/10.3389/fped.2019.00202. PubMed PMID: 31165053; PubMed Central PMCID: PMCPMC6536658.
[50] G. Keskindemirci, N. Aktay Ayaz, N. Melikoğlu, H. Bornaun, Ç. Aydoğmuş, E. Aldemir, et al., Systemic onset juvenile idiopathic arthritis with macrophage activation syndrome and coronary artery dilatation misdiagnosed as Kawasaki disease, Turk. J. Pediatr. 57 (5) (2015) 518–521. Epub 2016/07/15. PubMed PMID: 27411422.
[51] E.D. Belay, J. Abrams, M.E. Oster, J. Giovanni, T. Pierce, L. Meng, et al., Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic, JAMA Pediatr. 175 (8) (2021) 837–845, https://doi.org/10.1001/jamapediatrics.2021.0630. PubMed PMID: 33821923; PubMed Central PMCID: PMCPMC8025123 Disease Control and Prevention Epidemiology and Laboratory Capacity for Prevention and Control of Emerging Infectious Diseases (ELC) during the conduct of the study. No other disclosures were reported.
[52] S.E. Petersen, M.G. Friedrich, T. Leiner, M.D. Elias, V.M. Ferreira, M. Fenski, et al., Cardiovascular magnetic resonance for patients with COVID-19, Epub 2021/10/18, JACC Cardiovascular imaging 15 (4) (2022) 685–699, https://doi.org/10.1016/j.jcmg.2021.08.021. PubMed PMID: 34656482; PubMed Central PMCID: PMCPMC8514168.