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A 9-Year-Old Child with Kawasaki Disease Complicated with Mycoplasma Infection: A Case Report and Literature Review

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Abstract

Kawasaki disease (KD), also known as cutaneous mucosal lymph node syndrome, is an immune-mediated vasculitis, which is easy to involve small and medium-sized arteries, especially coronary arteries, and can cause a variety of cardiac sequelae. It primarily affects children from 6 months to 5 years old. In recent years, it has been reported that the incidence of KD is gradually increasing, and there are some reports of KD in teenagers and even adults. By reporting the clinical data of a 9-year-old KD child with mycoplasma infection who presented to children's Hospital of Second Affiliated Hospital of Shaanxi University of Chinese Medicine and reviewing relevant literature, this paper aims to provide clinical reference for the prevention and treatment of missed diagnosis of KD in older children.

Keywords: Kawasaki disease, older children, risk factors, clinical treatment

1. Introduction

Kawasaki disease (KD) is a rush and fever illness with systemic vasculitis as the main lesion, first reported by a Japanese named Kawasaki in the 1970s (Kawasaki, T., 1967), so it is called Kawasaki disease. It usually occurs in children below 5 years old throughout the year. In recent years, the incidence of KD has increased significantly in East Asia, and the reports of KD among adolescents and even adults have gradually increased (Subspecialty Group of Cardiology the Society of Pediatrics, Subspecialty Group of Rheumatology the Society of Pediatrics, Subspecialty Group of Immunology the Society of Pediatrics, et al., (2022; Marchesi, A., Tarissi, D. J. I., Rigante, D., et al., 2018; Falcini, F., Capannini, S., & Rigante, D., 2011). However, the rate of early misdiagnosis of KD in adolescents is still high due to its atypical symptoms (Liu, X., Wang, F., Zhou, K., et al., 2021). The cause of the KD is still unknown, but it is considered to be related to infection factors at present. The main clinical manifestations of KD include acute fever, rash,

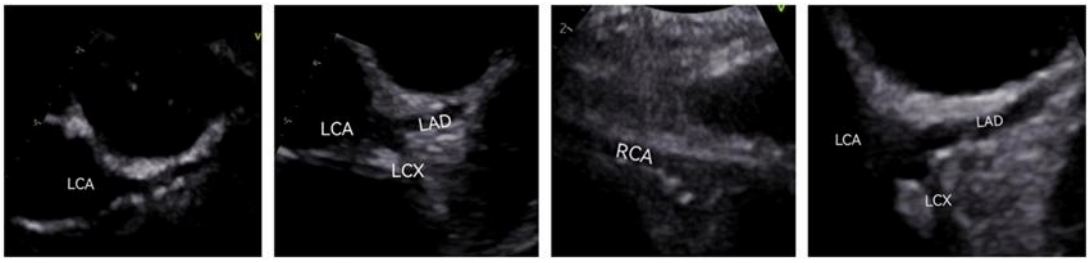
eye conjunctival congestion, oral mucosal hyperemia, swelling of hands and feet, etc. The most common complications are cardiovascular complications, acute phase can be combined with myocardial inflammation. Diagnosis of typical KD is made on the basis of the evidence of fever along with 4 out of the 5 other symptoms (Table 1). According to reports, some children have left ventricular enlargement with systolic dysfunction, and it can even cause segmental myocardial dyskinesia and ventricular aneurysm formation. Coronary artery disease will be gradually developed into persistent coronary aneurysm and coronary dilation, etc. Severe cases may even develop into coronary aneurysm rupture, myocardial infarction and other serious consequences, which is the main cause of acquired heart disease in children (Subspecialty Group of Cardiology the Society of Pediatrics, Subspecialty Group of Rheumatology the Society of Pediatrics, Subspecialty Group of Immunology the Society of Pediatrics, et al., 2022). This paper reported the clinical data of a 9-year-old child with KD admitted to the Children's Hospital of the Second Affiliated Hospital of Shaanxi University of Chinese Medicine, and analyzed the prognosis of the child after using IVIG and aspirin, in order to provide clinical reference for the diagnosis of KD and treatment plan in older children.

2. Case Presentation

We describe a case of KD in a 9-year-old child with mycoplasma infection, presented with persistent fever, coughing, conjunctivitis and swollen cervical lymph nodes. The boy's condition had not improved with empirical antibiotic treatment. His white blood cells rose to 18.42×10^9/L, neutrophil percentage to 84.2%, C-reactive protein (crp) to 109.4mg/L, serum amyloid over 200 mg/L, PCT to 0.41 ng/mL, IL-6 to 132.1 pg/mL, and erythrocyte sedimentation rate (esr) over 40MM/H, Cardiac ultrasound examination results showed that the inner diameter of the left main coronary artery was 4.3mm, and the ratio of the left main coronary artery was increased (Figure 2 B , Figure 2 C). Combined with clinical manifestations and auxiliary examination: 1) Fever lasting more than 5 days, 2) Cervical lymph node enlargement, 3) The mouth mucosa is chapped, 4) Bulbar conjunctival congestion, 5) Cardiac ultrasound suggested that the inner diameter of the left main coronary artery was widened, so the diagnosis of KD was established. According to the consensus recommendation of KD, intravenous infusion of human immunoglobulin (IVIG)2g/kg should give, a total of 78g, to prevent coronary artery injury. Aspirin enteric-coated tablet was added 0.2g/ time, and oral administration once a day was used to inhibit platelet aggregation. The white blood cells in the blood were checked again to the normal value and the crp was 42.7mg/L. On the 8th day after admission, the patient had peeling skin on the end of the finger, which was consistent with the clinical manifestations of KD. Re-examination of cardiac ultrasound indicated that there was no further dilation of the left coronary artery (Figure2 D). One month after discharge, the patient's blood indices were normal, and the results of a repeat cardiac ultrasound showed there was no significant change in the diameter of the left coronary artery. Outpatient clinic continued observation.

Table 1. Clinical features of classical Kawasaki disease patient and the supporting laboratory findings

Classical clinical case definition	**Supportive laboratory findings**
Persistent fever for 5 days with additional at least 4 of the 5 following symptoms: ● Bilateral conjunctival injection ● Changes in lips and oral mucosa ● Polymorphous exanthema ● Cervical lymphadenopathy, usually unilateral ● Changes in hands and feet: erythema, edema and desquamation.	● Elevated Erythrocyte sedimentation rate (ESR) ● Elevated C Reactive Protein (CRP) ● Leukocytosis with neutrophilia ● Hyponatremia ● Hypoalbuminemia ● Anemia



A B C D

Figure 2.

(Echocardiographic images of normal children and children with KD: figure A: Left coronary artery (LCA) in normal children B: The child's 1st left coronary artery examination. LAD (Left anterior descending), LCX (Left circumflex artery) C: The child's 1st right coronary artery (RCA) examination DS review of left coronary artery.)

3. Discussion

The incidence of KD has been reported is gradually increasing worldwide. The etiology of KD is still unclear, but it may be related to the following factors: (1) Pathogen infection and vaccination, but no specific infectious pathogen has been found (Nakamura, A., Ikeda, K., & Hamaoka, K., 2019); (2) environmental factors (Abrams, J. Y., Blase, J. L., Belay, E. D., et al., 2018); (3) genetic susceptibility, and it has been studied that there are 5 genes related to susceptibility to KD, coronary artery complications, and IVIG resistance (Alphonse, M. P., Duong, T. T., Shumitzu, C., et al., 2016; Onouchi, Y., Suzuki, Y., Suzuki, H., et al., 2013; Peng, Q., Deng, Y., Yang, X., et al., 2016; Kawasaki, K., Freimuth, J., Meyer, D. S., et al., 2014; Shimizu, C., Jain, S., Davila, S., et al., 2011), namely ITPKC, CASP3, SMAD3, TGFB2, TGFBR2; (4) Immune response. The exact mechanism of the inflammatory response in KD leading to coronary artery injury is unknown, and is currently considered to be related to pro-inflammatory cytokines released by inflammatory cells, including complement and immune complex (Watanabe, T., 2018), matrix metalloproteinase (MMP) (Alexander, M. R., Moehle, C. W., Johnson, J. L., et al., 2012) and microRNA (Si, X., Cao, D., Chen, J., et al., 2018) promoting the transformation and proliferation of coronary vascular smooth muscle cells. In previous statistical analysis, coronary artery damage was believed to be related to the following factors (Beiser, A. S., Takahashi, M., Baker, A. L., et al., 1998; Kavey, R. E., Allada, V., Daniels, S. R., et al., 2006): Male, age < 12 months or > 8 years, fever duration > 10 days, leukocytosis > 15,000/mm^3, low hemoglobin (< 10 g/dL), thrombocytopenia, hypoalbuminemia, hyponatremia, and persistent fever or recurrent fever 36 hours after IVIG administration. In this case, the degree of coronary artery dilatation was obvious in a 9-year-old KD child, and later follow-up recovery was slow, we considered whether it was related to his older age and combined mycoplasma infection. A clinical observation of Wuhan Union Medical College Hospital (Cai, Z., Zuo, R. & Liu, Y., 2011) showed that children with KD in the older group (> 5 years old) had a more obvious inflammatory response and a higher incidence of coronary artery abnormalities than those in the younger group (< 5 years old),the cause is still unknown. A statistical analysis in Spain showed that children under 12 months of age are more likely to suffer from coronary aneurysms than older children (Fernandez-Cooke, E., Barrios, T. A., Sanchez-Manubens, J., et al., 2019). However, another study in China (Peng, Y., Liu, X., Duan, Z., et al., 2021) concluded that the risk of coronary artery damage in children with KD under 1 year old was not significantly different from that in other age stages in the acute stage, but 2 months after echocardiography, the risk of coronary artery damage in children under 1 year old was still higher than that in other age stages. Meanwhile, patients with larger CAL (Coronary artery lesions), ≥ 60 months old, and with recurrent status or parental history may result in worse coronary outcome (Cai, Z., Zuo, R. & Liu, Y., 2011). Therefore, at this stage, the only thing we know is that the risk of KD coronary artery damage and later prognosis may be related to age. However, due to the limited number of

children with KD at all ages, we still need a large number of experimental data studies to further study the relationship between age and KD, and determine the age limit to provide conditions for the effective prediction of CAL. This report may also be used in subsequent studies.

Is KD associated with mycoplasma infection? Some clinical observations (Vitale, E.A., La Torre, F., Calcagno, G., et al., 2010; Lee, M.N., Cha, J.H., Ahn, H.M., et al., 2011) indicate a possible association between KD and mycoplasma infection. Meanwhile, mycoplasma infection is thought to be an important factor in the recurrence of KD (Tan, A.X. & Tang, X.M., 2021). However, there are clinical experiments (Lan, Y., Li, S., Yang, D., et al., 2020) showed that although the release of inflammatory factors in children with KD with MP infection is more than that in children without MP infection, it did not increase the probability of coronary artery damage. Therefore, the correlation between MP and KD coronary artery damage degree still needs to be proved by a large number of clinical trial data. If there is a correlation, the specific mechanism needs to be further discussed.

The initial treatment of acute KD, especially the dosage and time of high-dose aspirin, are not consistent with the recommendations of different medical institutions at home and abroad. The general consensus in China is that IVIG (2g/kg) infusion should be given immediately after the diagnosis of KD is confirmed. Children with large body weight (>20kg) can be given 1g/kg infusion every day for 2 consecutive days, while aspirin should be given 30-50mg (kg•d) orally in 3 times, and the recovery period is low dose (3-5) mg/ (kg•d). However, KD Diagnosis and Treatment Guidelines of The American Heart Association in 2017 (McCrindle, B.W., Rowley, A.H., Newburger, J.W., et al., 2017) recommended that high-dose aspirin (80-100mg /kg/ day) be given 4 times/day in KD acute phase, and 3-5 mg/kg/ day in low-dose aspirin after 48-72h fever withdrawal.

As a non-steroidal anti-inflammatory drug, aspirin is mainly metabolized through liver in the body, and its cumulative effect can cause hepatotoxicity, the mechanism of liver injury is not clear yet (Wen, C., Zhuang, Z., Song, H., et al., 2018). By referring to domestic and foreign literature in recent years, some children (Han, Y., Hu, C. & Yu, Y., 2020) with no history of liver disease and normal liver function had drug induces liver injury due to the use of large doses of aspirin (within the prescribed dosage range) during the acute stage of KD. Some other reports (Kuo, H.C., Lo, M.H., Hsieh, K.S., et al., 2015) claimed that high-dose aspirin may affect abnormal iron metabolism and lead to anemia in children with KD treated with IVIG, and believed that high-dose aspirin would not have any benefit on inflammation in the acute phase of KD and would not improve treatment results. In a meta-analysis of high-dose aspirin (>30mg/ day) and low-dose aspirin (<10mg/ day) in the acute phase of KD (Jia, X., Du, X., Bie, S., et al., 2020), comparing the effects of different doses of aspirin on the number of days of fever, coronary artery injury and days of hospitalization in children with KD, concluded that low-dose aspirin plus IVIG may be related to high doses of aspirin and IVIG in initial treatment of KD and there was no significant difference. High doses of aspirin in children with fever can shorten the time, but it has no obvious protective effect on the heart, and can't prevent coronary artery lesion. This conclusion is the same as a Korean investigation (Kim, G.B., Yu, J.J., Yoon, K.L., et al., 2017). This child in this case was an older child with a large body weight. Considering the above factors, the initial dose of aspirin in this case report was maintenance dose of 3 ~ 5mg/ (kg•d). In view of the particularity of children's physiology and pathology, there were many adverse reactions in the early treatment of KD with high-dose aspirin. In addition, recent experimental results show that high-dose aspirin cannot prevent coronary artery injury and does not significantly reduce inflammation. Does this mean that low-dose aspirin combined with IVIG can be used as first-line medication? We still need a large number of clinical trial data and theoretical studies to prove this conclusion.

As for the dosage of IVIG, all current guidelines recommend 2g/kg IVIG as the first-line drug for KD. However, a Japanese study compared the coronary artery abnormalities, adverse reactions, IVIG resistance, length of hospital stay and costs of children with KD who received low dose (1g/kg) and high dose (2g/kg) of IVIG from 2010 to 2017, which found that there was no significant distinction between the two groups except hospitalization costs. This research is consistent with the results of a study in Shanghai (He, L., Liu, F., Yan, W., et al., 2021)

which may indicate that the dosage of IVIG is in doubt.

No response to standard treatment for KD, or IVIG resistance occurs, many national guidelines suggest that all patients should be given a second dose of IVIG at the same dosage (Scherler, L., Haas, N.A., Tengler, A., et al., 2022). Although glucocorticoid is the first IVIG additive, it has not remarkable effect on reducing CAA (Coronary artery anomalies) rates (Miyata, K., Kaneko, T., Morikawa, Y., et al., 2018; Chen, S., Dong, Y., Kiuchi, M. G., et al., 2016) as second-line treatment. Biological drugs, mostly proposed as third-line treatment when KD patients are irresponsive to two IVIGs and corticosteroid courses. TNF-α blockers: infliximab and etanercept added to first-line IVIG treatment indicated no effect on IVIG resistance (Portman, M. A., Dahdah, N. S., Slee, A., et al., 2019; Tremoulet, A. H., Jain, S., Jaggi, P., et al., 2014), but can reduce duration of fever and systemic inflammation, and etanercept appears to ameliorate CA dilation. Human IL-1 receptor antagonist: Anakinra, may have some effects on reducing fever, markers of systemic inflammation, and coronary artery dilatation in individuals with IVIG-refractory KD (Kone-Paut, I., Tellier, S., Belot, A., et al., 2021). CsA (ciclosporin-A) inhibiting the Ca^{2+}/NFAT pathway might contribute to prevent the development of CAA (Hamada, H., Suzuki, H., Onouchi, Y., et al., 2019).

4. Conclusion

The etiology of KD is unclear, we can derive the factors associated with its onset and causing coronary artery damage through data analysis, which can lead to a deeper understanding of KD, thus raising pediatricians' vigilance, diagnosing early, slowing down the rate of missed diagnosis and misdiagnosis, and effectively preventing further coronary artery damage. In terms of treatment, individual differences in treatment, controversies over the usage and dosage of aspirin and IVIG, and inconsistencies in the treatment of KD protocols across countries have created much confusion and uncertainty in the treatment of KD. We need more high-quality experiments to provide more evidence for the treatment of KD.

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