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Viral infections associated with Kawasaki disease

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Kawasaki disease (KD) is a febrile, acute, and self-limiting form of vasculitis that affects middle-sized arteries, particularly coronary arteries. It is generally reported in children younger than five years of age. A diagnosis of KD is based on the presence of a prolonged fever, accompanied by four of the following five findings: conjunctival injection, oral changes, cervical lymphadenopathy, extremity changes, and polymorphous rash. The etiopathogenesis of KD remains unclear, and it has been suggested that various infectious agents may trigger KD development in genetically susceptible individuals (1). Additionally, several features of KD resemble the features of viral infectious diseases, such as influenza, Epstein-Barr virus (EBV), and adenovirus. Therefore, the differential diagnosis of KD may be challenging for clinicians. In this study, we have highlighted the cases of five patients diagnosed with KD who presented with concomitant viral symptoms. We aimed to increase awareness among physicians that viral infections might coexist with KD, and a diagnosis of KD should not be easily excluded in patients presenting with concomitant viral symptoms and documented viral infections.

All patients who had been referred to our clinic presented with a prolonged fever, non-suppurative conjunctivitis, cervical lymphadenopathy, strawberry tongue, fissured lips, edema on the hands, and/or a maculopapular rash. In addition to these findings, patients presented with otorrhea, cough, nasal discharge, and/or arthritis. Demographic, clinical, laboratory, and microbiological data of the patients are presented in Table 1. All patients fulfilled the established KD criteria. The patients' acute-phase reactant levels were elevated. Viruses were identified in the patients' nasopharyngeal secretions using a real-time polymerase chain reaction (rt-PCR). Influenza, parainfluenza, rhinovirus, and/or enterovirus were identified. Patients were treated with intravenous immunoglobulin (IVIG) (2 g/kg) and aspirin (50 mg/kg). The anti-platelet dose of aspirin (3-5 mg/kg) was ceased in all patients at the end of the third month. Patients 1 and 2, who had concomitant influenza infection, were subjected to the administration of a second dose of IVIG treatment owing to persistent fever lasting for a duration of 36 hours. During the follow-up examination, typical desquamation of the distal fingers was observed in all patients. Mild coronary artery lesions that were detected in patients 3 and 5 could not be detected during the follow-up period. We did not observe any findings suggestive of Reye syndrome associated with aspirin usage. Informed consent was obtained from all individual participants.

In KD, concomitant infections may be observed during the course of the disease. The coexistence of typical KD symptoms and viral symptoms, such as cough, nasal discharge, and otorrhea, results in confusion during formulation of a differential diagnosis.

Several bacterial and viral infectious agents have been isolated from patients with KD. However, it remains unclear whether these agents are etiological triggers or simply concomitant infections. (1). Prior reports concerning concomitant infections in patients with KD, including adenovirus, klebsiella, parainfluenza, EBV, bocavirus, influenza, coxsackievirus, Varicella Zoster virus, enterovirus, and rhinovirus, were reported (2-9). In the previous year, KD-like disease associated with severe acute respiratory syndrome coronavirus 2 infection was reported, with children presenting with myocarditis, toxic shock syndrome,

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Table 1. Demographic, clinical, laboratory, and microbiological characteristics of patients

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (months)	42	52	54	94	64
Gender	Male	Female	Female	Male	Male
Day number of fever	10	9	7	6	6
Non-suppurative conjunctivitis	+	+	+	+	+
Cervical lymphadenopathy	+	+	+	+	+
Strawberry tongue and ragats	+	+	+	+	+
Maculopapular rash	+	+	+	+	-
Peeling-edema on hands and toes	+	+	+	+	+
Concomitant viral infection	Influenza	Influenza	Parainfluenza	Enterovirus+ Rhinovirus	Rhinovirus
Echocardiography findings	Normal	Normal	Milder aneurysm of LCA	Normal	Milder aneurysm of LCA
Z score	Normal	Normal	+2.7	Normal	+5
Additional findings	Otorrhea, cough	Cough, nasal discharge	Arthritis of the knee, cough, nasal discharge	Cough, nasal discharge	Cough, nasal discharge
ESR (mm/h)	92	75	80	74	60
CRP (mg/dL)	75	26	21	100	51
WBC/mm^3	15.000	23.300	19.700	16.300	16.800
Hemoglobin g/dL	9.8	10.6	11.8	10.9	10.9
Platelet/mm^3	512.000	729.000	561.000	452.000	403.000
Sodium (mEq/L)	136	133	131	136	133
Albumin (g/dL)	3.2	3.3	2.9	3.1	2.6
Sterile pyuria	-	+	-	+	-
Number of IVIG treatments	2	2	1	1	1
Hospitalization time (number of days)	11	9	13	7	7

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IVIG: intravenous immunoglobulin; LCA: left coronary artery; WBC: white blood cell.

and KD symptoms during the coronavirus disease (COVID-19) pandemic (10). Chang et al. (7) compared viral isolation rates among patients with KD and healthy controls and showed that patients with KD exhibited significantly higher rhinovirus (26.5%), enterovirus (16.8%), adenovirus (8.1%), and coronavirus (7.1%) isolation rates. They also identified concomitant viral infection symptoms, such as cough (69%), rhinorrhea (58%), and diarrhea (51%), in addition to the typical KD symptoms. Another study showed that 8.8% of the 349 patients with KD had concomitant viral infections, whereas atypical KD and coronary artery aneurysms were commonly reported in patients with KD with documented viral respiratory infections (8). In a large cohort, three patient groups, including patients with KD, patients with influenza infection (Flu), and patients with KD with concomitant influenza infection (KD+Flu), were evaluated. When compared with the other groups, the KD+-Flu group exhibited higher morbidity, higher levels of acute-phase reactants, longer period of fever, and longer time for the diagnosis of KD (6). In contrast, Turnier et al. (9) did not observe any differences in the clinical findings, laboratory features, treatment requirements, and coronary artery lesions of patients with KD with or without viral respiratory infections.

In conclusion, KD can be misdiagnosed as respiratory viral infections, and vice versa, owing to the similarities in symptoms. Both diseases often present as co-occurring comorbid conditions. Raising awareness among physicians about possible links between KD and respiratory viral infections may improve patient outcomes through early diagnosis and treatment.

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References

1. Barut K, Şahin S, Adroviç A, Kasapçopur Ö. Diagnostic approach and current treatment options in childhood vasculitis. Turk Pediatri Ars 2015; 50: 194-205. [Crossref]
2. Embil JA, Mcfarlane ES, Murphy DM, Krause VW, Stewart HB. Adenovirus type 2 isolated from a patient with fatal Kawasaki disease. Can Med Assoc J 1985; 132: 1400.
3. Kanegane H, Tsuji T, Seki H, et al. Kawasaki disease with a concomitant primary Epstein-Barr virus infection. Acta Paediatr Jpn 1994; 36: 713-6. [Crossref]
4. Santos RA, Nogueira CS, Granja S, Babtista JB, Ribeiro ML, Rocaha MG. Kawasaki disease and human bocavirus--potential association? J Microbiol Immunol Infect 2011; 44: 235-7. [Crossref]
5. Rigante D, Cantarini L, Piastra M, et al. Kawasaki syndrome and concurrent Coxsackie virus B3 infection. Rheumatol Int 2012; 32: 4037-40. [Crossref]

6. Huang X, Huang P, Zhang L, et al. Influenza infection and Kawasaki disease. Rev Soc Bras Med Trop 2015; 48: 243-8. [Crossref]
7. Chang LY, Lu CY, Shao PL, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc 2014; 113: 148-54. [Crossref]
8. Jordan-Villegas A, Chang ML, Ramilo O, Mejias A. Concomitant respiratory viral infections in children with Kawasaki disease. Pediatr Infect Dis J 2010; 29: 770-2. [Crossref]
9. Turnier JL, Anderson MS, Heizer HR, Jone PN, Glodé MP, Dominguez SR. Concurrent Respiratory Viruses and Kawasaki Disease. Pediatrics 2015; 136: 609-14. [Crossref]
10. Toubiana J, Levy C, Allali S, et al. Association between SARS-CoV-2 infection and Kawasaki-like multisystem inflammatory syndrome: a retrospective matched case-control study, Paris, France, April to May 2020. Euro Surveill 2020; 25: 2001813.