Leptospirosis Associated Kawasaki Disease. Differential Diagnosis or Disease Association? Case Report and Review of The Literature.

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Case Report

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Abstract

Background: Kawasaki disease (KD) is a systemic vasculitis which affects medium-sized arteries. Although diagnostic and classification criteria exist, differentiation from other diseases can be difficult.

Case Presentation: We present a 3-year old patient with a diagnosis of complete KD with positivity for urine-PCR on leptospirosis.

In our patient conjunctivitis, rash, fever, cervical lymphadenopathy, palmar swelling, exanthema were seen, indicating all criteria for complete KD. After 2 weeks periungual desquamation developed. Besides this patient two further cases were retrieved form the literature with similar clinical courses indicating leptospirosis associated KD.

Conclusion: These cases indicate that leptospirosis may not only mimic but also be associated with KD shown by specific findings like desquamation of fingers, toes and oropharyngeal mucous membrane changes. To distinguish between KD, leptospirosis and leptospirosis associated KD a proper history taking including travel history and contact to animals is fundamental as well as thorough clinical and cardiac examinations in the course of the disease. While diagnostic procedures and observation might take time, treatment of acute KD should not be delayed.

Introduction

Kawasaki disease (KD) is a systemic vasculitis which affects medium-sized arteries. The exact pathophysiology is not known. [1]

Besides genetic predisposition, immunologic and infectious associations are reported. [2,3,4] Moreover, in the recent pandemic multiple cases of pediatric patients diagnosed with KD or hyperinflammation associated with positive COVID-19 (pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)) were reported, indicating infectious triggers. [5,6,7,8]

KD should be considered mainly in pre-school children, who present with fever, conjunctivitis, lymphadenitis, oropharyngeal mucous membranes, palmoplantar swelling and generalized skin rash.[2,9] The patients can develop desquamation of the fingers and the toes in the second week of the disease, which is a hallmark of KD. [10] The correct diagnosis can be challenging as no confirmatory test exists.

In this article we present a case of a 3-year old patient diagnosed as complete KD including desquamation of the fingers. This girl also tested positive for Leptospirosis. A comprehensive literature review in PubMed was done revealing only two other cases of leptospirosis associated KD patients.

Case Presentation

A 3-year old female patient was admitted to our hospital with fever for the last 4 days. She had cervical lymphadenitis, conjunctivitis and developed an erythematous skin rash mainly on the trunk. She could not walk properly because of arthralgia and myalgia. She had also mild diarrhea without vomiting. A strawberry tongue was noticed during the examination, as well as palmar and plantar swelling. No abnormalities in other organs systems were reported. The mother gave a history of mouse outbreak in her home. Blood investigation showed elevated inflammation parameters; CRP 12,4 mg/dl (<,3); ESR 90 mm/h (< 20); Leukocytes 5,2 × 10^3/µl (5,5–15 × 10^3/µl); Thrombocyts 313 × 10^3/µl(210–500 × 10^3/µl); AST 105 U/l (< 60); ALT 105 U/l (< 35); NT-ProBNP991 pg/ml(< 400). Urine showed mild proteinuria (Protein/Creatinine ration 0,9 g/g creatinin). Serologic tests for Epstein-Barr virus, adenovirus, puumalavirus, measles and COVID-19 were negative.

As the patient fulfilled all criteria for complete KD IVIG and Aspirin were started. Since the patient was clinically severely ill, had high inflammation parameters as well as high NT-Pro BNP, prednisolone was additively commenced. In less than 24 hours, the fever subsided, and the patient improved clinically. Echocardiography showed no signs of cardiac involvement. Inflammations parameters decreased subsequently showing normal CRP on day 7 of the disease course.

Due to the mother´s report on mouse contact and the described symptoms in combination with proteinuria leptospirosis examinations were ordered. As urine PCR for leptospirosis was positive penicillin was started over a course of 14 days. Specific leptospirosis antibodies in the serum were negative. In the second week of the disease the patient developed marked desquamation of the fingers (Fig. 1). At follow up at 6 weeks the patient remained asymptomatic and showed no heart abnormality through echocardiography or other KD complications like hearing impairment.

Literature Review

A comprehensive literature review revealed two further cases KS and positivity for Leptospirosis blood values. Humphry et al reported a 2-year-old girl with a 3 day history of fever, pharyngitis, conjunctivitis, abdominal pain and vomiting. She had also, erythematous, macular rash involving the trunk. She had close contact with several dogs one of whom died about three weeks prior to the onset of this illness. On examination, she had lymphadenopathy, swollen lips, and a “strawberry tongue”. Laboratory values showed high CRP, ESR and high liver function test. Over the course of the disease she developed acral swelling and arthralgia progressing to arthritis. Initial viral cultures and antibody titers were negative, including leptospirosisa antibody titers. A diagnosis of KD was made.

Interestingly control of leptospira antibody titer drawn on the twelfth hospital day was highly positive. In the third week of her illness the patient developed desquamation of the skin of her hands and feet indicating leptospirosis associated KD.[17]

In 2017 Yao Foo et al described another case of a 7-year old girl with fever for 4 days associated with a papular rash over her chest and limbs, lymphadenitis, conjunctivitis, diarrhea, and headaches. Her family

gave a history of travelling to South India a month before presentation. On physical examination, her lips were red and she had a “strawberry tongue”. Initial laboratory investigations showed high CRP and ESR. The child was unsuccessfully treated with Amoxicillin. On day 7 of the illness a diagnosis of KD was made and the girl was treated with IVIG and Aspirin leading to deferescence. Post discharge leptospira serology was traced and turned out to be positive for IgM. At day 14 of the illness –when performing an unremarkable echocardiography skin peeling distally over her fingers was noted.[18]

Discussion

Leptospirosis is a zoonosis caused by a spirochetal bacteria that can be shed in the urine of different animals such as dogs, livestock and rodents. Transmission occurs mostly via contact with contaminated urine. [11] Rapid dissemination of the pathogen leads to the clinical presentation with a septicaemic stage of 3–7 days with fever, headache, myalgia in 40–97% of the cases, nausea, conjunctival suffusion in 28–99%, accompanied or followed by an immune mediated phase (0 days – 1 month with meningitis, uveitis, rash and fever. [11,12,13] Leptospira can affect any tissue, and primarily cause proteinurea and hemorrhagic vasculitis, as well as hepatocellular dysfunction. Although more than one million human infections are estimated to occur worldwide annually, in Germany less than 20 pediatric cases are reported each year.[16]Antibiotic treatment is recommended, to prevent long-term sequelae such as uveitis. As many signs and symptoms between leptospirosis and KS are identical it can not only mimic but also be associated with KD (Fig. 2), although desquamation, oropharyngeal mucous membrane changes and coronary aneurysms are specific for KD.[2,11]

In our case the patient presented with a clinical picture of complete KD bearing in mind that non-classification criteria like nephritis is seen regularly in leptospirosis but is also a –rare- manifestation in KD.[11,12]

Besides the clinical symptoms with fever, conjunctivitis, headache, myalgia, exanthema, meningism, proteinurea, the history of contact to mice and the DNA positivity in the urine proves the infection with leptospira. The latter being the most sensitive test for Leptospirosis. [11]

Negative serologic results –despite confirmed diagnosis- are reported in the literature.[11,13]

In the literature review, another two cases (Foo et al and Humphry et al) had been found, which also fulfill the criteria of KD and showed a positive serology for Leptospirosis. [17,18] In all three cases the patient developed desquamation of the fingers that are a hallmark of KD. All the three patients showed a positive history of contact with animals, animals' product or travel history to an endemic area indicating the importance of a specific history taking. A summary of the cases is shown in Table 1.

Conclusion

There is a broad clinical overlap between KD and Leptospirosis which might represent distinct diagnosis but also leptospirosis associated KD.

According to the rarity of leptospirosis in developed countries we would like to remind this differential diagnosis and emphasize the importance of timely treatment of KD. A proper history including travel history and contact to animals is fundamental to reach the right diagnosis.

Abbreviations

KD
Kawasaki disease; COVID-19:Corona Virus Disease 2019; PMIS-TS:pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; EULAR:European League Against Rheumatism; PRES:Pediatric Rheumatology *European* Society; CRP:C-reactive protein; ESR:erythrocyte sedimentation rate; AST:aspartate transaminase; ALT:alanine transaminase; EBV:Epstein-Barr-Virus; IVIG:Intravenous immune globulin; NT-ProBNP:The N-terminal prohormone of brain natriuretic peptide; PCR:polymerase chain reaction; MLSN:mucocutaneous lymph node syndrome.

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Informed consent was obtained in written and for publishing the case report and the pictures.

Availability of data and materials

Not applicable

Competing interests:

The authors declare that they have no competing interests.

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Authors'contribution:

MN interpreted the patient data in rheumatological view, FR interpreted the patient data in infectious view, FB collected the data from pubmed research, AH collected the data from pubmed research, CS wrote the introduction, FN critical reviewed he article, KT interpreted the nephrological data.TH write the discussion

and reviewed the article critically. All authors read an ap-proved the final manuscript and agreed both to be personally accountable for the contribution.

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Tables

Table 1 summary of the three cases

		our case	Yao Foo et al	Humphry et al
Symptoms	Age	3y	7y	2y
	Duration of fever	4d	4d	4d
	Lymphadenitis	+	+	+
	Conjunktivitis	+	+	+
	Skin rash	+	+	+
	Palmer swelling	+	-	+
	mucous membrane changes	+	+	+
	Arhralgia/arthritis	+	-	+
	Gastrointestinal symptoms	+	+	+
	Neurological symptomes	+	-	-
	Travel history or contact to animals	+	+	+
Investigation	Leukocytosis	+	+	+
	Elevated CRP/ESR	+	+	+
	Elevated transaminase	+	-	+
	Low albumin levels	+	+	n.n
	High Ferritin levels	-	n.n	n.n
	Proteinurea	+	-	-
	Thrombocytosis	-	-	-
	High Sodium levels	+	n.n	-
Therapy	IVIG	+	+	n.n
	ASS	+	+	n.n
	Prednisolone	+	-	n.n
	Antibiotic	+	+	n.n

Figures

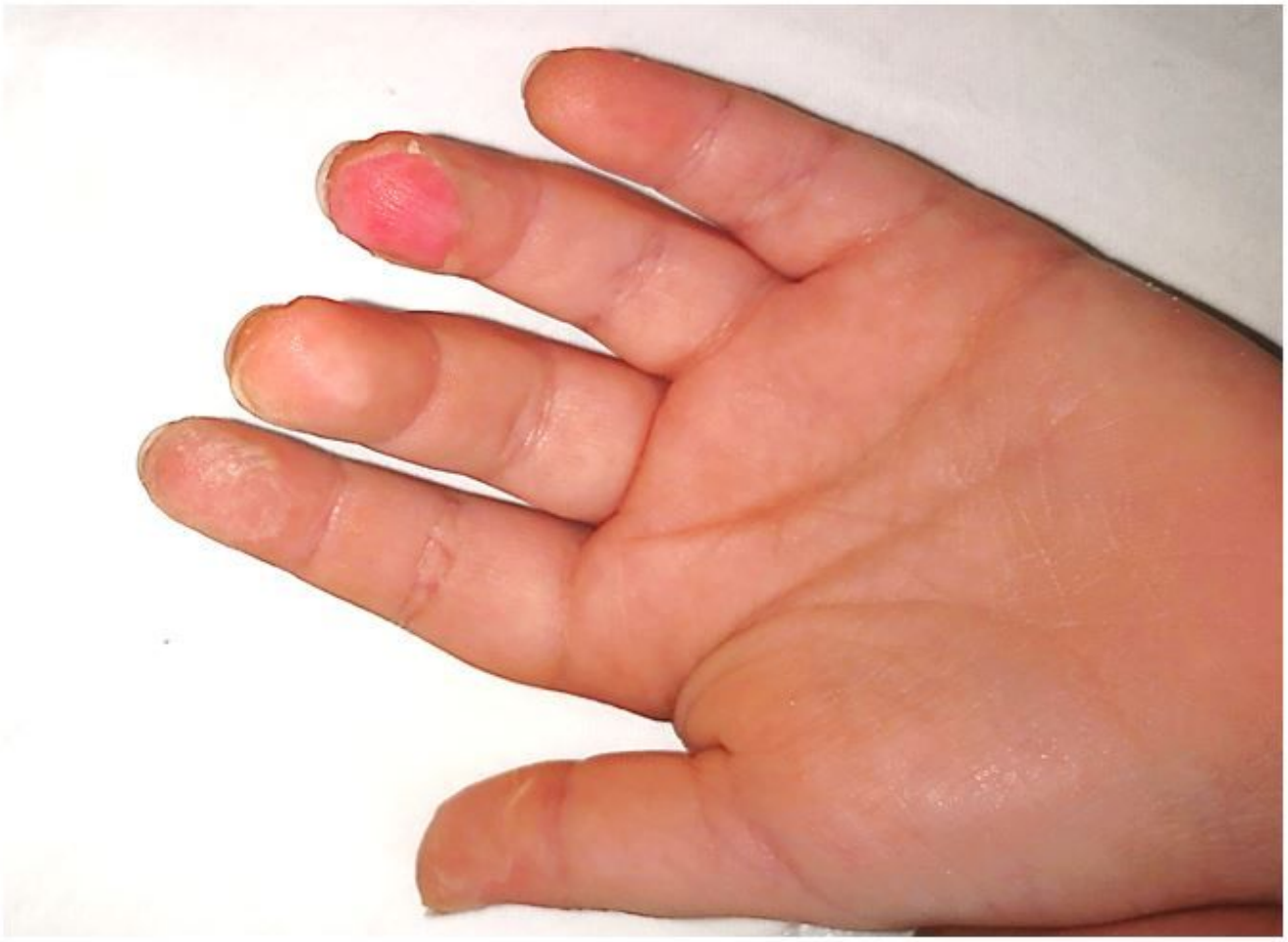

Figure 1

mucus membrane involvement (Desquamation of the finger)

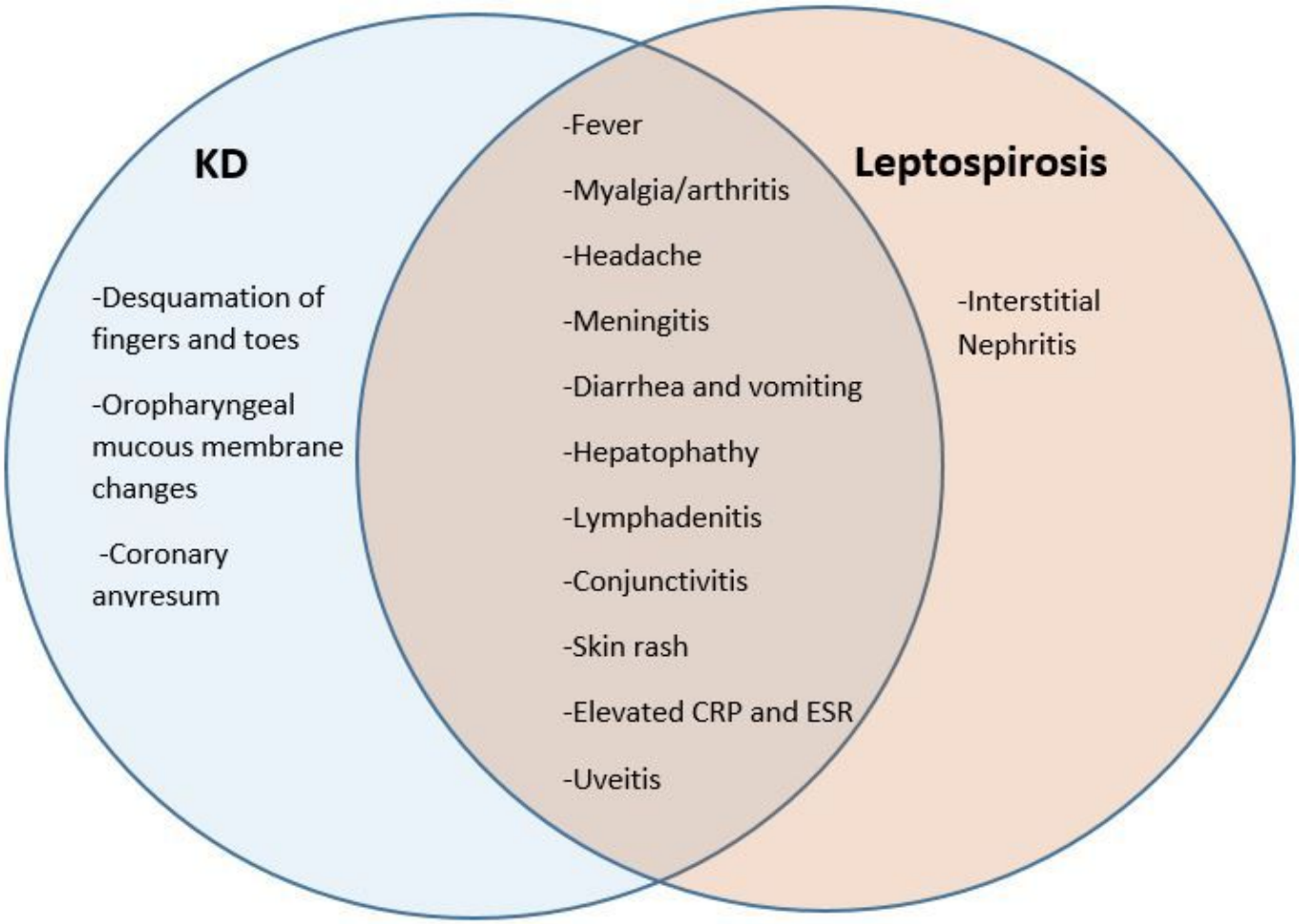

Figure 2

Comparison between signs and symptoms of KD and Leptospirosis