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A Child With Kawasaki Disease and *Yersinia enterocolitica* Infection: A Closer Look at Pathogenesis

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Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome and infantile polyarteritis nodosa, is a febrile illness manifested by a vasculitis that can potentially affect the coronary arteries. The etiology of KD has long been investigated, and to this day, there is no known single causative agent. The diagnosis of KD remains a clinical one with algorithms established for incomplete cases that include additional laboratory criteria.[1] Different infections and inflammatory conditions may present with manifestations that may mimic KD. Among these, *Yersinia pseudotuberculosis* infection has long been reported in Japanese children with KD including those who developed coronary artery lesions.[2,3] We describe a child who developed all clinical manifestations of KD including a retropharyngeal phlegmon during the course of *Yersinia enterocolitica* gastroenteritis.

Case Report

A 4-year-old African American boy with Fragile X syndrome presented to the emergency department at Children's Hospital of Michigan with diarrhea for 9 days and fever for 2 days. He had 4 to 7 nonbloody, nonmucoid, loose stools per day associated with abdominal pain. He had persistent fever in the last 2 days with maximum temperature of 39°C despite antipyretic therapy. On the day of admission he had decreased activity and appetite. There was no reported history of vomiting or skin rash; and he had no sick contacts and does not attend day care.

On admission, he was tachycardic and febrile. He was noted to have pharyngeal erythema and left anterior upper cervical lymphadenopathy of approximately 1.5 cm. He was noted to have abdominal tenderness most pronounced in the right lower quadrant. The rest of the physical examination was normal. His initial labs revealed leukocytosis of 14.2 (59% neutrophils) and thrombocytosis of 475 000. His electrolytes, amylase, lipase, and liver transaminases were all normal. Rapid strep test and a throat culture were negative. Abdominal ultrasound showed multiple prominent mesenteric lymph nodes in the right lower quadrant with no evidence of appendicitis. Stool studies including culture, selective stool culture for *Yersinia*, and *Clostridium difficile* toxin assay, as well as a blood culture were sent.

He continued to have fever despite antipyretics. On day 3 of admission a repeat complete blood count showed an increase in white blood cells to 21 700 (Table 1). C-reactive protein and lactate dehydrogenase were also elevated. His cervical lymph nodes increased in size, now 3 cm on the left and a palpable 1 cm node on the right, and became tender to palpation. He was given intravenous clindamycin and ceftriaxone for possible bacterial lymphadenitis.

On day 4, he developed a maculopapular rash beginning on his trunk and spreading to his extremities and neck. He developed erythema and swelling of his palms and soles and red, cracked lips. He also developed bilateral conjunctivitis with no exudates. The patient was diagnosed with clinical KD. In addition, his labs showed leukocytosis with left shift, elevated erythrocyte sedimentation rate and C-reactive protein, normocytic anemia (hemoglobin 10.5 with mean corpuscular volume 80.5 fL) and hypoalbuminemia (2.6 mg/dL). He developed thrombocytosis after 1 week of fever onset (Table 1). His urinalysis did not show pyuria, and his liver enzymes were normal. An echocardiogram was within normal limits. He was given intravenous immunoglobulin (IVIG) and high-dose aspirin.

The patient had persistent fever and the manifestations of KD were only mildly improving. He was noted to have worsening of the left upper cervical lymphadenitis and

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Table 1. Laboratory Data Trend During the Course of Illness.

	WBC (000/mm^3)	Neutrophil %	Lymphocyte %	Platelet (000/mm^3)	CRP (mg/L)	ESR (mm/h)	Albumin (g/dL)
Day 1	14.2	59	34	475			
Day 3	21.7 (3% bands)	84[a]	6	397	29.72	77	2.6
Day 4	20.7	89	8	477	37.80		
Day 7	14.1	70	23	478	28.20		
Day 11	13.0	82	16	653	23.01		

Abbreviations: WBC, white blood cells; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
[a]Segmented neutrophils with vacuoles present.

restricted neck movements. He was also noted to have difficulty swallowing and episodes of stridor. A computed tomography of the neck showed a retropharyngeal phlegmon extending to the superior mediastinum with no abscess visualized. Ceftriaxone and clindamycin were continued. Due to persistent fever and lack of clinical improvement, a second dose of IVIG was given on day 7 of admission. Following that, his fever resolved and the manifestation of KD were improving. His lymphadenitis gradually improved over the next few days.

On day 8 of admission, the stool culture grew *Yersinia enterocolitica* that was susceptible to ceftriaxone. All his blood cultures were negative, serologic testing for cytomegalovirus, Epstein–Barr virus, and parvovirus B-19 were negative for acute or past infection. Stool was negative for *Clostridium difficile* by DNA amplification. He completed a total of 9 days of ceftriaxone and 14 days of clindamycin.

On day 11 of admission, the patient was noted to have swollen, erythematous proximal interphalangeal joints and swollen bilateral knee joints. He refused to bear weight, and attempts to have him ambulate were unsuccessful. Radiographs of the pelvis and bilateral knees were normal. Rheumatology evaluation revealed negative HLA B27, and C3/C4 complement levels were normal. His symptoms were attributed to reactive arthritis from *Y enterocolitica*. He was given intravenous steroids followed by naprosyn. He also received physical therapy and prior to discharge he was able to ambulate. He was sent home to continue low-dose aspirin and naprosyn after 14 days of hospitalization.

Following discharge, he had peeling of skin on his hands and feet during the first week. He continued naprosyn for 6 days after discharge, and the swelling of his knees completely resolved. At follow-up 4 weeks after discharge, he had no signs or symptoms of KD, no cervical lymph node enlargement, and his musculoskeletal examination was normal. His repeat echocardiogram 5 weeks into his illness was normal.

Discussion

Our patient developed the clinical criteria for complete KD during the course of acute gastroenteritis. He continued to be febrile and have KD manifestations after the first dose of IVIG and required a second dose before improvement. KD has never been reported in association with *Y enterocolitica* infection except in one case of incomplete KD.[4] Our case is unique in that the patient met clinical features of complete KD, in addition to several supportive laboratory criteria. Our patient had systemic yersiniosis with gastroenteritis and mesenteric adenitis at presentation followed by significant cervical adenitis associated with retropharyngeal phlegmon. He later developed arthritis that required treatment with steroids. These findings suggest that *Y enterocolitica* was the causative agent of the clinical syndrome in our patient. He did not develop coronary artery disease.

Although the etiology of KD is largely unknown, several seasonal, geographic, and biologic associations have been found.[3,5,6] KD occurs most frequently in Japan and nearby countries in the Far East.[6] Most outbreaks occur in the winter months, between October and May, with very few epidemics in summer months.

It has been postulated that the disease manifestations occur due to an infection in a genetically predisposed child.[7] Oligoclonal immune responses with IgA plasma cell infiltration of the respiratory tract have been demonstrated in fatal acute-stage KD patients suggesting a respiratory pathogen.[8] Other have suggested that the superantigen activity of an infectious agent is implicated in KD, given certain features such as diffuse rash and fever that are likewise present in toxin-mediated diseases such as staphylococcal toxic shock syndrome.[9] In addition, levels of all immunoglobulins are elevated in the subacute phase of the illness, suggesting a strong antibody response.[10]

While many pathogens have been investigated in the etiology of KD, *Yersinia pseudotuberculosis* has been one of the most extensively studied.[2,3] Reported infections have a similar temporal pattern as KD. Vincent et al showed that the incidence of KD was higher during

Table 2. Similarities of the Clinical Manifestations of Kawasaki Disease and Systemic Yersiniosis.[12-14].

	Kawasaki Disease	Systemic Yersiniosis
Cardiovascular	Myocarditis, pericarditis, aneurysms of medium-sized noncoronary arteries	Mycotic aneurysms
Respiratory	No significant findings	Lung abscesses, ARDS, pneumonia
GI	Diarrhea[a]	Diarrhea[a], hepatic abscesses
Neurologic	Aseptic meningitis	Meningitis, CSF pleocytosis
Integument	Polymorphic exanthem[a]	Erythema nodosum
Musculoskeletal	Arthritis[a], arthralgia[a]	Arthritis[a], osteomyelitis, synovial fluid leukocytosis
Ophthalmologic	Conjunctivitis[a], anterior uveitis	Uveitis
Oropharynx	Injection of oropharyngeal mucosa[a]	Exudative pharyngitis
Lymphatic	Cervical lymphadenopathy[a]	Mesenteric lymphadenitis[a]
Hematologic	Leukocytosis[a]	Leukocytosis[a]
Other	Elevation in inflammatory markers[a]	Elevation in inflammatory markers[a]

Abbreviations: ARDS, acute respiratory distress syndrome; GI, gastrointestinal; CSF, cerebrospinal fluid.
[a]Findings present in our patient.

seasons with higher reported incidence of *Y pseudotuberculosis* infection; other winter pathogens did not show the same relative rise or fall in incidence that matched the variation of KD.[3] In a retrospective analysis to compare KD patients who had *Y pseudotuberculosis* infection versus those without infection, Tahara et al demonstrated that the use of more than one dose of IVIG and the incidence of coronary artery lesions were higher in the *Y pseudotuberculosis*–infected patients.[2] These findings support the important role *Yersinia* plays in the pathogenesis of KD.

Uncomplicated yersiniosis presents as enterocolitis with diarrhea, fever, and abdominal pain that may be accompanied by mesenteric lymphadenitis, much like the initial presentation of our patient.[11,12] Septicemia is less common, most often occurring in very young children (<3 months of age) and immunocompromised persons.[12] Systemic infection is associated with splenic and hepatic abscesses, osteomyelitis, meningitis, endocarditis, and mycotic aneurysms. Exudative pharyngitis, pneumonia, empyema, lung abscess, and acute respiratory distress syndrome rarely occur. Immune-mediated complications include arthritis as in our patient, as well as erythema nodosum, and the uveitis rash syndrome.[12-14] Table 2 illustrates clinical presentations of *Yersinia* species infections that may overlap with KD manifestations.

Patients with *Y pseudotuberculosis* infection can develop a severe form of disease called Izumi fever. These patients present with a scarlet fever–like syndrome including conjunctivitis, strawberry tongue, edema, and scarlatinoid rash with cutaneous desquamation, findings that are suggestive of KD.[15] These findings have not been previously described in patients with *Y enterocolitica* infection. Our patient fulfilled the strict clinical criteria of KD and had periungual skin peeling in the convalescent stage of the illness.

Different clinical and biological findings suggest that *Y pseudotuberculosis* infection could contribute to the pathogenesis of KD. In Japanese children, a study demonstrated that 57 (35%) of *Y pseudotuberculosis*–infected children had KD.[16] Another study has shown that KD was diagnosed in 29 of 329 children with *Y pseudotuberculosis* infection.[17] Some of these infected children developed cardiac complications including coronary artery dilatation and aneurysms. *Y pseudotuberculosis* has been described to produce an exotoxin with superantigenic activity called the *Y pseudotuberculosis*–derived mitogen (YPM), which was also derived from stools of children with KD.[18,19]

The mechanism of development of systemic complications following gastroenteritis with this organism is unclear. However, the tendency of this bacterium to involve lymphoid tissue including mesenteric lymph nodes with associated lymphoid hyperplasia suggests that activation of T-cell populations may be involved in the pathogenesis of disease.[20] Abe et al have demonstrated that patients with systemic complications have higher anti-YPM antibody titers than controls as well as expansion of the YPM-responsive T-cells in peripheral blood and in mesenteric lymph nodes.[21] *Y enterocolitica* is not known to produce YPM mitogen but may possess another antigen that acts as superantigen for human T-cells in vitro.[22] The presence of mesenteric adenitis as well as cervical and retropharyngeal lymphadenitis in our patient may indicate that similar mechanisms were involved in development of the strong proliferate T-cell responses via a superantigen mediated immune mechanism.[21]

Our case emphasizes the possible infectious origin of KD. It is the first reported case of classical KD that occurred during the course of systemic *Y enterocolitica* infection and that required 2 doses of IVIG to control the inflammatory response. This case supports prior reports implicating *Y pseudotuberculosis* in the pathogenesis of KD. The clinical findings in our patient may have been due to an exotoxin produced by *Y enterocolitica*. Further studies are needed to understand the role of bacterial superantigens, including those produced by *Yersinia* species, in the pathogenesis of KD.

Author Contributions

SAH and NAH contributed to conception, acquisition of data and writing of the manuscript. AR and SS contributed to acquisition of data and critical review of the manuscript.

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