ACUTE SURGICAL ABDOMEN AS PRESENTING MANIFESTATION OF KAWASAKI DISEASE

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Ten children (4.6%) among a cohort of 219 with Kawasaki disease (KD) had their onset with severe abdominal complaints. Incomplete KD presentation at the time of acute abdomen was present in nine of 10 patients. Acute abdominal pain and distension, vomiting, hepatomegaly, and jaundice were the most common symptoms at onset. Hematemesis was present in one; toxic shock syndrome requiring care in the intensive care unit occurred in four. Five patients had laparotomy, three had percutaneous transhepatic biliary drainage, and one had a gastrointestinal endoscopy. Postoperative diagnosis was gallbladder hydrops with cholestasis in five, paralytic ileus in three, appendicular vasculitis in one, and hemorrhagic duodenitis in one. All patients completely recovered, but 50% developed coronary aneurysms despite early intravenous gammaglobulin treatment. Acute surgical abdomen can be the presenting manifestation of KD. In older children with fever, rash, and acute abdominal pain or hematemesis, KD should be considered in the differential diagnosis. *(J Pediatr 2003;142:731-5)*

Gastrointestinal symptoms are a common feature of Kawasaki disease (KD). Hydrops of the gallbladder is a particularly well known complication of this disease,[1,2] and hepatic dysfunction with moderately elevated transaminases may occasionally occur.[3]

We present a series of 10 children with an acute abdomen as a presenting manifestation of KD requiring admission to a pediatric surgery ward and subsequent surgical intervention.

PATIENTS AND METHODS

Study Design and Patient Selection

The charts of 219 patients from two pediatric rheumatology centers, in Padua and Florence, who met KD diagnosis criteria[4,5] were reviewed.

Patients with an acute surgical abdomen as the presenting manifestation of KD were analyzed. Their clinical and laboratory characteristics were compared with those of patients with classic KD (cKD) onset.

Data Collection

The following clinical variables were evaluated for each patient: sex, race, age and season at onset, diagnostic criteria for KD, coronary artery abnormality (CAA) prevalence, associated clinical manifestations, clinical characteristics of the patients with surgical-onset KD (symptoms at onset, preoperative surgical diagnosis, surgical intervention, final diagnosis), and type of treatment.

Coronary artery abnormality included both dilatation (lumen diameter 3–4 mm) and aneurysms (lumen diameter >4 mm).[6,7] Echocardiograms were performed as soon as the KD diagnosis was suspected, before discharge, at the fourth and eighth weeks, and then on the basis of the degree of coronary involvement.

ALT	Alanine aminotransferase	GGT	Gammaglutamyltransferase
AST	Aspartate aminotransferase	IVIG	Intravenous immunoglobulin
CAA	Coronary artery abnormality	KD	Kawasaki disease
cKD	Classic Kawasaki disease	US	Ultrasound
CRP	C-reactive protein	WBC	White blood cell count
ESR	Erythrocyte sedimentation rate		

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Laboratory investigations at the time of the first admission to the hospital included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count (WBC), hemoglobin, platelet count, and hepatic transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gammaglutamyltransferase [GGT]). ESR and CRP were considered abnormal if >35 mm and 0.5 mg/dL, respectively, according to our laboratory standards; WBC and hemoglobin were considered abnormal if 2 SD greater or lower than mean values for age.[8] Platelet count was considered abnormal if $>400\times10^3/mm^3$. ALT and AST were considered abnormal if >40 U/L and GGT if >45 U/L. The laboratory work-up was similar in the two hospitals.

Statistical Analysis

The differences between the groups of patients with surgical-onset KD and cKD in their clinical and laboratory findings were analyzed by *t* test, χ^2, or Fisher exact test, as appropriate.

CASE HISTORIES

We selected four case histories as examples of the different clinical pictures included in the current series.

Patient 1

A 5.4-year-old previously healthy boy had a sudden onset of high fever (39–40°C) and acute abdominal pain.[9] Two days later the pain became severe, and he was admitted to the Surgical Unit of the Department of Pediatrics at Padua. Physical examination revealed an acutely ill child. His abdomen was tense and painful, particularly on the lower right side. Laboratory studies at this time showed ESR 90 mm/h, CRP 6.9 mg/dL, WBC 21600/mm^3 (neutrophils 90%), hemoglobin 11.2 g/dL, platelet count 320,000/mm^3, ALT 74 U/L, AST 57 U/L, and GGT 106. Abdominal ultrasound (US) showed effusion in the peritoneal cavity, mild ectasia, and hypomotility of the ileum as well as enlargement of the appendix in the right iliac fossa. Soon after admission, his general condition and abdominal symptoms worsened. Therefore, laparotomy was performed. At surgery, inflammation of the peritoneum and appendix was noted. An appendicectomy was performed, and the histologic examination revealed an acute transmural inflammation with diffuse arteritis. The patient remained febrile. One day later (day 5), the onset of maculopapular rash on the trunk and lower limbs, conjunctivitis, mucositis, and edema of both hands and feet led to the diagnosis of KD. Intravenous immunoglobulin (IVIG) was then administered with rapid amelioration of the general condition and disappearance of fever. Electrocardiogram and two-dimensional echocardiogram were normal. After a 2-year follow-up, he is well, with no cardiac involvement.

Patient 2

A 5.1-year-old boy presented with high fever (39–40°C), vomiting, and diarrhea. Two days later, the clinical picture was complicated by abdominal pain and distension. On day 3 he was still febrile and irritable because of pain. A maculopapular rash appeared on the trunk and in the perineal area. Because the patient rapidly deteriorated and refused feeding, he was admitted to a peripheral hospital. High fever, dehydration, hypotension, and oliguria led to a diagnosis of toxic shock syndrome. Standard radiographs revealed mild liver enlargement and distension of ileocolic loops. Abdominal US showed effusion in the peritoneal cavity and ruled out malrotation and appendicitis. He was treated with antibiotics, diuretics, dopamine, and hydrocortisone.

On day 6 the abdominal symptoms worsened and he was admitted to the Surgical Unit of the Department of Pediatrics at Padua. Physical examination revealed a very irritable child; the abdomen was diffusely tense and painful. On day 7, laparotomy was performed, showing peritoneal effusion and paralytic intestinal subocclusion. One day later, the onset of bilateral conjunctivitis; dry, fissured lips with injected pharynx; and edema of hands and feet led to the diagnosis of KD. IVIG was administered, with rapid improvement in his general condition and disappearance of fever. Two-dimensional echocardiogram showed a coronary dilatation (3.7 mm) of the right coronary artery that disappeared within 6 months.

Patient 9

A 10-year-old boy presented with high fever, cervical lymphadenitis, and pharyngitis, followed by maculopapular rash and conjunctivitis. On day 7 of illness, the child became lethargic and developed abdominal pain, vomiting, jaundice, and acholic stools. Because his general condition rapidly worsened, he was admitted to the Department of Pediatrics of Padua. On physical examination, the child appeared febrile and jaundiced, with dry, fissured lips. The abdominal pain was associated with marked abdominal distension and tenderness. Laboratory investigations showed elevation of inflammatory indices, conjugated bilirubin, and transaminases. Abdominal US showed gallbladder distension with intrahepatic biliary duct enlargement and hepatomegaly. Because IVIG was not available for the treatment of KD at that time, the child was treated with aspirin, with no significant improvement. Percutaneous transhepatic biliary drainage was then performed, and the patient completely recovered.

Two-dimensional echocardiogram and electrocardiogram were normal. On day 17, membranous periungual desquamation was evident on both hands and feet. Currently, 13 years later, the patient is well, with no gastrointestinal or cardiac sequelae.

Patient 10

A 20-month-old boy presented with high fever (39–40°C), rash, and conjunctivitis. Four days later he developed edema of both hands and feet and mild abdominal discomfort. A diagnosis of KD was made, and IVIG was then administered, with rapid improvement in his general condition but persistence of fever and abdominal pain. Aspirin was not administered because of a positive history of allergic reaction to this drug. Two days after admission, he had sudden onset of hematemesis. An urgent gastrointestinal endoscopy revealed diffuse hemorrhagic duodenitis with signs of recent bleeding on the upper side of the duodenal bulb. Blood transfusion and a

second bolus of IVIG were administered to treat significant anemia and persistence of fever. The patient completely recovered with no further gastrointestinal or cardiac complications.

RESULTS

Ten children (4.6%) among a cohort of 219 with KD had disease onset with severe abdominal complaints requiring surgical intervention or invasive procedures. Seven were seen at the Pediatric Department, University of Padua, and three at the Pediatric Department, University of Florence, Italy.

There were seven male patients and three female patients, all white. The mean age at onset was 4.2 years (range, 3 mos–10 y); one was less than 1 year, and six were older than 5 years.

Criteria for the Diagnosis of Kawasaki Disease

On admission, nine patients had an incomplete presentation of the disease.[10,11] In fact, three patients only had fever and abdominal complaints at onset. Two had only two criteria for the diagnosis of KD, two had three criteria, two had four, and one had five. Two to 4 days after surgical intervention, the full clinical picture was evident in nine of 10 patients, and they were therefore treated with IVIG between 5 and 11 days after fever onset.

Cardiac involvement (valvulitis, pericardial effusion, or myocardial alterations) was present in five patients who later developed CAA. The first echocardiogram was performed between the fifth and 11th day, and in only one patient, a coronary aneurysm was present at this early stage. In the other four, CAA was detected between day 10 and 18 from the onset of fever. In four of nine treated patients, IVIG did not prevent the development of CAA. Patients presented with respiratory (five patients), osteoarticular (three patients), or urogenital (one) symptoms, or a combination of these, in addition to gastrointestinal symptoms.

Most of the patients were admitted to the hospital quite early in the course of the disease. Laboratory studies were performed a mean of 5.7 days (range, 3–10) after fever onset. Surgical intervention or invasive procedures were performed after a mean of 7.7 days (range, 3–10) after onset. In seven of 10 patients, the diagnosis of KD was made at the time or 2 to 4 days after surgical intervention.

Acute Surgical Symptoms

Various degrees of abdominal pain were present in all patients. Abdominal distension was present in seven of 10, vomiting and hepatomegaly in six of 10. Other symptoms included jaundice (four), diarrhea (three), and hematemesis (one). Four patients presented a clinical picture of toxic shock syndrome requiring admission to the ICU for 3 to 6 days.

Surgical or Invasive Procedures

The clinical picture and the results of laboratory and radiologic studies led to a preoperative surgical diagnosis of acute appendicitis in one patient, intestinal occlusion or peritonitis in two, gallbladder hydrops with cholestasis in three, obstructive cholestasis in two, and hematemesis in one.

Table. Comparison between surgical-onset KD and cKD

	Surgical-onset KD N = 10	cKD N = 209	Significance*
Age at onset, mo			
Mean (± SD)	52 (± 33)	39 (± 32)	ns
<1 y, %	10	20	ns
>5 y, %	60	17	$P < .05$
Sex distribution (M:F)	2.3:1	1.7:1	ns
Associated clinical manifestations, %			
Cardiologic	50	25	ns
Respiratory	50	20	ns
Osteoarticular	30	16	ns
Urogenital	10	4	ns
Coronary artery disease	50	22	ns
ESR, mm, mean ± SD	86.7 ± 29.6	72.5 ± 30.8	ns
CRP, mg/dL, mean ± SD	13.3 ± 7.9	8.8 ± 7.6	ns
WBC, cell × $10^3/mm^3$, mean ± SD	23.8 ± 5.8	14.8 ± 5.6	$P < .01$
(>2 SD of normal for age)	100%	40%	$P < .0001$
Hemoglobin, g/dL, mean ± SD	10.7 ± 1.2	10.9 ± 1.1	ns
Platelets, cell × $10^3/mm^3$, mean ± SD	337.0 ± 435.4	352.3 ± 362.0	ns
ALT, U/L, mean ± SD	86.1 ± 23.9	27.9 ± 16.7	$P < .001$
(>40 U/L)	80%	26%	$P < .001$
AST, U/L, mean ± SD	74.2 ± 17.9	28.0 ± 19.9	$P < .001$
(>40 U/L)	80%	29%	$P < .001$
GGT, U/L, mean ± SD	239.1 ± 38.4	31.0 ± 27.3	$P < .0001$
(> 45 U/L)	60%	7%	$P < .0001$

*Chi-square test, *t* test, or Fisher exact test.

Five patients had laparotomy (two associated with appendicectomy, two with cholecystectomy, and one exploratory). Three patients had percutaneous transhepatic biliary drainage, one patient underwent an urgent upper intestinal tract endoscopy for hematemesis, and one had a percutaneous liver biopsy.

Postoperative diagnosis was gallbladder hydrops with cholestasis in five, paralytic ileus in three, and vasculitis leading to appendicitis in one and to hemorrhagic duodenitis in one.

Clinical Course

On long-term follow-up, all patients completely recovered. Five of 10 patients (50%) developed CAA (four aneurysms and one dilatation) even though IVIG was administered within 5 to 11 days after illness onset. One patient had recurrence of KD 3 years after the first episode, and at onset, the clinical picture was identical to the previous one. Patient 9 was the only one not treated with IVIG because of its unavailability at that time. Nevertheless, he did not develop any cardiac sequelae.

Comparison between Surgical-Onset Kawasaki Disease and Classic Kawasaki Disease

The Table summarizes the clinical and laboratory characteristics of patients with surgical-onset KD and with cKD presentation.

Patients with surgical-onset KD were older than patients with cKD. Sixty percent of patients in our series were older than 5 years, which was significantly different from the cKD group ($P < .05$). The male to female ratio was higher in surgical-onset KD (2.3:1) than in cKD (1.7:1).

A higher rate of associated clinical manifestations and CAA was found in surgical-onset KD when compared with cKD, but this finding was not statistically significant.

White blood cell count and hepatic transaminase were abnormal in a significant number of patients with surgical-onset KD, in contrast to the patients with cKD. The same results, but with a different degree of significance, were observed when these laboratory parameters were compared as continuous variables (Table).

DISCUSSION

Acute surgical abdomen was the clinical presentation of KD in 4.6% of our patients. We have no clear explanation for this high incidence. However, because our study was not epidemiologic but was based on the experience of two tertiary care institutions, the most likely reason is referral bias. On the other hand, because epidemiologic data regarding KD in Italy are lacking, possible, and still unknown, differences in genetic and environmental factors could also explain the higher prevalence of this unusual presentation.

Nine of 10 patients underwent a surgical intervention before the diagnosis of KD was evident.

Abdominal pain with distension, vomiting, and jaundice was the most common presenting sign of the disease. In nine cases, the surgeons saw the patients during a stage of incomplete development of the disease, which partially delayed the diagnosis. However, in three patients in whom the diagnosis was made early (patients 5, 9, and 10), IVIG treatment could not arrest the development of the abdominal complications or delay surgical interventions.

Gastrointestinal symptoms are quite common in KD,[3,12] and gallbladder hydrops particularly is a typical complication of this disease.[1,2]

In our patients with surgical-onset KD, a postoperative diagnosis of gallbladder hydrops with cholestasis was made in five patients. Surgical intervention was performed either because the criteria for KD diagnosis were so few that this diagnosis was not suspected or because, despite a prompt diagnosis, IVIG treatment was ineffective or the associated hepatobiliary involvement was so severe that surgery could not be further postponed.

Three patients presented with functional obstruction of the small intestine secondary to paralytic ileus. This condition has been described in three case reports of patients with KD.[13,14] Vasculitis and even thrombosis of small intestinal arteries can be the pathogenetic explanation of these abdominal events.[15,16] A true mechanical occlusion of small bowel has been reported in patients with KD and probably represents the final event of a mesenteric vasculitic process leading to ischemic bowel stricture.[15,17]

One patient in our series presented with histologically proven appendicular arteritis with a clinical picture of acute appendicitis. A mild elevation of transaminases, unusual in classic appendicitis,[18] may be considered in the differential diagnosis.

One patient presented with hematemesis caused by a hemorrhagic duodenitis. Hematemesis can be observed in other types of vasculitis involving the upper gastrointestinal tract such as polyarteritis nodosa,[19] Henoch-Schönlein purpura,[20] and systemic lupus erythematosus.[21] It can also be related to gastric or duodenal ulcers caused by treatment with nonsteroidal anti-inflammatory drugs. Non-iatrogenic hematemesis has never before been reported as a presenting sign of KD and should be added to the possible manifestations of the disease.

Surgical abdominal complications of KD have been reported in the literature as single case reports in 12 patients.[13–17,22–25] Gallbladder hydrops with cholestasis has been described in three cases,[17,25] small intestinal occlusion in four,[15,16,23,24] functional obstruction caused by paralytic ileus in three,[13,14] ischemic colitis in one,[22] and abdominal vasculitis with massive liver necrosis in one.[17] In most of these cases, however, the diagnosis of KD was made 4 to 6 weeks after disease onset.[15,16,23,24] In our patients, acute abdominal symptoms occurred earlier, and in nine of 10 they were the presenting signs of the disease.

We do not have a clear explanation for why some patients with KD have gastrointestinal complaints at the onset of the disease. However, it is interesting to note that a selective expansion of circulating $V\beta_2$ T cells has been demonstrated both in the blood and in the jejunal mucosa of patients with KD in the acute phase.[26–28] As suggested by some authors, it is possible that in patients with acute abdominal symptoms, bacteria colonizing the small intestine mucosa may produce exotoxins acting as superantigens with subsequent $V\beta_2$ T-cell expansion.[29]

Some clinical features of patients with surgical-onset KD were different from those with cKD. They were older and had a male predominance. Eight of 10 patients showed internal organ involvement other than gastrointestinal, with a higher prevalence than in cKD. Remarkably, cardiac involvement with persistent CAA was present in 50% of patients with surgical-onset KD despite early IVIG treatment.

These characteristics seem to suggest that surgical-onset KD represents the severe side of patients with KD with ab-

dominal symptoms and the expression of a more aggressive and sometimes life-threatening disease.

In older children with fever and acute abdominal pain or hematemesis, KD has to be considered in the differential diagnosis of acute surgical abdomen, particularly in the presence of rash, lymphadenopathy, or hepatomegaly.

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