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Clinical Case Seminar

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Gallbladder hydrops: when the clinical signs lead to the diagnosis of Kawasaki disease

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Abstract

Kawasaki disease (KD) is a vasculitis of the middle and little caliber arteries that specifically affects the coronary arteries. It represents the main cause of acquired cardiopathy in the pediatric population of western countries and in 25% of cases it leads to coronary artery aneurism (1). Atypical KD is nowadays considered a challenge for pediatrics, due to all of its possible clinical manifestations: it is characterized by a long-lasting fever (5 or more days) associated with some of the typical signs and symptoms and other unusual clinical manifestations (as neurological, nephrological, respiratory, gastrointestinal, rheumatological manifestations), variably associated with coronary arteries aneurism. Early diagnosis and treatment are essential to reduce the risk of coronary artery aneurysms (2,3).
We report the case of a 5-year-old boy who came to our attention for skin rash, abdominal pain, increased liver enzymes, and hydrops of the gallbladder. He presented a fever for less than 5 days. 2 weeks later, the appearance of peeling on the fingers and the toes confirmed the diagnosis of an atypical, incomplete KD.

Keywords: Kawasaki syndrome, gallbladder hydrops, hypertransaminasemia

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Introduction

KD is a multi-systemic vasculitis of the middle and little caliber arteries that specifically affects coronary arteries, typical of the pediatric population younger than 5 years old. The incidence ranges from 3.4 to 218.6 cases per 100000 children under 5 years of age. It is variable in different geographical areas and seasons. It is most frequent in Asia, Europe, and North America. Etiology is unknown (1). The pathogenesis is not fully elucidated, but it is believed that KD is a consequence of dysregulation of the immune system in a pro-inflammatory direction. In genetically predisposed individuals, an infectious trigger (staphylococcal and streptococcal toxins) may act as a superantigen and activate the immune system response (4). The diagnosis is clinical and it is based on the association of a long-lasting persistent fever (5 or more days, poorly responsive to paracetamol), considered the major criterion, with at least 4 of the 5 minor criteria: aseptic conjunctivitis, mucosal changes, skin chances, polymorphic erythema, lymphadenopathy usually unilateral. Coronary artery aneurysm is the main complication. Incomplete KD is characterized by the presence of fever

associated with 2 or 3 of the minor criteria. Atypical KD is defined by the association of fever and some of the typical signs with other unusual clinical manifestations, possibly involving every system and organ (1,3,5). Nowadays in recent literature, cardiovascular (myopericarditis, shock), respiratory (empyema, pleural effusion, pulmonary nodes, interstitial bronchitis), musculoskeletal (arthralgia, arthritis), gastrointestinal (abdominal pain, vomiting, diarrhea, increased liver enzymes, jaundice, hydrops of the gallbladder, pancreatitis), neurological (irritability, aseptic meningitis, facial nerve paralisis), genitourinary (urethritis, hydrocele, phimosis) and mucocutaneous (desquamation of the groin, retropharyngeal phlegmon) manifestations are reported (6). Infusion of intravenous (IV) human immunoglobulins (IVIg) 2 g/kg is considered the first-line treatment in order to reduce the risk of coronary artery aneurysms, the duration of the fever, and the severity of associated symptoms. After IVIg therapy, during the acute phase, it is necessary to start oral therapy with aspirin at 30-50 mg/kg/day and subsequently at 3-5 mg/kg/day. In case of severe disease, it is possible to make recourse to a second bolus of IVIg (2 g/kg) and eventually an intravenous (iv) steroid bolus therapy (methyl prednisone 30 mg/kg) or other nonglucocorticoid immunomodulatory immunosuppressive agents (Anakinra, Infliximab, ciclosporin) (7, 8, 9).

In this report, we describe a case of an atypical, incomplete KD with gastrointestinal onset symptoms (abdominal pain, hypertransaminasemia, and hydrops of the gallbladder).

The aim of our report is: 1) to show that in the presence of clinical symptoms and/or laboratory and instrumental examinations suggestive of KD can be diagnosed, even if the fever lasted less than 5 days, as confounding factors may mask this symptom; 2) Remember that gastrointestinal manifestations are potential onset symptoms of atypical KD, although infrequently.

Case Report

A 5-year-old boy was admitted to our pediatric unit for skin rash, abdominal pain, increased liver enzymes, and hydrops of the gallbladder. Past history points out isolated wheezing episodes and 2 SARS-CoV-2 infections (in 2020 and 2022). 3 days before the hospitalization the patient presented an erythematous skin rash on the face, the trunk, and the limbs, treated with oral betamethasone (1 mg/day for 3 days). 2 days after, a blood test showed a marked increase of liver enzymes (aspartate-aminotransferase (AST) 4,4 times the normal value (n.v); alanine aminotransferase (ALT) 14 times n.v.), mild hyperbilirubinemia (total bilirubine 1,6 mg/dL, direct bilirubinemia 1,3 mg/dL) and positivity of the phlogosis index (c- protein reactive (CRP) 8 times n.v.); an abdominal ultrasound described a dilatated gallbladder (longitudinal diameter 72 mm) with normal biliary tract. At the admission, the patient was irritable and presented abdominal pain in the right hypochondrium. During the physical examination, widespread skin erythema, right cervical lymphadenopathy, and

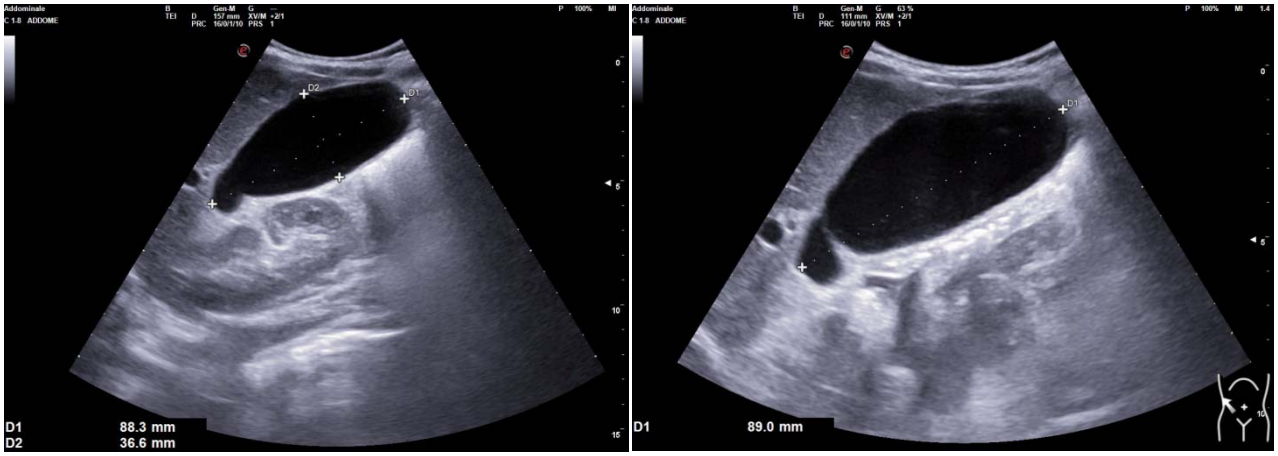
abdominal pain at deep palpation in the right hypochondrium were noticed. Empirical large-spectrum antibiotic therapy was started and during the first 3 days of recovery, the patient presented a fever.

After 10 days from the beginning of the hospitalization, desquamation of the groin was noticed (Fig.1).

Fig. 1 Periungual desquamation palmar and plantar in the subacute phase.

Serial blood tests confirmed a persistent increase of liver enzymes with cholestasis and positivity of the phlogosis index, whereas metabolic, infectious, autoimmune, or accumulation diseases were excluded. Possible anatomical causes with the abdominal ultrasound (Fig.2) and cholangitis-magnetic resonance imaging that confirmed the persistence of a dilatated gallbladder, were also excluded.

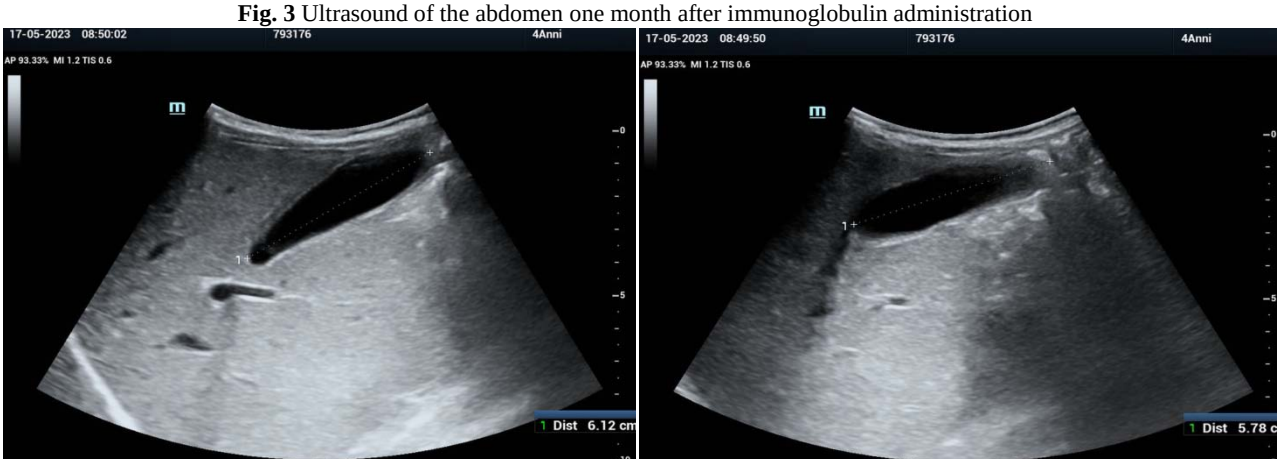
Fig. 2 Ultrasound of the abdomen before immunoglobline treatment.



In our case, the child presented fever and abdominal pain as an onset symptom associated with a laboratory finding of hypertransaminasemia and radiologically documented hydrops of the

gallbladder. In the diagnostic procedure, in accordance with the most recent guidelines on hypertansaminasemias and cholestasis in children (10,11), we have also ruled out: infectious causes (major and minor hepatotropic viruses, brucellosis, salmonella), hematological, autoimmune (coeliac disease, autoimmune hepatitis, systemic lupus erythematosus), accumulation (Wilson's disease, hemochromatosis). Once all of the possible causes of increased liver enzymes were excluded, the inflammatory cause was strongly taken into consideration since the beginning, but the lack of the major criterion discouraged us from suddenly starting the IVIg therapy. After the appearance of peeling of the extremities, almost a pathognomonic sign of KD, we confirmed the diagnosis of an atypical KD, also confirmed by the good response to IVIg therapy (Fig.3).

Fig. 3 Ultrasound of the abdomen one month after immunoglobulin administration



After 14 days of the onset of the fever, the patient presented a decreasing trend of transaminases, associated with thrombocytosis (platelets 735000/mmc) and increasing values of erythrosedimentation rate (ESR 44 mm/h), suggesting a systemic inflammatory disease. Despite a fever duration lower than 5 days, the following appearance of peeling on the fingers and the toes allowed us to confirm the diagnosis of an atypical, incomplete KD, so IVIg therapy (2 g/kg) was administered in 12 hours as protocol. The cardiac ultrasound exams were normal, excluding possible coronary artery involvement.

After 1 month, laboratory exams were normal, and the abdominal ultrasound showed a normalization of the previous pathological findings described. No evidence of cardiac changes at the cardiac ultrasound was present.

Discussion

Despite the atypical and incomplete form of KD represents about 50% of total diagnosis of KD, frequently the diagnosis is delayed due to the various heterogeneity of the clinical manifestations and thus predispose to a greater risk of coronary artery aneurism (5,8). The presentation of atypical KD can be miscellaneous and include the most disparate symptoms, which can affect any organ system with varying frequency. Before making a diagnosis of KD, it is advisable to make a

differential diagnosis with measles, bacterial and viral infectious diseases, hypersensitivity reactions to drugs, and the onset of systemic juvenile idiopathic arthritis (3,6). In our case, the child presented fever and abdominal pain as an onset symptom associated with a laboratory finding of hypertransaminasemia and radiologically documented hydrops of the gallbladder. In the diagnostic procedure, in accordance with the most recent guidelines on hypertansaminasemias and cholestasis in children (10,11), we have also ruled out: infectious causes (major and minor hepatotropic viruses, brucellosis, salmonella), hematological, autoimmune (coeliac disease, autoimmune hepatitis, systemic lupus erythematosus), accumulation (Wilson's disease, hemochromatosis). Once all of the possible causes of increased liver enzymes were excluded, the inflammatory cause was strongly taken into consideration since the beginning, but the lack of the major criterion discouraged us from suddenly starting the IVIg therapy. After the appearance of peeling of the extremities, almost a pathognomonic sign of KD, we confirmed the diagnosis of an atypical KD, also confirmed by the good response to IVIg therapy. We speculate that the oral corticosteroid therapy, domiciliary assumed a few days before, could have masked the fever and for that reason, our patient presented only 2 days of fever. Nevertheless, Li et al in a recent review pointed out that “5 days” represent the medium value of the duration of the fever that, looking at several observational studies present in literature, may range from 2 to 21 days (6). Thus, it is possible to consider that in selected cases, the diagnosis of KD is possible although fever duration is lower than the usual 5 days. Even the latest American Heart Association (AHA) guidelines report several experiences of KD patients who presented only 3 days of fever associated with typical or atypical signs of the disease (3).

Conclusions

KD is the main cause of acquired cardiovascular disease in the pediatric population. Long-lasting fever is the major criterion but in selected cases, it is possible to diagnose atypical or incomplete forms of KD with less than 5 days of fever. In the presence of hydrops of the gallbladder, unexplained by other causes and associated with other typical or atypical signs, it is mandatory to think about KD. Early diagnosis and treatment are essential to prevent long-term cardiovascular disease, such as coronary artery aneurysms.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

Informed consent obtained

References

1. Marchesi, A., Tarissi de Jacobis, I., Rigante, D., et al.(2018). Kawasaki disease: guidelines of the Italian Society of Pediatrics, part I - Definition, epidemiology, etiopathogenesis, clinical expression and management of the acute phase. Ital J Pediatr. 44(1):102.doi: 10.1186/s13052-018-0536-3.
2. Marchesi, A., Tarissi de Jacobis, I., Rigante, D., et al.(2018). Kawasaki disease: guidelines of Italian

Society of Pediatrics, part II - treatment of resistant forms and cardiovascular complications, follow-up, lifestyle and prevention of cardiovascular risks. Ital J Pediatr. 44(1):103.doi: 10.1186/s13052-018-0529-2.3.
3. McCrindle, B.W., Rowley, A.H., Newburger, J.W., et al. (2019). Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals from the American Heart Association. Circulation. 140(5):e181-e184. doi: 10.1161/CIR.0000000000000484.
4. Rife, E., Gedalia, A. (2020). Kawasaki Disease: an Update. CurrRheumatol Rep. 22(10):75. doi: 10.1007/s11926-020-00941-4.
5. Li, T., Feng, J., Li, N., Liu, T. (2021) Correct identification of incomplete Kawasaki disease. J Int Med Res. 49(3):3000605211001712. doi: 10.1177/03000605211001712.
6. Gorelik, M., Chung, S.A., Ardalan, K., et al. (2022). 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease. Arthritis Rheumatol. 74(4):586-596. doi: 10.1002/art.42041.
7. Mossberg, M., Mohammad, A.J., Kahn, F., et al. (2021). High risk of coronary artery aneurysm in Kawasaki disease. Rheumatology (Oxford). 60(4):1910-1914. doi: 10.1093/rheumatology/keaa512.
8. Scherler, L., Haas, N.A., Tengler, A., et al. (2022). Acute phase of Kawasaki disease: a review of national guideline recommendations. Eur J Pediatr. 181(7):2563-2573. doi: 10.1007/s00431-022-04458-z
9. Scherler, L., Haas, N.A., Tengler, A., et al. (2022). Acute phase of Kawasaki disease: a review of national guideline recommendations. Eur J Pediatr. 181(7):2563-2573. doi: 10.1007/s00431-022-04458-z.
10. Mandato, C.,Tripodi, M., Vajro, P. (2015) Approccio diagnostico al bambino con ipertransaminasemia. Qaudreni acp 2015; Volume. 22, N. 5, Pag. 214-221.
11. Poddighe, D., Sazonov, V. (2018) Acute acalculous cholecystitis in children. World J Gastroenterol. 24(43):4870-4879. doi: 10.3748/wjg.v24.i43.4870.

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