

COVID-19 and abdominal pain: a pediatric case report and a point of view in pediatric emergency medicine

V.E. RINALDI¹, R. D'ALONZO¹, G. DI CARA², A. VERROTTI²

¹Pediatric Unit, San Giovanni Battista Hospital, Foligno, Italy

²Pediatric Unit, Department of Medicine and Surgery, University of Perugia, Perugia, Italy

Abstract. – COVID-19 is to date a global pandemic that can affect all age groups; gastrointestinal symptoms are quite common in patients with COVID-19 and a new clinical entity defined as Multisystem Inflammatory Syndrome in Children (MIS-C) has been described in children and adolescents previously affected by COVID-19. Presenting symptoms of this new disease include high fever and severe abdominal pain that can mimic more common causes of abdominal pain; patients can rapidly deteriorate presenting severe cardiac dysfunction and multiorgan failure. Some fatalities due to this serious illness have been reported. We describe the case of a ten-year-old patient presenting with persistent high fever associated with continuous and worsening abdominal pain. Various hypotheses were performed during his diagnostic workup and an initial appendectomy was performed in the suspect of acute appendicitis. As his clinical picture deteriorated, the child was subsequently diagnosed and successfully treated as a case of MIS-C.

The objective of this case report and brief review of abdominal pain in children throughout the age groups is to provide the emergency pediatrician with updated suggestions in diagnosing abdominal pain in children during the COVID-19 pandemic.

Key Words:

Abdominal pain, COVID-19, MIS-C, Pediatric emergencies.

Introduction

The first reports of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection were recognized at the end of 2019 and, in the following months, Coronavirus disease 2019 (COVID-19) became a pandemic. It was initially believed that this disease mainly affected elderly people and that children were mostly asymptomatic

or mildly symptomatic. However, in spring-time 2020 around the world the first cases of a rapidly progressing and sometimes even fatal disease, similar to Kawasaki Syndrome were reported in children and adolescents who had been previously infected with COVID-19. This condition was later defined by the Centers for Disease Control (CDC) and the World Health Organization (WHO) as multisystem inflammatory syndrome in children (MIS-C)¹. MIS-C is a serious postinfectious syndrome resulting in cytokine storm and multiorgan dysfunction often affecting the cardiovascular system, the hematopoietic system, and the gastrointestinal tract². Presenting symptoms of MIS-C often include abdominal symptoms and, in particular, those that may suggest the need for surgical treatment, such as severe abdominal pain possibly with the presence of peritoneal symptoms, high levels of inflammatory markers, intestinal inflammation etc. We describe the case of a 10-year-old boy presenting with severe abdominal pain and fever, initially diagnosed and treated as a case of appendicitis but that subsequently revealed to be a case of MIS-C. The parents gave consent to the participation of the patient in this study. The importance of this case consists in drawing attention to the fact that complications of COVID-19 may present with a picture that can mimic a surgical emergency in children and adolescents. The objective of our paper is to raise awareness among emergency pediatric physicians of the new clinical entities that have been described in these past one and a half years of COVID-19 pandemic, that can easily be mistaken for more common and widely known causes of acute abdominal pain.

Case Report

A 10 year and a half old boy referred to our local Emergency Department (ED) mid December

2020 for persistent high fever lasting 3 days associated with continuous and worsening abdominal pain, pharyngodynia and diffuse myalgias. Stools were reported to be slightly less formed than usual. He reported two episodes of vomiting. The first and second day of the symptoms he presented a polymorphic cutaneous rash, that had lasted 24 hours. His general practitioner had prescribed oral Amoxicillin which he had been taking for 3 days, without previously performing a pharynx swab for Streptococcus. The patient's past medical history was substantially negative apart from reported frequent falls from the bicycle and a Coronavirus disease 2019 (COVID-19, SARS-CoV-2) completely asymptomatic infection from the end of October 2020 to the middle of November 2020. Family history was positive for Celiac Disease and Crohn's Disease.

On presentation, the boy was awake and alert in good clinical conditions and his vital signs were normal apart from presenting fever (38.9°C) and tachycardia (heart rate 150/min). Oxygen saturation and respiratory rate were within normal

range. Clinical examination revealed abdominal pain with tenderness prevalently in the right iliac fossa, in particular, in the Mac Burney Point. The cardiorespiratory clinical examination was negative. The polymorphic cutaneous rash that had been previously reported was absent on admission, but the boy presented a slight erythema of the face and a hyperemic pharynx on inspection of the oral cavity. Palpable lymph nodes were normal apart from a slight enlargement of lateral cervical lymph nodes. Routine blood tests showed elevation of inflammatory markers, leucopenia, normal values of hemoglobin and platelets, normal blood biochemistry, negative blood and stool cultures and negative nasopharyngeal swab for both COVID-19 and other tested respiratory viruses; COVID IgG serology was positive (Table I). The abdominal ultrasound reported a thickened and inflamed abdominal loop in the right iliac fossa. However, this finding was visualized with some difficulties and described as being compatible either with terminal ileitis or with an elongated inflamed appendix. In the suspicion

Table I. Most significant laboratory values in our patient.

Laboratory tests	Day 1	Day 3	Day 4
Leucocytes	3.400/mmc	6.470/mmc	7.410/mmc
Hemoglobin	12.4 g/dl	11.1 g/dl	10.6 g/dl
Platelets	227.000/mmc	203.000/mmc	252.000/mmc
Neutrophils	2.500/mmc	5.000/mmc	5.500/mmc
Lymphocytes	500/mmc	900/mmc	1.500/mmc
Monocytes	200/mmc	100/mmc	100/mmc
Eosinophils	100/mmc	400/mmc	200/mmc
Basophils	100/mmc	100/mmc	100/mmc
Coagulation	PT 24 sec; aPTT 0.9 ratio; fibrinogen 648 mg/dl	PT 24 sec; aPTT 0.9 ratio; fibrinogen 641 mg/dl	
C-Reactive Protein	13.95 mg/dl	21.85 mg/dl	23.34 mg/dl
Procalcitonin	1.51 ng/ml	1.06 ng/ml	0.76 ng/ml
Nasopharyngeal swab for COVID-19 and respiratory viruses	Negative		
Blood culture and stool culture	Negative for all tested pathogens.	Negative for all tested pathogens.	
Fecal viruses	Negative for all tested pathogens.		
COVID-19 serology	IgG positive		
ANCA; ASCA; ENA [†] ; antinuclear antibodies		Normal range values	
ESR [‡]		19 mm/h	
Troponin			20.4 ng/l
NT-proBNP [§]			254.3 pg/ml

[†]Antineutrophil Cytoplasmic Antibodies (ANCA), Anti-Saccharomyces Cerevisiae Antibodies (ASCA), Extractable Nuclear Antigen (ENA). [‡]Erythro sedimentation rate (ESR). [§]N-terminal pro b-type natriuretic peptide- (NT-proBNP).

of an acute abdomen, a surgical exploration was required but revealed a very slightly inflamed appendix (catarrhal appendicitis) associated with terminal ileitis. In particular, histologic findings revealed only a mild serosal inflammation and an edematous mesothelium, not showing the transmural acute inflammation that is typically found in acute appendicitis.

Oral amoxicillin therapy was substituted with intravenous (IV) empiric antibiotic therapy in the operating room. Less than 24 hours after the surgical intervention, the boy presented high fever with shivering, worsening abdominal pain and an increase in inflammatory indexes, with persistently negative blood cultures. An abdominal scan confirmed terminal ileitis and the antibiotic spectrum was broadened with the introduction of metronidazole. Given the positive family history of Inflammatory Bowel Diseases, a laboratory workup comprehensive of serologic autoantibodies and erythrocytation rate was performed and a gastroenterologist consult was scheduled for the following days but eventually never performed as the clinical picture changed.

The following day in fact, the child was ill-appearing, apathic, with persistent high spiking fevers (40°C) and presented dyspnea requiring oxygen supplementation because of desaturation (oxygen saturation values between 92-93% in ambient air). On auscultation, breath sounds were slightly reduced throughout the lung fields, but no pathological crackles or wheezes were found. In the suspect of pneumonia, a chest X-ray was performed and resulted negative (absence of pleuro-parenchymal alterations, normal cardio-mediastinal profile), along with a negative electrocardiogram and negative heart ultrasound. However, by the evening of the same day, a bilateral non exudative conjunctivitis and mucositis of the oral cavity had appeared and the whole case was reviewed by the medical staff.

Considering the whole clinical picture characterized by the previous COVID-19 infection, a polymorphic fugacious erythema, the persistent high fever, the presence of terminal ileitis, an elevation of inflammatory markers and dyspnea and finally the appearance of a bilateral non secretive conjunctivitis and mucositis, the diagnosis of COVID-19 Associated Multisystem Inflammatory Syndrome in Children (MIS-C) was performed. Cardiac functionality markers were tested resulting normal, and the patient was treated with one dose of intravenous immunoglobulins 2 g/kg. The boy responded to the single dose

of immunoglobulins with a stable defervescence within the first 12 hours of immunoglobulin administration. The following day another heart ultrasound was performed, and a minimal dilation of the circumflex artery was shown (Z score 2.58 SD) therefore, steroid therapy with prednisone at a dosage of 2 mg/kg/day was administered for three days (then gradually tapered orally for a total of 15 days) and antiaggregant therapy with acetylic acid (at a dosage of 3 mg/kg/day) was initiated and continued for a total of six weeks. The abdominal symptoms gradually disappeared along with the ultrasound ileitis images and the patient was discharged after a total of 13 days of hospital stay. After a 2 months follow-up, when the patient was not on any treatment, the coronary artery dilation had completely regressed.

Discussion

Abdominal pain is one of the most frequent reasons for admission to a pediatric ED³. Children with abdominal pain can be basically divided into two groups: those with a structural gastrointestinal diagnosis (e.g., surgical emergencies) and those who lack a clear, identifiable cause for their pain during the visit (e.g., functional abdominal pain disorders)⁴. Moreover, the diagnosis of children coming to the ED complaining abdominal pain can include diseases such as pneumonia or testicular torsion, not directly involving the abdomen. It is extremely important for the emergency physician to initially be able to distinguish between surgical and non-surgical causes of abdominal pain and an accurate patient history and clinical examination is what usually permits to classify the patient into one of these two groups, along with eventual laboratory testing and ultrasound/radiology examinations.

Table II shows a brief list of the so called “red flags” that should always be sought by the emergency physician during the collection of patient history and during clinical examination. Considering our case, we suggest adding the notion of a previous or contemporary COVID-19 disease to these classical features. The presence of one or more “red flags” should drive the physician to pursue diagnostic testing for the abdominal pain excluding causes of functional abdominal pain.

Physical examination should be thorough, and ultrasound is often the preferred imaging technique for many diseases. In fact, although having a high sensitivity and specificity for many

Table II. Red flags” for abdominal pain that suggest a higher risk of organic disease in children.

Weight loss, deceleration in linear growth Vomiting, dysphagia, odynophagia Gastrointestinal blood loss Chronic severe diarrhea Nighttime stooling and pan awakening the child at night Persistent abdominal pain Abnormal physical findings (clubbing, localized tenderness, mass, hepatomegaly, splenomegaly, perianal abnormalities) and/or abnormal laboratory testing (elevated C-reactive protein/erythrocyte sedimentation rate, occult blood in stool) Unexplained fever Family history of inflammatory bowel disease Tenesmus or defecation urgency Previous or concomitant COVID-19 infection

intra-abdominal diseases, computed tomography exposes children to ionizing radiation and therefore its indications are very strict⁵. Moreover, children ranging from pre-school age to adolescents can frequently complain abdominal pain as the principal symptom actually caused by extra-abdominal illnesses such as pneumonia, asthma, diabetic ketoacidosis, gynecological and urological causes. Physical examination of the pediatric patient should therefore always include a complete general examination.

Abdominal pain most frequent diagnosis varies according to patients' age; briefly a very short overview of the most common causes of abdominal pain throughout the ages. The objective of this short overview is to provide a “quick glance” helpful reminder for emergency pediatric physicians dealing with children of all ages presenting with this common symptom, in particular in these past one and a half years of COVID-19 pandemic, considering the new clinical entities that have been described (Figure 1).

Infants (<2 Years of Age)

Surgical Causes of Abdominal Pain

Among surgical causes, intussusception is the most common cause of bowel obstruction in children between 3 months and 6 years of age⁶, peaking in children less than one year of age. Causes are idiopathic although there can be predisposing factors (mainly viral infectious triggers, lymphoid hyperplasia etc.). Intussusception occurs when a segment of bowel invaginates into the distal segment resulting in venous congestion and, if unrecognized and untreated, in bowel necrosis and perforation⁷. The classic triad of a palpable mass, red currant jelly stools and intermittent abdominal pain are rare (40% of pa-

tients)⁸ whereas a young child with intermittent abdominal pain, vomiting and possibly lethargy should raise immediate concern for this surgical emergency. Ultrasound has revealed to be sensitive (98-100%) and specific (88-100%) in the diagnostic process of intussusception⁹ and in the guiding of its treatment which consists in an air, barium or liquid contrast enema and if this fails, in surgical treatment.

Volvulus of the midgut is a surgical emergency in which a loop of bowel twists around its mesenteric attachment⁷. It occurs during the first months of life and in particular within the first year of life and it should be suspected until proven otherwise in every young infant with bilious vomiting and possibly absent abdominal pain until strangulation of the bowel occurs and hematochezia appears with possible shock and rapid deterioration¹⁰. Diagnosis is radiologic (plain radiograms showing signs of intestinal obstruction and upper gastrointestinal series to assess the Treitz ligament position; less commonly with ultrasound)⁷ and treatment consists in aggressive fluid resuscitation and surgical treatment¹¹.

Other surgical causes of abdominal pain in neonates and infants can be due to rarer causes, such as complications from urachal anomalies that include umbilical discharge, local infection, lower abdominal pain and urinary tract infections¹². In particular, urachal remnants may become symptomatic when infected, causing acute abdominal pain and mimicking the more common causes of acute abdominal pain¹².

Non-Surgical Causes of Abdominal Pain

Infantile colic has recently been classified in the Rome IV Classification among the childhood functional gastrointestinal disorders of neonates and toddlers, and broadly defined as “recurrent and prolonged periods of infant crying, fussing

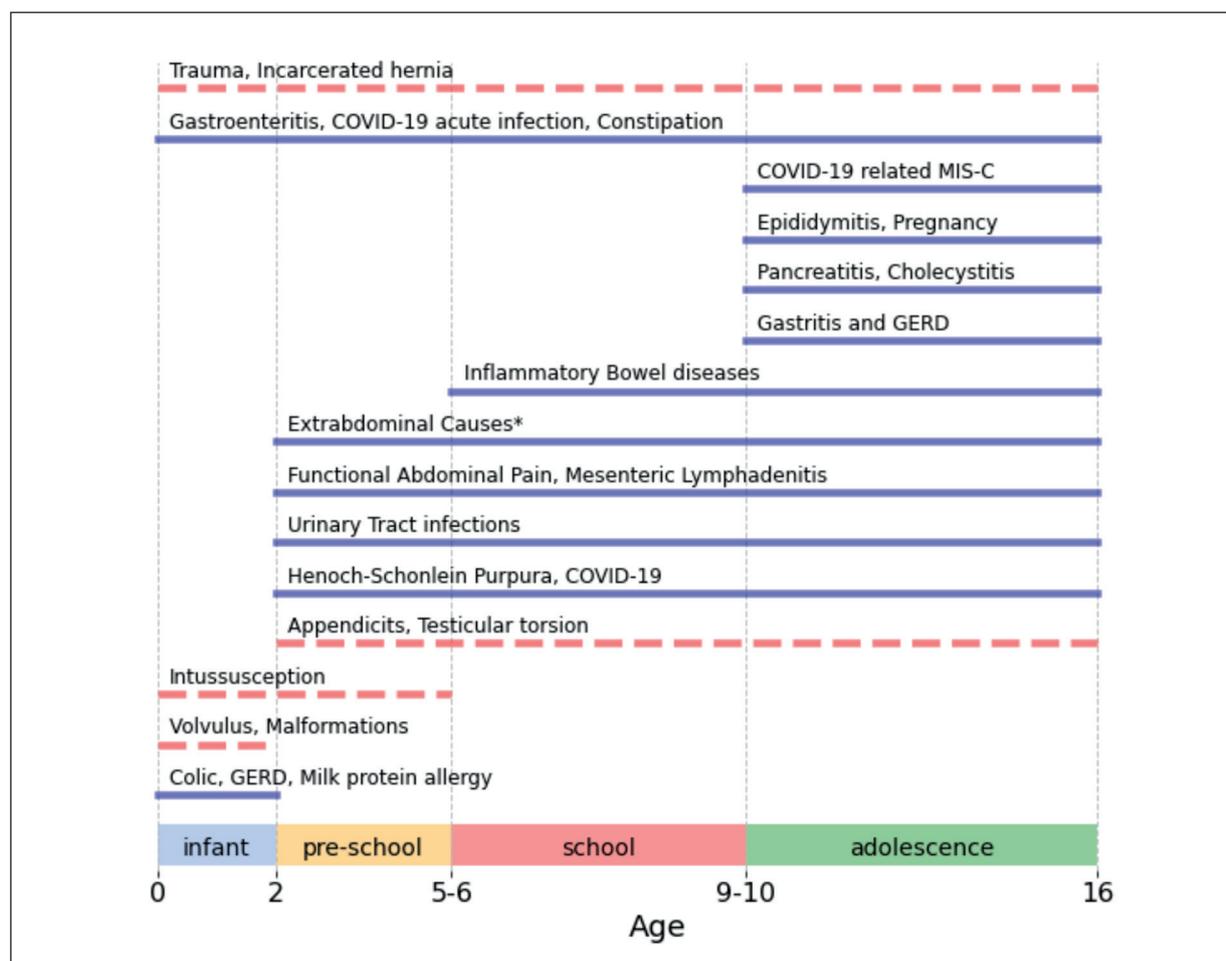


Figure 1. Brief overview of the most common causes of abdominal pain throughout the ages. In blue the non-surgical causes, in red the surgical causes. *Extra-abdominal causes of children presenting with abdominal pain: pneumonia, asthma, diabetes, streptococcal pharyngitis, sickle cell disease vascular occlusion crises, dysmenorrhea.

or irritability without an obvious cause¹³. Diagnosis is clinical and, in most cases, treatment consists in helping caregivers get through this challenging period¹³. There is some evidence, although contradict, that probiotic supplements (e.g., *Lactobacillus reuteri* DSM 17938) can reduce infant crying¹⁴.

Regurgitation of stomach contents is classified as the most common functional gastrointestinal disorder in the first year of life and it is recognition avoids unnecessary treatment and investigations¹³. On the other hand, the prevalence of pathologic gastroesophageal reflux disease (GERD) increases with age up to adolescence¹⁵. In infants, unless there are alarming features such as choking/gagging (sometimes configuring as Brief resolved Unexplained Events-BRUE), abnormal posturing (Sandifer's Syndrome), fail-

ure to thrive etc., regurgitations need not to be investigated. On the other hand, empirical proton pump inhibitor (PPI) for 4-8 weeks is justified in older children and sometimes a pH/impedance or an endoscopy can be necessary¹⁵.

Children (Pre-School, School Age and Adolescence)

Surgical Causes of Abdominal Pain

Appendicitis is the most frequent surgical cause of abdominal pain in children presenting to the Emergency Department and in up to 1/3 of these patients, the appendix ruptures before surgery, especially in children younger than 4 years of age¹⁶. Moreover, in this particular age group, presenting symptoms usually include generalized

peritonitis that requires immediate recognition and treatment. In fact, around 1 to 2 years of age, the appendix becomes more susceptible to appendicitis and lymphoid follicle hyperplasia increases throughout childhood, peaking in adolescence, with the highest incidence of appendicitis in this age group⁷. Clinical presentation is usually characterized by right lower quadrant pain (tenderness at the McBurney point), vomiting and nausea, involuntary guarding, pain on movement and possibly fever. Clinical signs are rebound tenderness (Blumberg sign), Rovsing sign and Psoas sign whereas diagnostic laboratory test include white blood cell count (typically elevated, although nonspecific) and elevation of inflammation markers¹⁷. Abdominal ultrasound can often show enlargement of the appendix, as well as changes in the abdominal wall, presence of fluid or hyperechoic fat surrounding the appendix¹⁷. Moreover, trained pediatric emergency physicians are able to confirm their diagnosis through POCUS with a 60-96% sensitivity and 68-98% specificity¹⁸. Treatment is mainly surgical alongside with hydric replenishment and large spectrum antibiotic coverage for gram-negative and anaerobic bacteria.

Abdominal trauma remains a cause of significant morbidity in children and blunt injuries account for approximately 90% of pediatric trauma¹⁹. According to a review of several trauma databases, approximately 8%-12% of children suffering blunt trauma will have an intra-abdominal injury¹⁹. Common mechanisms are motor vehicle crashes and falls but also bicycle accidents, all-terrain vehicle injuries and particularly in smaller children, child abuse must always be taken into account. Blunt impact trauma accounts for 80% to 90% of abdominal injuries in pediatrics²⁰; in particular the liver is the most common organ injured in blunt abdominal trauma followed by the spleen²⁰. Recently the use of the "Focused Assessment with Sonography for Trauma" (FAST) examination has been shown to reduce the need for computed tomography scans or diagnostic peritoneal lavage and to reduce the time of appropriate intervention in pediatric patients²¹. Luckily, most of the children suffering blunt abdominal trauma have an excellent prognosis with a good survival rate and nonoperative management has become the preferred strategy for most blunt abdominal traumas²².

Inguinal hernias occur in 1% to 3% of all children, more frequently in males and in premature infants¹¹. Clinical findings include a history of an

intermittent bulge in the groin when crying and the diagnosis is mainly clinical but can be confirmed by scrotal ultrasound⁷. An incarcerated hernia requiring emergent surgical reduction occurs mostly during the first year of life and rarely after 8 years of age²³.

Among extra-abdominal causes of children presenting with abdominal pain, a surgical cause requiring immediate recognition and treatment is acute scrotum. This is defined in childhood or in adolescence as scrotal pain, edema and redness of acute onset²⁴. Testicular torsion must be ruled out rapidly in any suspect and differential diagnosis includes hydatid torsion, infection, trauma and other rarer causes (leukemia, Schoenlein Henoch Purpura etc.).

Finally, rarer causes of abdominal pain due to anatomic abnormalities such as omphalomesenteric duct malformations may become symptomatic at any age and the most frequent symptoms include abdominal pain, intestinal bleeding, intestinal obstruction, umbilical drainage, and umbilical hernia²⁵. The most common omphalomesenteric abnormality is Meckel's Diverticulum; its relative complications such as bleeding with lower gastrointestinal hemorrhage can cause acute abdominal pain at all ages²⁶.

Non-Surgical Causes of Abdominal Pain

Gastroenteritis and constipation are among the most frequently performed non-surgical diagnosis of abdominal pain in children of all ages, presenting at the Emergency Department.

The prevalence of constipation in the first year of life is 2.9%, increasing up to 10.1% in the second year of life²⁷. Functional constipation is classified among Childhood Functional Gastrointestinal Disorders in the Rome IV criteria¹³. It is often the result of repeated attempts of voluntary withholding of feces by a child avoiding painful defecation¹³. The diagnosis is usually performed through an accurate patient history and clinical examination and organic causes should always be considered and excluded.

Among other rarer causes of functional abdominal pain that concern children from pre-school age onwards, some childhood episodic syndromes can be included. In particular, Cyclic Vomiting Syndrome (6-10 years of age) is characterized by recurrent and self-limited episodes of severe nausea and vomiting, abdominal pain, and dramatic autonomic dysfunction interspersed with symptom-free periods²⁸. Abdominal Migraine affects older children (7-10 years of age)

and it is characterized by recurrent, acute-onset abdominal pain lasting for hours or days and accompanied by dysautonomic signs²⁹. Treatment of these conditions to the present day is mainly symptomatic, but additional clinical studies could investigate whether patients with pain-related functional gastrointestinal disorders could benefit from antimigraine drugs³⁰.

Gastroenteritis is characterized by acute diarrhea, vomiting, possibly fever and abdominal pain³¹ and it is one of the most common reasons a child presents to the Emergency department with abdominal symptoms. Causes of acute gastroenteritis are mainly viral or bacterial and in immunocompetent patients, treatment consists mainly in rehydration according to level of dehydration and supportive therapy.

Inflammatory Bowel Diseases (IBD) are not uncommon in children from school age onwards with up to 25% of patients diagnosed before the age of twenty³². IBD must be suspected in all patients presenting with a story of chronic diarrhea with or without blood, abdominal pain and poor growth, in the presence of the so called “red flags” (see above). Celiac disease can also present with diarrhea, abdominal pain, weight loss, poor growth, and low bone mineral density but it is not associated with bloody diarrhea³². IBDs (classically Crohn Disease and Ulcerative Colitis) have a wide range of phenotypes in the pediatric population that also concern growth, development, bone health and maturation. Diagnostic workup includes laboratory exams, esophagogastroduodenoscopy and colonoscopy and referral to a pediatric gastroenterologist. Exclusive enteral nutrition (EEN) is the induction therapy of first choice in Crohn’s Disease and most patients with pediatric-onset Crohn Disease require immunomodulator based maintenance therapy³³.

Abdominal Pain During COVID-19 Pandemic

The COVID-19 is to date a global pandemic, that to the 18.06.2021 has affected approximately 176.945.596 people in the world with 3.836.828 deaths. It can affect all age groups although severe forms of COVID-19 in the pediatric population are rare³⁴. Gastrointestinal symptoms are quite common in patients with COVID-19, and the feces of COVID-19 patients are potentially an infection source³⁵.

During infection, the virus enters into host cells by binding its spike protein (protein S) with the membrane-bound angiotensin-convert-

ing enzyme 2 (ACE2)³⁶. We can find this virus receptor in lung cells but also in epithelial cells of the small intestine and in other tissues directly correlated with extrapulmonary manifestations of COVID-19. In particular, the clinical spectrum of COVID-19 acute infection in children and adolescents is characterized mainly by fever and cough, but also diarrhea³⁴ and other extrapulmonary and in particular gastroenteric symptoms, such as abdominal pain, vomiting, pharyngeal erythema, reduced feeding and possible alterations of liver enzymes³⁶.

Treatment of COVID-19 in children mainly relies on supportive care; home isolation has been the first step in the management of children with mild symptoms³⁷. Hospitalization may be considered if rapid deterioration takes place and in the case of underlying diseases. Hospital treatment basically consists in patient monitoring, oxygen support, if necessary, hydration and antipyretics³⁸. Antiviral drugs should be used with caution and in particular a low dosage of interferon- α nebulization has been used in combination with oral ribavirin³⁹. Remdesivir should be preferred in children but when not available or when patients are not good candidates to remdesivir, hydroxychloroquine can be considered⁴⁰.

In April 2020, an alarming warning was given by the National Health Service in England about cases of SARS-CoV-2 positive older school-aged children and adolescents presenting with fever, hypotension, severe abdominal pain, and cardiac dysfunction³⁶. High levels of inflammatory markers suggested a cytokine storm and children generally ended up requiring inotropic support; some cases were even fatal⁴¹. Parallels have been drawn between the presenting features of this condition and other known diseases, such as incomplete, complete, and atypical Kawasaki disease (with or without coronary artery dilatation), viral sepsis, toxic shock syndrome and macrophage activation syndrome¹. This condition was later defined by the Centers for Disease Control (CDC) and the World Health Organization (WHO) as Multisystem Inflammatory Syndrome in Children (MIS-C). However, another frequently used synonym is Pediatric Inflammatory Multisystem Syndrome temporally associated with COVID-19 (PIMS-TS)¹.

Diagnostic criteria for MIS-C defined by the World Health Organization on the 15 May 2020 are reported in Table III⁴².

The pathophysiological mechanisms of MIS-C remain unclear. Some Authors have proposed that

Table III. Diagnostic criteria for MIS-C defined by the World Health Organization on the 15 May 202042.

<p>Children and adolescents 0-19 years of age with fever ≥ 3 days AND two of the following:</p> <ul style="list-style-type: none"> – Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet). – Hypotension or shock. – Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated Troponin/NT-proBNP), – Evidence of coagulopathy (by PT, PTT, elevated d-Dimers). – Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain). <p>AND Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.</p>

this condition is not the result of an acute viral infection, but it is a post-infectious condition related to IgG antibody-mediated enhancement of the disease⁴³. In particular, the virus could be replicating in the gastrointestinal tract⁴³.

Moreover, several authors^{44,45} have reported the rare occurrence of coronary aneurysms in children with MIS-C. In particular, a mild transient dilation of the coronary arteries is often reported in MIS-C, as it occurs in another pediatric conditions that are associated with high serum inflammatory markers⁴⁶. The most common symptoms in MIS-C gastrointestinal (87%), followed by dermatologic (73%) and cardiac (71%) manifestations; fever is present in 100% of cases. Up to 2% of children with MIS-C described in literature died from MIS-C⁴⁷.

Initial treatment of MIS-C consists in judicious fluid support and broad-spectrum antibiotics since symptoms overlap with severe bacterial infections. Antibiotic therapy is chosen according to the severity of the disease and to the organs mostly involved (e.g., if gastrointestinal symptoms are predominant, it is advisable to add metronidazole)⁴⁸. Children presenting with shock benefit from cardiac and respiratory support in Intensive Care Unit. Many centers have treated children that present similar clinical features to Kawasaki Disease with intravenous immunoglobulins 2 g/kg and aspirin 80-100 mg/kg/day plus a three-day pulse methylprednisolone if cardiac aneurysms are present⁴⁸.

The abdominal pain in MIS-C can be so severe that in many cases reported in literature, patients were presumed to have peritonitis or another surgical abdominal condition⁴⁹. This exactly what happened to our patient that presented with high fever, vomiting and continuous, worsening abdominal pain with tenderness in the right iliac fossa, in

particular, in the Mac Burney Point. These symptoms are compatible with the initial diagnosis of appendicitis and therefore surgical treatment was pursued. However, in these past one and a half years of COVID-19 pandemic, we became familiar with new clinical entities, such as the COVID-19 acute infection and MIS-C and in particular we have learnt that there is a vast spectrum of gastrointestinal clinical features also in MIS-C⁵⁰. The importance and innovation of our paper consist precisely in underlining that COVID-19 may cause a picture that can mimic a more common surgical emergency in children and that as knowledge about COVID-19 in children evolves, physicians should be aware of possible new misdiagnosis. MIS-C has revealed to be an extremely dangerous and sometimes life-threatening disease if not recognized and treated; with this report we therefore suggest that every physician dealing with children and adolescents should recognize this disease among the causes of abdominal pain.

Some cases similar to ours have already been described in literature; in particular, in the USA, Anderson et al⁵¹ describe two cases of patients (respectively 8 years old and 9 years old) initially diagnosed with appendicitis who either presented with or developed signs of shock and were found to have MIS-C. In another case series in South Africa, three children initially diagnosed with appendicitis who underwent surgery, were then treated for MIS-C after they developed shock requiring inotropic support⁵². In particular, one of these children presented transmural chronic inflammation, extensive venous microthrombi, and a markedly inflamed mesentery. Similarly, Mahajan et al⁵³ describe a case of an 8-year-old boy previously in contact with a COVID-19 positive family member, presenting simply with abdominal pain and persistent fever, whose abdominal

MRI showed diffuse thickening of bowel walls throughout the ileum and large intestine and whose cardiovascular conditions rapidly deteriorated requiring inotropic support. The inconstant presence of mucocutaneous signs can make the diagnosis of MIS-C easy to miss among more common clinical abdominal pictures, similarly to what happened to our patient who developed mucocutaneous signs only after a few days from symptoms onset. Enteritis, ileitis and hemorrhagic colitis can also be a manifestation of acute COVID-19 infection in adolescents without features of multisystem inflammatory syndrome in children (MIS-C) or a prior history of inflammatory bowel disease (IBD) as reported by Gupta et al⁵⁴.

A clinical picture very similar to our patient was reported by Hwang et al⁵⁵, who describe the case of a 16 years old girl with clinical symptoms suggestive of appendicitis and an abdominal computed tomography (CT) that revealed suspect features for appendicitis, in the absence of a compatible histopathology after surgical appendectomy. In particular, like in our patient, laboratory criteria (specifically low-normal white blood cell count) were not compliant with acute appendicitis and could have been a tool to precociously differ MIS-C from acute appendicitis, even though MIS-C had determined a clinical and radiologic mimic of appendicitis. We therefore suggest that laboratory findings, such as lymphopenia, thrombocytopenia, and inappropriately normal WBC count could help in differentiating MIS-C from other abdominal clinical pictures, as previously suggested⁵⁵.

Another report⁵⁶ described a case of MIS-C that mimicked appendicitis clinically and on ultrasound imaging; like our patient, this patient underwent surgery that revealed an inflamed segment of the ileum with a necrotic mesenteric lymphangitis and vasculitis, before treatment with IVIG and steroids was initiated.

A cohort of 35 pediatric patients was described by Sahn et al⁵⁷ which can manifest as cardiovascular, pulmonary, neurologic, and gastrointestinal (GI) to analyze the spectrum of intestinal disease associated with MIS-C. The study⁵⁷ revealed that >95% of the children presented with gastroenteric symptoms and more than 50% had terminal ileitis with bowel wall thickening on CT imaging. This presentation, like in our case, raised suspicion for an inflammatory bowel disease in the differential diagnosis. However, the Authors underlined that CRP levels were typically higher

in MIS-C patients than the levels seen in children with a classical IBD onset, as was the case of our patient, and platelet counts were often normal or low⁵⁷ which can manifest as cardiovascular, pulmonary, neurologic, and gastrointestinal (GI). Moreover, other inflammatory biomarkers, such as D-dimer, fibrinogen, pro-BNP and troponin could help distinguish IBD from MIS-C. Generally, there is a vast spectrum of gastrointestinal clinical features in MIS-C⁵⁰ and as the knowledge about novel manifestations of COVID-19 in children evolves, it is imperative to recognize the spectrum of MIS-C symptoms for timely initiation of appropriate patient management⁵⁸.

Conclusions

The patient we describe was a challenging case of febrile abdominal pain and various hypothesis were performed during his diagnostic workup. In literature there are various reports of abdominal pain and COVID-19-related misdiagnosis as these cases may pose a greater clinical challenge. MIS-C is a serious condition characterized by multiorgan dysfunction and presenting symptoms of MIS-C often include fever and abdominal pain that can be easily mistaken for other surgical or non-surgical pediatric conditions. Patients can rapidly become unstable in particular when cardiovascular compromise arises, requiring immediate treatment. This consists briefly in fluid support, possibly cardiac and respiratory support and treatment similar to that of Kawasaki Disease with intravenous immunoglobulins 2 g/kg and eventually aspirin and steroids.

The objective of this case report and brief review of abdominal pain in children is to provide the emergency pediatrician with updated suggestions in diagnosing abdominal pain in children during the COVID-19 pandemic. We would like to remind all health providers to always keep in mind the atypical presentations of MIS-C in children which may mimic more routine diagnosis. In particular, we suggest that MIS-C should be routinely considered in the differential diagnosis of pediatric school age patients presenting with febrile abdominal pain and general gastroenteric symptoms, especially in patients with a positive history for COVID-19 infection.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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