Acute abdominal pain and nephrotic syndrome: pediatric case reports and review of the literature

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Abstract

Background: Acute abdominal pain in nephrotic syndrome (NS) is a well-known clinical symptom and is mainly related to peritonitis. The presence, although rare, of red umbilicus may guide the diagnosis as a suggestive sign of peritonitis also in the non-neonatal period. Instead, the association between intussusception and NS is quite limited. We reviewed all published cases in the literature, and to our knowledge, this is one of the few pediatric cases of spontaneous resolution of intussusception in the setting of NS. Finally, a review of the causes of abdominal pain during the course of NS was made.

Cases presentation: We report two pediatric patient cases who complained of acute abdominal pain during a relapse episode of their NS. The first case is a 4-year-old boy with NS (fourth relapse) who presented with acute abdominal pain, ascites, and red umbilicus. Our suspect of primary peritonitis was clinically confirmed because of the subsequent appearance of the classical peritoneal signs. The second case is a 4-year-old boy who developed an ileo-ileal intussusception during the treatment of his first NS relapse, with spontaneous reduction.

Conclusions: Gastrointestinal disorders are frequently encountered in the course of NS. The appearance of acute abdominal pain in children with NS requires quick management, both clinical and instrumental. A multidisciplinary team approach needs to be encouraged to lead to an accurate diagnosis and a correct treatment.

Keywords: Nephrotic syndrome, Pediatric case reports, Acute abdominal pain, Peritonitis, Intussusception

Background

Nephrotic syndrome (NS) is one of the most common pediatric glomerular diseases, with an incidence of around 2–7 cases per 100,000 children per year. Renal histology reveals the presence of minimal change disease (MCD) in about 76% of these patients while only 10–20% of them show focal segmental glomerulosclerosis. Subjects with MCD have a 95% response rate to steroids; however, 75% will relapse and 50% (frequent relapers or steroid-dependent subjects) will require higher and prolonged doses of steroids thus increasing the risk of side effects [1–3]. Idiopathic forms have a higher incidence in the pediatric population; conversely, in adults, it is mandatory to exclude secondary forms because they are the most frequent [4]. The cause remains unknown but the pathogenesis of idiopathic NS is thought to involve immune dysregulation, systemic circulating factors, or inherited structural abnormalities of the podocyte [5]. NS is defined by the presence of heavy proteinuria (≥ 50 mg/kg/day or ≥ 40 mg/m²/h) or a proteinuria/creatininuria ratio (> 2 mg/mg), hypoalbuminemia (< 2.5 g/dl), and edema [1]. Complications of NS may occur as a part of the disease itself (because of the large loss of plasma proteins in the urine) or as a consequence of drug treatment (corticosteroids, cyclophosphamide, calcineurin...
inhibitors, mycophenolate mofetil). Disease-associated complications include infections, thromboembolism, hypovolemic crisis, cardiovascular problems, acute renal failure, anemia, and hormonal and mineral alterations [6].

We report two unusual cases of NS-related abdominal disease (one case of primary peritonitis and one of intussusception), describing their clinical presentation and their management as notable complications in nephrotic patients. In addition, we carefully reviewed the literature concerning acute gastrointestinal disorders during NS. It is widely reported that acute abdominal pain is a relatively common feature in patients with NS. The clinical picture, along with blood and instrumental tests, can help clinicians to make a differential diagnosis and to determine the suspected condition. Among the several causes of abdominal pain in the setting of NS, pediatric nephrologists should consider spontaneous bacterial peritonitis, especially if fever is present [5], and intussusception, less common, but remarkable disease, whose early recognition may improve prognosis [7].

Case presentation
A Caucasian 4-year-old boy was admitted to our unit for the fourth relapse of his steroid-dependent NS. He was diagnosed as having idiopathic NS at 3 years of age. The third relapse happened about 40 days before the last one and was treated with oral prednisone (60 mg/m²/day) with rapid remission of proteinuria, but as soon as we tried to switch to alternate-day prednisone therapy, the fourth relapse happened. At the admission, the patient showed facial swelling, peripheral (scrotal and pretibial) edema, and ascites with a 2-kg weight gain. His body temperature was 36.7 °C, heart rate 100 beats/min, respiratory rate 21 breaths/min, and blood pressure 115/75 mmHg. Blood tests revealed the following: total proteins 3.9 g/dl, serum albumin 1.3 g/dl, serum sodium concentration 125 mmol/l, potassium 5.7 mmol/l, and calcium 7.6 mg/dl. Urine volume was 650 ml/24 h with severe proteinuria (15.6 g/24 h). The summary of all investigations is shown in Table 1.

A decision was made to start intravenous methylprednisolone pulse therapy, at a dosage of 10 mg/kg/day for 3 consecutive days, together with calcium gluconate and albumin infusion. About 48 h after the beginning of this treatment, the boy gradually showed severe generalized abdominal pain without initial signs of peritoneal inflammation. The periumbilical area was abnormal in its appearance: erythema was centralized within the umbilicus and extended 1.5 cm about the entire umbilicus. A few hours later, we documented a sudden worsening of the clinical conditions. A pediatric surgical consult was required and confirmed the patient’s serious conditions, with the following features: marked abdominal distension, ascites, diffuse tenderness to superficial and deep palpation, hypoactive bowel sounds, and positive Blumberg’s sign. The child laid up in a semi-sitting position with superficial breathing. No fever or vomiting was documented. The umbilical erythema gradually developed all around the umbilical area that became severely painful at palpation but did not show any mass or purulent discharge. Emergency blood tests suggested a bacterial infection. An abdominal X-ray demonstrated a paralytic ileus with severe gastrectasia, several air-fluid levels, and an abnormal gas pattern with no intestinal loops visualized. An abdominal ultrasound showed a considerable amount of “corpusculated” fluid and distention of small bowel loops especially in correspondence of the umbilical region. Despite the increase of D-dimer (4.5 μg/ml, normal < 0.5 μg/ml), mesenteric and renal vascular flows were normal. Physical, laboratory, and radiological findings suggested the hypothesis of primary peritonitis. Considering that the timing and worsening of the clinical presentation could have been influenced by the immunosuppressive treatment of the patient, in agreement with the pediatric surgeon, a conservative approach was carried out starting the patient on empirical antibiotic treatment with intravenous broad-spectrum antibiotics to cover resistant pneumococci and bowel organisms: metronidazole (7.5 mg/kg every 8 h) and ceftazidime (100 mg/kg/day). The paracentesis was delayed in case of no antibiotic response. The steroid treatment was suspended. Furthermore, enteral feeding was

| Table 1 Summary of investigations (*beginning of the antibiotic treatment) |
|-----------------|-------|-------|-------|-------|-------|-------|
| Day of hospitalization | Day 1 | Day 3* | Day 4 | Day 5 | Day 6 | Day 10 |
| White cell count (mm³) | 10,000 | 19,400 | 23,000 | 18,000 | 15,000 | 9800 |
| Neutrophils (%) | 45 | 87 | 90 | 85 | 70 | 50 |
| Hemoglobin (g/dl) | 15.1 | 12.9 | 13.0 | 14.1 | 14.0 | 14.9 |
| Platelets (10³/mm³) | 690 | 555 | 505 | 410 | 350 | 250 |
| C-reactive protein (mg/dl) | 0.1 | 1.2 | 13 | 21.9 | 11.5 | 0.5 |
| Total proteins (g/dl) | 3.9 | 3.6 | 4.0 | 4.1 | 4.5 | 5.6 |
| Albumin (g/dl) | 1.3 | 1.9 | 2.1 | 2.4 | 2.8 | 3.0 |
stopped, and an intravenous infusion with a balanced electrolyte solution (55 mL/h) was started. Serial surgical evaluations were performed in order to check the potential need for a surgical intervention, in case the conservative management turned out to be unsuccessful.

Just a few hours later, we assisted in a prompt improvement of the boy’s general conditions and to a gradual disappearance of abdominal pain. The blood tests repeated at 24 and 48 h after the beginning of the antibiotic treatment showed an increase of infection markers, in spite of clinical improvement. A laboratory response started only after 72 h with a slow normalization of the tests within a week. Abdominal tenderness reduced gradually in the following days. Red umbilicus persisted for a week.

A Caucasian 4-year-old male was admitted to our unit due to periorbital swelling and edema of the sovrapubic region and of the legs that had lasted for 7 days. The patient had a past history of NS diagnosed 3 months earlier, for which he was treated with steroids. At the admission, vital signs were normal with a blood pressure of 85/45 mmHg. Laboratory investigations confirmed the clinical suspicion of a first relapse of his NS: total serum proteins 4.8 g/dl, albumin 2.1 g/dl, and urinary proteins 9.2 g/day (920 mg/m²/day) with a gradual but slow clinical and laboratory improvement. Eight days post-hospitalization, the child complained of diffuse and progressively worsening abdominal pain. Physical examination revealed a mildly distended abdomen with no palpable mass. The abdominal X-ray ruled out a bowel obstruction or perforation. An abdominal ultrasound was performed being suggestive of ileo-ileal intussusception with a positive “target sign” (a single hypoechoic ring with a hyperechoic center) of 25 mm in diameter (Fig. 1).

In accordance with the pediatric surgeon and the pediatric radiologist, the child was managed conservatively because he was hemodynamically and clinically stable without any evidence of bowel perforation. Enteral feeding was stopped, and an intravenous infusion with a balanced electrolyte solution (60 mL/h) was started. A follow-up ultrasound done 24 h later showed a shorter invaginated segment (“target sign” of 16 mm). After 48 h from the initial study, the ultrasound did not visualize the intussusception, which coincided with the NS remission.

**Discussion**

Primary peritonitis is a well-described infectious complication of NS. It usually occurs within the first 2 years of diagnosis, especially during relapse periods; its incidence is about 1.4–3.7% of children with NS, with a mortality rate of 9%. *Streptococcus pneumoniae* is the most common organism causing bacterial peritonitis and sepsis in these patients [8–10]. In our first case, a Caucasian 4-year-old boy with NS (fourth relapse) presented with abdominal pain, ascites, and red umbilicus. Our suspect of primary peritonitis was clinically confirmed because of the subsequent appearance of the classical peritoneal signs. Steroid treatment for NS is also likely to have led to a delayed diagnosis. Our patient was managed conservatively with empirical antibiotic therapy and with the continuous support of the pediatric surgical team, always ready for surgery in case of clinical deterioration. The diagnosis of peritonitis is only presumed in the absence of peritoneal fluid analysis: in many cases, a diagnostic paracentesis may not be available, and patients may be treated empirically with broad-spectrum antibiotics with the disadvantage of antibiotic resistance [8, 9]. Unfortunately, in our case, it was not possible to perform right away paracentesis, but the diagnosis was also eased suspected by the appearance of red umbilicus. Red umbilicus results from an inflammatory process that spreads to the subcutaneous fascial plane and infiltrates the umbilical skin. If unrecognized or untreated, the infection may complicate in a necrotizing fascitis of the abdominal wall with a high mortality rate. In the neonatal period, red umbilicus is often a troubling sign of infection, such as funisitis, omphalitis, or underlying gangrenous bowel and peritonitis like in the necrotizing enterocolitis [11, 12]. But among non-neonatal patients, red umbilicus is extremely rare as a sign of peritonitis. To our knowledge, this unusual presentation of red umbilicus caused by acute peritonitis in the non-neonatal period has rarely been reported [12–14].
In children with NS who present with abdominal pain, spontaneous bacterial peritonitis should be considered as the most important differential diagnosis [10], but it is not the only cause, as shown in Table 2.

Intussusception represents one of the most frequent abdominal emergencies of infancy and early childhood and is characterized by bowel wall invaginating into another segment of the bowel. The classic symptomatology is intermittent abdominal pain, vomiting, and bloody stools, sometimes associated to a palpable right upper quadrant mass. The most common type of intussusception is ileocolic, and the majority of pediatric cases occur in patients <1 year of age. Intussusception has also been described as a rare but serious complication of NS and may present atypically unusual location (small bowel), absence of a palpable mass due to ascites, older age at presentation, and absence of the classic triad of symptoms [15]. The most popular hypothesis is that a combination of patchy bowel wall edema and peristaltic incoordination could provide the “pivot (lead point) and torque” in patients with NS [16, 17]. It is possible that prolonged edema was the major cause of intussusception in our second patient, who developed acute abdominal pain after approximately 15 days of the NS relapse. It has been indeed reported that intussusception in NS may be due to generalized edema sustained for more than 2 weeks [18]. Treatments of ileocolic intussusception are nonoperative resolving procedures (air or barium contrast) and surgery (manual treatment with laparotomy). Ileoileal intussusception has no indication for radiological treatment, and given the frequent spontaneous resolution, it does not usually even require surgery. Treatments reducing bowel wall edema, such as infusion of albumin and diuretics, have been reported to play a significant role in the resolution of intussusception in NS as bowel wall edema would be the major cause of the condition, which is in contrast to typical intussusception [17]. In our case, it was very difficult to decide the treatment choice because the patient was clinically stable and a potential spontaneous reduction could not be ruled out. Furthermore, the intussusception interested the small bowel; Doi et al. first considered small bowel intussusception to be nonischemic and, therefore, benign and susceptible to spontaneous reduction [19]. Supported by the literature [15, 17, 19–21], we decided to adopt a conservative approach that led to a spontaneous reduction of intussusception. To our knowledge, this is one of the few pediatric cases of spontaneous resolution of intussusception in NS [15, 17]. The association between intussusception and NS was first reported in 1975 [22]. Subsequently, in the following 45 years, only 11 case reports have been described in the literature [15, 17, 18, 20–26]. Characteristics of these patients are summarized in Table 3.

MCD minimal change disease, DMS diffuse mesangial sclerosis

Eight patients (73%) were children at the time of intussusception, and surprisingly, only one case was younger than 1 year. Six of the 11 patients (55%) presented intussusception during the first episode of NS, while 5 patients developed this disease-related complication during a relapse episode. All patients complained of abdominal pain; vomiting was reported in 5 cases (45%), bloody stool in 3 cases (27%), and a palpable abdominal mass (right upper quadrant) in 1 case (9%). The intussusception occurred in an unusual location (small bowel) in 5 patients (45%). Regarding the treatment, surgery was performed in 5 patients (45%), whereas nonoperative resolving procedures were performed in 2 patients (18%). Remarkably, a spontaneous reduction was observed in 4 patients (36%); all of these cases were described in the last 10 years, after the first patient-reported by Cho et al. in 2009 [17].

Ischemic colitis is a disease caused by ischemia of the intestinal vessel, which presents with a sudden onset of abdominal pain and hematochezia. Diagnosis is confirmed by colonoscopy. Although thromboembolism is an important and frequent complication in patients with NS (presumably attributable to a hypercoagulable state), reports of ischemic colitis in the setting of NS are extremely rare, and only 3 cases (2 adults and 1 child) have been reported [27–29]. About our first patient, we ruled out the suspect of ischemic colitis because the child never showed bloody diarrhea or suggestive radiological signs. In regard to the mild increase of blood D-dimer we found, it is been described that its rise is not exclusively a marker of thromboembolic disease but can be an expression of other conditions, such as infections or inflammation [30].

Pneumatosis intestinalis is another rare cause of abdominal pain in nephrotic patients, described in 3 adults and 1 child [31–34]. It is a condition characterized by the linear or cystic accumulation of gas within the gastrointestinal wall. Patients may be asymptomatic or present with bloody diarrhea, abdominal pain, abdominal distension, constipation, and tenesmus from rectal

Table 2 Causes of acute abdominal pain in nephrotic patients

| Peritonitis                           |     |
|---------------------------------------|-----|
| Intussusception                       |     |
| Ischemic colitis                      |     |
| Pneumatosis intestinalis              |     |
| Hypovolemic crisis                    |     |
| Anecdotal                             |     |
| Eosinophilic gastroenteritis          |     |
| Congenital peritoneal encapsulation   |     |
| Splenic infarction                    |     |
| Renal infarction                      |     |

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Table 3  Review of patients with intussusception during the course of nephrotic syndrome

| Patient | 1 | 2          | 3         | 4          | 5          | 6          | 7          | 8          | 9          | 10         | 11         | 12         |
|---------|---|------------|-----------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Authors |   | Takano et al. [22] | Crawshaw et al. [23] | Fitz-Henry et al. [24] | Kietkajornkul et al. [25] | Asai et al. [18] | Cho et al. [17] | Long et al. [20] | Ete et al. [21] | Al-Mardini and Hiddad [26] | Kelly et al. [15] | Present case |
| Year of publication | 1975 | 1991 | 1992 | 2003 | 2005 | 2009 | 2010 | 2014 | 2014 | 2016 | |
| Age | 19 years | 6 months | 4 years | 5 years | 2 years | 5 years | 39 years | 27 years | 7 years | 3 years | 4 years | 4 years |
| Gender | Male | Female | Female | Male | Male | Female | Female | Male | Male | Male | Male | Male |
| NS episode | First | First | First | Relapse | First | Relapse | First | Relapse | Relapse | Relapse | First | Relapse |
| Histological diagnosis | MCD | DMS | MCD | IgM nephropathy | – | MCD | MCD | MCD | MCD | DMS | – | – |
| Δt NS episode intussusception | 35 days | – | – | – | 14 days | 21 days | 13 days | 19 days | 3 days | 4 days | – | 19 days | 15 days |
| Classic triad of symptoms: | | | | | | | | | | | | |
| 1. Abdominal pain | + | + | + | – | + | + | + | + | + | + | + | + |
| 2. Vomiting | – | + | – | – | + | – | – | – | – | + | + | – |
| 3. Bloody stool | + | + | – | – | + | – | – | – | – | – | – | – |
| Palpable abdominal mass | – | – | + | – | – | – | – | – | – | – | – | – |
| Location | Ileocolic | Ileocolic | Ileocolic | Jejun ileal | Ileocolic | Ileoleal | Ileoleal | Ileocolic | Small bowel | Ileoleal | – | Ileoleal | Ileoleal |
| Reduction | – | Pneumatic surgery | Surgery | Surgery | Pneumatic | Spontaneous | Spontaneous | Spontaneous | Surgery | Pneumatic | Spontaneous | Spontaneous |
involvement. Gut edema, the use of immunosuppressive agents, and preceding viral gastroenteritis are possible predisposing factors [31].

As pointed out by Wang et al. [35], abdominal pain may also be a symptom of the hypovolemic state (hypovolemia-induced ischemia) in children with NS. Hypovolemic crises typically occur early in the course of NS (first episode or relapse), even before edema is evident [36, 37].

Finally, few case reports documented the association between NS and other causes of abdominal pain: eosinophilic gastroenteritis (a rare disease characterized by prominent eosinophilic tissue infiltration of the gastrointestinal tract) [38], congenital peritoneal encapsulation (an accessory peritoneal flap that encloses the entire mass of the small intestine) [39], splenic infarction [40–42], and renal infarction [43, 44] (as a thromboembolic complication).

Conclusions

We reported 2 cases of pediatric patients suffering from NS who developed peritonitis (first case) and intussusception (second case) during a relapse episode. The most remarkable manifestation in our patients was the acute abdominal pain; the appearance of this symptom in the setting of NS requires prompt management, both clinical and instrumental. A close collaboration between a pediatric nephrologist and a pediatric surgeon may be necessary to lead to an accurate diagnosis and a correct treatment. Acute abdominal pain in NS is usually related to infectious peritonitis. The presence, although rare, of red umbilicus may be a suggestive sign of peritonitis also in non-neonatal period. Intussusception is an infrequent complication but should be considered among the complications of NS, especially in patients with prolonged edema. These two cases demonstrate the frequent surgical complications in nephrotic patients. Nevertheless, our experience shows how clinical management, together with tight surgical consulting, can represent a successful option of treatment.

Abbreviations

NS: Nephrotic syndrome; MCD: Minimal change disease; DMS: Diffuse mesangial sclerosis

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Authors’ contributions

GC and RC had the idea for the article. CV performed the literature search. NSC and VC wrote the first draft of the manuscript. PI, CV, and CR critically revised the work. All authors have read and agreed to the published final version of the manuscript. The author(s) read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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