Abdominal Pain in a Child with Nephrotic Syndrome

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Case History

- Winson was a 30 months old child

- First presented in August 2006 (23 months old) as general edema for 1 week.
  - There was no precipitating fever, no URI symptoms
  - There was no gross hematuria, no dysuria or frequency
  - Did not aware of any frothy urine but noticed a decrease in urine output for several days
  - Noticed a gain in body weight of 2kg in the past 2 weeks without significant change in appetite
Past history
- FTNSD, uneventful neonatal history except NNJ admitted for phototherapy and renal function test was normal at that time.
  - Thriving satisfactory all along

Family history
- The first child in the family
- Parents were non-consanguinous marriage
- No family history of nephrotic syndrome, renal disease or hearing deficit
- Physical examination

- BW 16kg, BP 100/60 pulse 95bpm
- Puffy eyelids
- Ankle edema
- Ascites++
- Scrotal edema++
- Abdomen soft nontender, no abnormal mass
- Other systems were normal
Laboratory results

- Na/K/Urea/Cr = 132/4.7/5.0/30
- Serum albumin = 15g/dL
- Cholesterol = 10.4 mmol/L
- C3/C4 = 1.62/0.4 (normal)
- ASOT/viral titer (uneventful)
- Autoimmune markers negative
- Anti-HBsAg: positive
- 24 hours urine protein showed 9.17gm/day
- CXR: no pleural effusion
- MT2-ve
- USG kidneys: normal
Idiopathic Nephrotic Syndrome of childhood

- Treated with prednisolone at 60mg/m²/day (35mg daily in divided doses)
- Occasionally complained of abdominal pain – treated with albumin infusion with diuretics
- Penicillin V orally for prophylaxis of primary peritonitis
- Low salt, high protein diet
Steroid responsive and Nephrotic Syndrome in remission on Day 10 of steroid therapy

Discharged with treatment regime of Prednisolone 60mg/m²/day for 6 weeks followed by 40mg/m²/day on alternate day for 6 weeks and slow tapering
- First relapse a few days after tapering to alternate day steroid
  - Put back to full dose steroid
  - Remitted again after 2 weeks of full dose steroid

- Second relapse, 2 weeks after tapering steroid to alternate day regime
  - Steroid tapered slowly on daily basis
  - Add on ACEI and levamisole
Third relapse

- Third relapse while taking prednisolone 20mg daily (1.1mg/kg/day) with enalapril at 0.3mg/kg/day

- Severe relapse with full blown picture of Nephrotic syndrome
Relapse of Full-blown Nephrotic Syndrome

- BP on admission was only 77/51
- Cushingoid features++
- Ascites++
- Scrotal edema
- Penile edema
- Lower limbs edematous
- Na/K/urea/creatinine = 131/5.1/5.7/51
- Albumin 15g/dL
- Hb 18g/dL, WBC 22.5 x10^9/L, platelet 719 x10^9/L
- 24 hours urine for proteinuria= 23.4g/day
- Renal USG repeated exclude renal vein thrombosis
Became steroid resistant

- Put on full dose steroid
- Became steroid resistant
- Both clinically and biochemically did not show any improvement
- Add on cyclophosphamide at 2mg/kg/day with presumptive diagnosis of minimal change disease versus FSGS
- Pros and cons of renal biopsy discussed with parents
Complicated by **Norovirus gastroenteritis**

- Developed severe watery diarrhoea, abdominal pain and dehydration required intravenous fluid therapy and repeated doses of albumin infusion.
- Stool viral study with RT-PCR showed positive Norovirus (Norwalk-like virus)
Despite on steroid + Cyclophosphamide (for 4 weeks)

- Persistently edematous, severe proteinuria and repeated complaints of abdominal pain - bowel ischemia?
- Noticed progressively increase in degree of abdominal distension
- Complained of right shoulder pain
Persistent abdominal pain

**DDX**
- Bowel ischemia
- Primary peritonitis
- Urinary tract infection
- Acute surgical emergency
- Acute pancreatitis
- Peptic ulcers/PPU
- Pneumonia
- gastroenteritis

**Management**
- Repeated doses of albumin infusion
- Urine culture
- Sepsis work up including blood culture, CXR
- Put on intravenous cefuroxime
- Blood test normal WCC, except persistently, elevated platelet count
- Repeated stool culture showed positive norovirus
Abdominal XR

Classical tramlines of intramural gases
Urgent CT abdomen and with oral contrast

- Extensive mural gas involving the whole colon down to the rectum.
- Pneumoperitoneum is noted, Air is seen in the retroperitoneum and the anterior pararenal space.
- No portovenous gas
- IMA, SMA, SMV were patents
- The small bowel is not dilated
- No leakage of oral contrast was noticed
Coronal view of CT scan

Anterior
Urgent CT abdomen and with oral contrast

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Investigations

- Stool
  - Microscopy for microsporidium, cryptosporidium and isosporia were negative
  - Clostridium difficile cytotoxin was negative
  - RT-PCR for Norovirus POSITIVE
  - Stool culture for salmonella and other bacteria were negative
  - Rotavirus was negative
  - Occult blood was negative
Investigations

- Blood culture negative
- CRP < 3mg/L (< 5 mg/L)
- WCC 12.7 x 10⁹/L (PMN 10.6, Lym 1.6)
- Platelet 674 x 10⁹/L
- Hb 12.4 g/dL
- ESR 68 mm/hr
- Na/K/Ur/Cr = 143/4.9/0.7/18
- Serum bicarbonate 22 mmol/L
- C3 0.8 g/L, C4 0.19 g/L
- Ig A 0.81 (0.2-1.0 g/L)
- Ig G 0.8 (4.53-9.16 g/L)
- Ig M 1.54 (0.19-1.46 g/L)
- Serum CMV antibody positive
Treatment options in our patients

- Indication for Surgical intervention
  - Pneumoperitoneum
  - Steroid can mask the signs of peritonitis

- Argument for Conservative treatment
  - Rupture of intramural blebs caused the free gas in abdomen. There was no true transmural perforation (benign pneumoperitoneum).
  - No signs of peritonitis. Vital signs were stable.
- Oral contrast CT abdomen to determine any perforation of gut

- **Conservative treatment**
  - Bowel rest
  - Antibiotics especially metronidazole
  - Monitor gut perforation and features of bowel necrosis
Treatment

- Off cyclophosphamide and oral prednisolone
- Intravenous methylprednisolone at 25mg daily
- Started intravenous Ampicillin, Claforan and flagyl
Conservative Treatment with Pneumatosis Intestinalis

- Decrease in abdominal distension and pain
- Passing normal stool
- Serial AXR showed resolution of Pneumatosis
- Slow resolution of free gas in abdomen
- IVI antibiotics for 10 days
- NPO for 10 days
- Resumed oral Prednisolone and added on Cyclosporin A
Follow up Abdominal X-ray – the next day

Marked decrease in severity of pneumatosis, dramatic improvement with conservative treatment
Add on Cyclosporin A

Normal Ur Tp/Cr < 0.4 g/g cr; < 45 mg/mmol
Pneumatosis Intestinalis (PI) in Children
PI is a condition characterized by linear or cystic accumulation of gas within the gastrointestinal wall.

With the exception of Necrotizing Enterocolitis (NEC) in premature babies, PI is rare in paediatrics.
Staging of PI

- **Stage I**: pneumatosis was observed in 1 or 2 abdominal quadrants.

- **Stage II**: pneumatosis was observed in more than 2 quadrants of abdomen

- **Stage III**: free abdominal air was noted in the presence of either stage 1 or 2

- **Stage IV**: the presence of portal venous gas
Presentation of PI

- May be asymptomatic
- Constellation of symptoms
  - Diarrhoea
  - Bloody stools
  - Abdominal pain
  - Abdominal distension
  - Constipation
  - Weight loss
  - tenesmus
Sources of gas

- Intramural gas
  - Arises from bacterial fermentation of malabsorbed carbohydrates or by gas producing organisms which enters the mucosa through a breach in the mucosa
  - Gases may also penetrate through an intact mucosa as a result of high intraluminal pressure, as in case of intestinal obstruction or excessive distension
Color drawing showing pneumatosis in the submucosal and subserosal layers of the bowel
Hematoxylin-eosin stain of resected small bowel in patient with necrotizing enterocolitis shows ulcerated epithelium with exudate. Note the marked congestion of blood vessels throughout the wall with minimal inflammation. Air bubbles (arrow) in the submucosa represent pneumatosis intestinalis. The muscularis layer (arrowhead) is intact.
Pneumatosis intestinalis and diarrhea in a child following renal transplant.

G. Chelimsky et al. *Pediatric Transplantation* 2003 7: 236-239

- Reported a 4-year-old female with end stage renal disease secondary to congenital nephrotic syndrome, received a cadaveric renal transplant.

- Initial immunosuppressive medications included prednisone, cyclosporine, and mycophenolate mofetil.

- Two months post-transplant she developed intermittent emesis, bloody stool and weight loss.

- Abdominal x-ray demonstrated extensive pneumatosis in the colon.

- No positive stool culture. Symptoms and pneumatosis resolved with a 10-day course of metronidazole.
Pneumatosis In Rotavirus gastroenteritis

A six month old with rotavirus gastroenteritis, on supine film of the abdomen shows pneumatosis (arrows) in left mid abdomen.
A 7 month old male presented with vomiting, diarrhea, and bright red stool per rectum.

Abdominal films showed pneumatosis and no free air.

Stool cultures were positive for salmonella.

The patient was treated conservatively with IV fluids; no antibiotics were given as this may increase the incidence of carrier states.

Pneumatosis resolved by the third day.
Fulminant Pneumatosis Intestinalis in a Patient with Diabetes mellitus and Minimal Change Nephrotic Syndrome
Yoshitaka Maeda et al. Internal Medicine 2006;41-44

- A 72 years old female with diabetic and minimal change nephrotic syndrome, receiving immunosuppressive drugs (prednisolone 30mg/day & Mizoribine 300mg/day) x 3 years.

- Presented with right lower abdominal pain.

- Abdominal CT showed massive air in the intestinal wall, compatible with pneumatosis intestinalis.

- Her general condition rapidly deteriorated requiring hemodialysis and ventilator support. She finally recovered uneventfully.
A 64-year-old man with chronic lymphocytic leukemia, presented to the emergency room complaining of sudden onset of shortness of breath and chest pain. During the work-up, an abdominal CT was obtained showed PI. Patient died subsequently with blood culture grew staphylococcus aureus. Autopsy showed extensive pneumatosis intestinalis.
Causes of PI

<table>
<thead>
<tr>
<th>Traumatic and mechanic</th>
<th>Inflammatory and autoimmune</th>
<th>Infections</th>
<th>Pulmonary</th>
<th>Drug induced</th>
<th>others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt abdominal trauma</td>
<td>Ulcerative colitis</td>
<td>Clostridium difficile</td>
<td>Asthma</td>
<td>Steroid</td>
<td>NEC</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Crohn disease</td>
<td>HIV and AIDS</td>
<td>COPD</td>
<td>Cytotoxic drugs</td>
<td>Intestinal obstruction</td>
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<tr>
<td>Jejunoileal bypass</td>
<td>Appendicitis</td>
<td>Cryptosporidium</td>
<td>Cystic fibrosis</td>
<td>Immunosuppressive agents</td>
<td>Hirschsprung disease</td>
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<tr>
<td>Pyloric stenosis</td>
<td>Diverticular disease</td>
<td>CMV</td>
<td></td>
<td>lactulose</td>
<td>Graft-vs-Host disease</td>
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<tr>
<td>Duodenal stenosis</td>
<td>Cholelithiasis</td>
<td>Rotavirus</td>
<td></td>
<td>Steroid</td>
<td>idiopathic</td>
</tr>
<tr>
<td>Malrotation</td>
<td>Lupus enteritis</td>
<td>Adenovirus</td>
<td>COPD</td>
<td>Cytotoxic drugs</td>
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<tr>
<td>Volvulus</td>
<td>Celiac sprue</td>
<td>Varicella-zoster</td>
<td>Cystic fibrosis</td>
<td>Immunosuppressive agents</td>
<td></td>
</tr>
<tr>
<td>Intussusception</td>
<td>Polymyositis</td>
<td>Candida</td>
<td></td>
<td>lactulose</td>
<td></td>
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<tr>
<td>Carcinoma</td>
<td>Dermatomyositis</td>
<td>Mycobacterium tuberculosis</td>
<td>Steroid</td>
<td>Steroid</td>
<td></td>
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<tr>
<td>Barium enema</td>
<td>Polyarteritis nodosa</td>
<td>Whipple disease</td>
<td>Steroid</td>
<td>Steroid</td>
<td></td>
</tr>
<tr>
<td>Enteric tube placement</td>
<td>Mixed connective tissue disease</td>
<td>Samonella infection</td>
<td>Steroid</td>
<td>Steroid</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steroid</td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms

- Luminal Compartment
  - Increased Pressure
  - Gas
  - Altered Content
  - Bacteria
  - Infection

- Mucosa
  - Cytotoxic Therapy
  - Inflammation

- Barriers
  - Gas Transfer
  - Vascular Disease
  - Trauma
  - Corticosteroids
  - Hypoxia
  - Bacterial Gas Production

- Immune
  - Immunodeficiency
  - Immunosuppression

- Mural Compartment
  - Pneumatosis Intestinalis
  - Vascular Disease
  - Corticosteroids
  - Pulmonary?
Risk for PI

- Decrease gut defense mechanism
  - Decrease immune response
  - Bowel ischemia
  - Trauma to gut mucosa/mucosal damage

- Bacterial overgrowth
Steroid and immunosuppressive agents

- Shrink Peyer’s patches, resulting in loss of structural integrity in the mucosa, allowing gas to enter into the mucosa
Risk factors in our patient

- Use of steroid and cyclophosphamide
- Norovirus infection
- Severe gut edema
- Gut ischaemia
Would early use of intravenous steroid decrease the risk of pneumatosis intestinalis in our patient???

- In view of severe gut oedema
- In the presence of diarrhoea
- Poor oral absorption of steroid and cyclophosphamide was anticipated
Outcome and Prognosis

Pneumatosis Intestinalis in Non-neonatal Pediatric Patients


- A retrospective review of all children (exclude neonates with NEC) with PI in a tertiary care children’s hospital during an 8-year period.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Age Range (Months)</th>
</tr>
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<tbody>
<tr>
<td>Healthy child</td>
<td>7</td>
<td>1–172</td>
</tr>
<tr>
<td>Transplant*</td>
<td>7</td>
<td>12–205</td>
</tr>
<tr>
<td>Congenital heart disease†</td>
<td>4</td>
<td>2–11</td>
</tr>
<tr>
<td>Gastrointestinal dysmotility‡</td>
<td>4</td>
<td>33–240</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>3</td>
<td>2–94</td>
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<tr>
<td>Short bowel syndrome</td>
<td>2</td>
<td>17–148</td>
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<tr>
<td>Cystic fibrosis</td>
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<td>184</td>
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<tr>
<td>Apert syndrome</td>
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<td>60</td>
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<tr>
<td>Polycystic kidneys</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>7p-syndrome</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>1</td>
<td>36</td>
</tr>
</tbody>
</table>

* Patients included 5 with bone marrow transplant, 1 with renal transplant, and 1 with heart transplant.
† Patients included 3 with hypoplastic left heart syndrome and 1 with postoperative compromise of left ventricular function.
‡ Patients included 2 with intestinal pseudo-obstruction and 2 with constipation requiring daily medication or intestinal diversion.
- PI preceded by bowel ischemia or graft versus host disease colitis has the worst prognosis

- The presence of portal venous gas and metabolic acidosis correlated with poor outcome. (50% stage IV has poor outcome meaning requiring surgical intervention or died)

- Not all patients with pneumoperitoneum required surgical intervention. 78% resolved on conservative treatment.

- Overall, outcome of PI in non-neonatal patients was better than that reported in neonates with necrotizing enterocolitis.

- Mortality was 8% as compared with 16% in neonates with NEC
Conclusion

- Pneumatosis intestinalis is one of the rare complications seen in renal patients on immunosuppressive agents

- Prompt awareness is important.

- Most patients recovered with conservative treatment