CASE REPORT

Acute pneumatosis cystoides intestinalis with atrophic desmosis of the colon in a child

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SUMMARY

Acute pneumatosis cystoides intestinalis (PCI) has been described after bone marrow transplantation (BMT). Several case series have demonstrated successful conservative treatment of PCI in children. We present a child with Fanconi anaemia, who developed severe graft versus host disease of the gastrointestinal tract, skin and liver after BMT and an acute, severe form of PCI. Our case report illustrates the complexity of diagnostic and therapeutic procedures in PCI in immunocompromised children.

BACKGROUND

Pneumatosis cystoides intestinalis (PCI) has been associated with a wide variety of underlying conditions.^{3,4} Chemotherapy, underlying malignancy and graft versus host disease (GvHD) with subsequent long-term steroid treatment have been reported as being associated with PCI. Gastrointestinal GvHD, which occurs infrequently in patients suffering from chronic GvHD following successful bone marrow transplantation (BMT) or peripheral blood stem cell transplantation, may lead to substantial mucosal damage and increased apoptosis among mucosal cells and cells within the bowel wall. These alterations can result in diarrhoea, abdominal pain, malnutrition and pseudo-obstruction which may increase the intraintestinal pressure and result in PCI.⁴ The spectrum of treatment modalities ranges from conservative treatment, bowel rest, antibiotic therapy and enteral nutrition to emergency surgery, bowel resection and stoma formation.^{4,5}

This case report illustrates the complex nature of diagnostic and therapeutic procedures in a child suffering from PCI.

CASE PRESENTATION

We describe a 14-year-old male patient who was first diagnosed with Fanconi anaemia (FA) at the age of 4 years when he developed severe pancytopenia. He required repeated blood transfusions and underwent BMT at the age of 13.8 years. **Figure 1** shows the clinical course after BMT. Prophylaxis of GvHD consisted of antithymocyte globulin (day -3 to day -1), cyclosporine A (from day -7) and mycophenolate mofetil (MMF) (from day -7). Conditioning was achieved with fludarabine and cyclophosphamide. He received stem cells from an unrelated human leukocyte antigen (HLA)-identical donor with a 9/10 HLA match. He engrafted neutrophils at day +19, and full chimerism was achieved

at day +100 after transplantation. In the post-transplantation period, the boy developed several severe complications: mucositis grade 3, Broviac-catheter infection with *Staphylococcus epidermidis*, contamination of transplanted bone marrow with *Staphylococcus saccharolyticus*, pulmonary aspergillosis, and acute GvHD of the skin (IV), gastrointestinal tract (III-IV) and liver (IV) from day +13 on. In addition, he presented with HHV-6 reactivation on day +19, transplantation-associated microangiopathy, transient renal insufficiency, as well as reactivation of an Epstein-Barr virus infection on day +71 and an adenovirus infection on day +100.

Treatment of GvHD consisted of cyclosporine A (from day -7 to day +28), MMF (from day -7 to day +64) and high-dose steroids (from day +13 onwards). Because of steroid-refractory GvHD, we installed additional treatment with alemtuzumab (three doses). Due to side effects (paraesthesia), we changed from cyclosporine A to tacrolimus on day +28. Long-term immunosuppression was maintained with steroids, in addition to tacrolimus. The patient suffered from severe malnutrition after BMT (body weight of 26 kg at the age of 14 years, weight loss 24% since BMT; body weight and height <3 percentile for age).

On day +152 after BMT, he developed gastroenteritis caused by norovirus. On day +170, he was readmitted to hospital because of progressive weight loss and persistent nausea, vomiting and diarrhoea. We undertook gastroscopy and colonoscopy but the mucosal biopsies did not support the macroscopic suspicion of progressive chronic GvHD. Treatment was adapted with a higher dose of cortisone (methylprednisolone instead of prednisolone) and higher tacrolimus dose (target blood level 15–20 µg/L vs 10–15 µg/L). Because of progressive diarrhoea after escalation, human normal immunoglobulin (INN; Privigen) was added. We established total parenteral nutrition (TPE) to ensure sufficient nutrition.

On day +205, the boy presented again with bloody diarrhoea, colicky abdominal pain and anaemia. Haemoglobin had dropped repeatedly, and transfusions were necessary. We repeated the colonoscopy and took another set of mucosal biopsies. However, we were unable to identify the source of gastrointestinal bleeding. Again, the highly suspected diagnosis of GvHD of the gastrointestinal tract was not supported by the biopsy results.

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Figure 1 Timeline of the clinical course of the patient after BMT leading to pneumatosis intestinalis and surgery. BMT, bone marrow transplantation; EBV, Epstein-Barr virus; GvHD, graft versus host disease; HHV-6, human herpesvirus 6.

INVESTIGATIONS

CT of the abdomen showed abundant-free intraperitoneal gas reaching the retroperitoneum and basal mediastinum. The CT scan revealed severe PCI of the terminal ileum, colon ascendens, transversum, and descendens, as well as hepatomegaly. Perforation of the intestine at the left colonic flexure was suspected by paediatric radiologists (Figure 2-3). The source for the continuous melena could not be identified. The relevant laboratory values were: leucocytes $8.5 \times 10^9/L$, C-reactive protein 1.7 mg/L , thrombocytes $77 \times 10^9/L$ and haemoglobin 71 g/L .

DIFFERENTIAL DIAGNOSIS

Perforated gastric ulcer, perforated duodenal ulcer, clostridium difficile enterocolitis, ulcerative colitis, necrotising enterocolitis.

TREATMENT

Laparotomy revealed no obvious free gastrointestinal perforation but a severe form of PCI (figures 3 and 4), mainly of the right and transverse colon and attached mesentery, but also of the terminal ileum, left colon and proximal sigmoid colon. The remaining

small intestine and distal sigmoid colon and rectum were not affected. Conservative treatment options were discussed with our oncologists and gastrointestinal consultants. Both agreed that conservative treatment was already at its limits and immunosuppressive therapy could not be escalated. In this severe case of PCI with anal bleedings requiring transfusions without identified source of bleeding, severe recurrent colicky abdominal pain and persistent metabolic acidosis (base excess -9.6 , pH 7.34), we opted for subtotal colectomy and creation of an ileostomy. The postoperative course was uneventful, pancytopenia improved and the abdominal colicky pain subsided. Enteral nutrition was increased using a percutaneous gastrostomy for additional enteral nutritional support.

OUTCOME AND FOLLOW-UP

Establishment of enteral nutrition was very difficult. Four months after the initial operation, the bowel segments were

Figure 2 CT scan of the abdomen. Axial view demonstrating massive pneumatosis intestinalis and free intraperitoneal air.

Figure 3 Intraoperative image demonstrating massive pneumatosis intestinalis of the transverse colon and sigmoid colon.

Figure 4 Intraoperative image demonstrating massive pneumatosis intestinalis of the transverse colon and sigmoid colon.

anastomosed. One year after the initial operation, the patient still requires 1 L of fluid administered intravenously, but otherwise tolerates enteral nutrition.

Histopathological investigation of the resected bowel segment showed multiple small penetrating ulcers with bacterial inflammation of the adjacent bowel wall and a severe segmental disturbance of the architecture of the muscularis propria with segmental loss of connective tissue. Paediatric gastrointestinal pathologists diagnosed an incomplete atrophic desmosis of the colonic bowel wall. Confirmation of this finding was obtained by sinus-red staining.

DISCUSSION

Among the main entities known to lead to mucosal damage, apart from iatrogenic sources, are inflammatory bowel disease, radiation, chronic GvHD, mixed connective tissue disease, systemic chemotherapy and various immune deficiency states with concomitant infectious complications.^{3 4} PCI has been described as occurring 2–3 months after allogeneic stem cell transplantation in patients requiring chronic steroid treatment for GvHD.^{1 2} Passage of intraluminal gas into the submucosa requires a damaged muscularis mucosae, which may occur during the course of an inflammatory process or in conjunction with an anatomical defect such as alteration of lymphoid follicles by steroid-induced lymphocyte depletion.⁶ The right colon, which is known to be more susceptible to ischaemia than other segments of the colon, is more frequently affected in PCI in immunosuppressed patients.

Most case studies and case series report that conservative treatment with hyperbaric oxygen therapy and broad-spectrum antibiotics was successful in most PCI cases.^{7 8} Therefore, surgical exploration and colonic resection should be reserved for patients with clinical symptoms such as worsening signs of peritonitis, severe lactic acidosis, signs of intestinal obstruction or intractable rectal bleeding, irrespective of the radiological appearance of PCI. The indications for surgical exploration may be extended in high-risk categories of patients such as those receiving prolonged immunosuppressive therapy, where an undetected intestinal pathology may have deleterious effects.^{3 9}

Up to date, BMT is currently the only treatment of FA with a curative potential. However, it carries several risks, such as graft failure and recurrence of disease, acute and chronic GvHD, as well as complications related to the toxicity of the treatment. The overall day-100 probability to develop acute GvHD after BMT for FA is 29%.¹⁰ Acute and chronic GvHD are major causes of morbidity and mortality after BMT especially in patients with FA, who receive unrelated donor BMT.¹¹ Especially in patients with FA, who have a high risk to develop a malignant disease in their life, prolonged immunosuppressive therapy for GvHD is a problem. In addition, the nutritive state is often poor. GvHD

with manifestation in the gastrointestinal tract presenting with diarrhoea, sloughing of the mucosal membrane and intestinal inflammation leading to weight loss led to additional TPE. In our patient, we thoroughly considered the consequences of subtotal colectomy regarding quality of life, long-term immunosuppression and dependence on TPE before proceeding with the surgery.

In a juvenile patient, anaesthesia is no longer necessary for diagnostic imaging, in contrast to colonoscopy and surgery. In order to find the source of persistent bleeding, which made transfusions necessary, we weighted the risks of anaesthesia against the ones of an uncertain diagnosis. The risk of anaesthesia in children is not regarded higher than that in adults with the same underlying disease.

In the present case, a severe form of PCI developed months after onset of steroid treatment for a chronic GvHD of the skin, liver and gastrointestinal tract. Bloody diarrhoea with anaemia and abdominal tenderness developed and was treated without success for 3 weeks. As treatment of GvHD was already maximised without any clinical improvement, and intraoperatively there was an extended PCI affecting the ascending, transverse, descending and sigmoid colon, the unusual decision for surgical resection and ileostomy formation was taken in this patient. The risk of persistence of gastrointestinal bleeding and possible intestinal perforation while on high immunosuppressive therapy was deemed higher than that associated with subtotal colectomy.

Learning points

- ▶ Free intraperitoneal gas in the setting of pneumatosis cystoides intestinalis (PCI) must not be interpreted as a sign of acute bowel perforation.
- ▶ Most paediatric patients suffering from PCI can be managed without operation.
- ▶ Surgical management must be considered in patients with signs of peritonitis, lactic acidosis, continued gastrointestinal bleeding or clinical deterioration.

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Reminder of important clinical lesson

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