Prediction and prevention of infectious complications in children with cancer
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Pseudomembranous and neutropenic enterocolitis in pediatric oncology patients

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Abstract:
Neutropenic enterocolitis in oncological patients represents a wide spectrum of clinicopathological pictures each with its own entity. Early diagnosis of enterocolitis can lead to improved supportive care and therefore better outcome. We present 2 cases, case A - a child with pseudomembranous colitis caused by Clostridium Difficile and case B - a child with neutropenic enterocolitis, where no organism was found. By gaining insight in the pathology, immunology and culture results we demonstrate that early diagnosis leads to an improved management and therefore improved outcome.
Introduction

The nomenclature of enterocolitis in oncology patients remains difficult and encompasses the pseudomembranous colitis most often caused by *Clostridium difficile* infection and the neutropenic enterocolitis (also called ileo-cecal syndrome, agranulocytic colitis or typhilitis) most often caused by other causes. Clinical signs and symptoms vary widely from mild infection to severe transmural colitis with a high mortality-rate [12].

We report 2 cases demonstrating neutropenic enterocolitis in the pediatric oncology patient. Understanding of these enterocolitis entities in an earlier stage of the disease, concerning the pathological, inflammatory and culture results will enable us to support these patients more adequately and therefore decrease the morbidity and mortality due to this complication.

Case A

A 17 year old boy presented with an Ewing sarcoma of the 7th left rib. Treatment was started on the high-risk Ewing protocol (EICES S 92 –European Intergroup Cooperative Ewing's Sarcoma Study). Chemotherapy was given consisting of etoposide, vincristin, adriamycin, and ifosfamide. After the first course of chemotherapy, he became neutropenic with a WBC of 0.2 x 10^9/L. He developed fever (>39 °C) and was admitted. Treatment with i.v. vancomycin and gentamycin was started. Twenty-four hours after starting these antibiotics, he developed profuse diarrhea and complained of severe abdominal pain with cramps.

A rectoscopy was performed which showed mucosa covered with membranes, (see Figure 1). Microscopically the histopathological changes fitted the diagnosis of pseudomembranous colitis. Stool cultures were positive for *C. difficile* and *C. difficile* toxin (B). No viruses, parasites or other bacteria were isolated. His blood-cultures were negative. Serum parameters for inflammation were determined. On the first day, low values of elastase (47 ng/L), IL-6 (85 ng/L), and IL-8 (194 ng/L) were found.

He was started on oral metronidazol 3 times daily, and adequate supportive care was given. On the third day a second rectal biopsy was performed which still showed pseudomembranes. Clinically he improved. The abdominal pain was less, his diarrhea less profuse, and his WBC started to recover. After a total period of 8 days his intravenous antibiotics were stopped, the metronidazol was continued for 14 days.

On stopping the metronidazol a third rectal biopsy was performed and showed a complete recovery of the mucosa. The patient is now in complete remission and doing well, he does not have any abdominal complaints.
Case B

A 6 year old boy presented with an abdominal Burkitt lymphoma. He was started on the LMB 96 protocol (Lymphoma protocol) consisting of cyclofosfamide, vincristin, prednisolon, doxorubicin and methotrexate. Two weeks after the first course of chemotherapy he became severely neutropenic with a WBC of $0.1 \times 10^9/L$ and no neutrophils. The Hb was 9.5 gr/dl, and the platelet count was $36 \times 10^9/L$. He developed fever and severe abdominal pain with a distended abdomen. He had bloody diarrhea and showed signs of sepsis with a low blood-pressure. Intravenous antibiotic therapy consisting of vancomycin and gentamycin was started. He was transferred to the intensive care unit for inotropic support. A rectal biopsy was performed. Macroscopically this showed severe mucosal lesions, and microscopically ulcerative changes with fibrinous exudate was shown with only a slight inflammatory reaction, representing a neutropenic enterocolitis (see Figure 2). Stool cultures were negative for bacteria, parasites and viruses. *C. difficile* toxin tests were negative, blood cultures were also negative. On the day of the biopsy, the CRP was elevated to 280 mg/L, other markers for inflammation showed a low elastase (62 ng/L), a moderately raised IL-6 (139 ng/L), and a high IL-8 (2391 ng/L). He continued with intravenous antibiotics and metronidazol was added orally even though no clostridium species were cultured. His oral feeds were stopped and he was started on parenteral nutrition. On day 5 a second rectal biopsy was performed and still showed mucosa covered with exudate, confirmed on histopathology. On day 5 the markers of inflammation showed a rise in elastase to 316 ng/l and a decrease in IL-6 (15 ng/L) and IL-8 (21 ng/L). The neutrophil count improved and he improved clinically, without surgical intervention. He completed his chemotherapy courses without subsequent episodes of enterocolitis. He is in complete remission and doing well.

**Figure 1:** Macroscopic aspect of rectum of patient A demonstrating the pseudomembranes caused by *Clostridium difficile*.
Pseudomembranous enterocolitis in pediatric oncology patients

**Figure 2:** Large bowel biopsy with ulcerative changes and fibrin exudate on the surface and only slight inflammatory reaction. Overview low powered HE staining with a detail of the fibrin exudate on high powered HE staining.

**Pseudomembranous colitis**

**Epidemiology**

*C. difficile* has become one of the most important hospital pathogens of the 90's. Anand and Glatt [1] reviewed that antibiotics are not the only agents capable of inducing *C. difficile* associated diarrhea. They reported on 23 oncology cases. A variety of anti-neoplastic agents were involved, most commonly methotrexate. Chemo-therapeutic agents alter the gut flora and this is most likely the predisposing factor. Any compound that affects the gastro-intestinal flora, either qualitatively or quantitatively, may reduce the colonization resistance and therefore predispose the individuals to infection with *C. difficile*.

The normal carriage rate in adults is 0-3%. In oncology units the carriage rate increases to 13-28% in hospitalized patients. Schuller et al [11] looked at prevalence of *C. difficile* infection on a pediatric oncology unit over a period of one year. The carriage rate was 13% as was found in the literature. Of these children 68% had signs and symptoms attributable to *C. difficile* infection. The authors conclude that the organism is probably endogenous and is provided with a favorable environment by the combination of cancer chemotherapy and broad spectrum antibiotics [10].

**Clinical findings**

Clinical findings in *C. difficile* enterocolitis can range from absolutely asymptomatic to severe colitis. In view of the discussion we will restrict us to the severe colitis syndromes. Symptoms are profuse debilitating diarrhea, abdominal pain and distension. Common systemic manifestations include fever, nausea, anorexia, malaise and dehydration. In the most severe situation this form of colitis can present as an acute abdomen. The patients are extremely ill with lethargy, fever, tachycardia and abdominal pain. The colonic muscular tone may be lost resulting in toxic dilatation or megacolon, eventually leading to colonic perforation and peritonitis [8].
Pathology
A grading system for pseudomembranous colitis was proposed by Price and Davies [9]:
- The Type-I lesion consists of focal necrosis of interglandular superficial intestinal epithelium with overlying neutrophilic exudates.
- The Type-II lesion results from fusion of this neutrophilic exudate over the necrotic upper parts of the neighboring glands and in the late part of this phase neutrophilic exudates are nearly confluent over mucosa, (pseudomembranes).
- The Type-III lesion shows complete coagulative necrosis of the intestinal mucosa.
When the C. difficile infection resolves the mucosa returns to normal.

Pathogenesis
The underlying pathogenesis involves a disruption of the normal bacterial flora of the colon, followed by colonization with C. difficile and the release of toxins causing mucosal damage and inflammation [4, 8].

Laboratory diagnosis
The golden standard at presentation is the stool cytotoxin test. It is a tissue culture assay based on the induction of cell rounding by C. difficile-toxin B in stool infiltrate. This assay has a high sensitivity (94-100%) and high specificity (99%) [4]. A stool culture for C. difficile is less efficient as many strains are non-toxicogenic. Rapid enzyme immunoassay’s have been developed detecting both toxin A and B (sensitivity 69-87% and specificity 99-100%) [4].

Therapy
Specific treatment aimed at eradicating C. difficile is used if symptoms are severe or persistent. Oral metronidazole and oral vancomycin are used as the drugs of choice. Both are equally effective. There is no difference in the rates of response, relapse or failure between these agents. Patients who cannot take oral medication can be treated with intravenous metronidazol. Excretion of the drug in the bile and exudation from the inflamed colon result in bactericidal levels in the faeces. Intravenous vancomycin is not indicated [4].

Neutropenic enterocolitis (Typhlitis)
Epidemiology
Typhlitis involves chemotherapy induced damage to the intestinal mucosa, primarily in the terminal ileum, ascending colon and cecum, and occurs when these patients are neutropenic [12]. In 1933 this entity was first described by Cooke when she described submucosal hemorrhage and appendiceal perforation in children with leukemia. Then from the 1960’s onwards autopsy studies reported an incidence of 12% to 46 % in leukemic children.
Clinical findings
Most patients are neutropenic more than one week before the onset of abdominal pain. Abdominal pain is diffuse in most cases and in a few cases localized to the right lower quadrant. The classical triad of symptoms is high fever, abdominal pain and diarrhea [13].

Organisms
The organisms involved are mainly Gram-negative organisms, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *enterobacter spp*, *enterococci*, and Gram-positive organisms like the *C. difficile* and the *C. septicum*. Fungal organisms can also be cause of severe neutropenic enterocolitis. In many cases no organism can be isolated [6].

Pathophysiology
This remains largely unknown but is believed to be multi-factorial:
- Destruction of the normal mucosal architecture due to chemotherapy and/or radiotherapy with possible coexistent leukemic or lymphomatous infiltrates.
- Intramural hemorrhage due to severe thrombocytopenia.
- A shift in the normal gastrointestinal microbial flora due to antibiotics, antifungals and nosocomial colonization by hospital flora [6].

Pathology
The bowel appears thickened and edematous, with scattered ecchymoses on the serosal surface and ulceration on the mucosal surface. Microscopically there is hemorrhage necrosis involving the mucosa and submucosa with striking scarcity of acute inflammatory reaction, few or no granulocytes. There may be an infiltration of bacteria or fungi. Sometimes an exudate resembling pseudo-membranes consisting of fibrin and cell debris may be found overlying the most severely ulcerated mucosal surfaces.
In later stages, the process may progress to involve the full thickness of the bowel wall and sometimes lead to perforation [14].

Laboratory findings
Routine laboratory tests are of little value in diagnosing typhlitis. Blood and stool cultures are important to identify the organisms involved in the process of enterocolitis

Therapy
The main mode of therapy is supportive care. Nasogastric suctioning, broad-spectrum antibiotics, administration of appropriate blood products and adequate fluid replacement.
4 criteria have been used for surgical intervention:
Persistent gastrointestinal bleeding and thrombocytopenia and clotting abnormalities.

Evidence of free intraperitoneal perforation.

Clinical deterioration requiring support with vasopressors or large volumes of fluid suggesting uncontrolled sepsis.

Development of symptoms of an intra-abdominal process in the absence of neutropenia which would normally require surgery.

The presence of localized peritoneal signs is not an adequate indication for exploration. With these criteria in mind most patients can be treated without surgery. The most important in these patients is the requirement of neutrophils. Growth factors are often indicated [12].

Differences between pseudomembranous colitis and typhlitis are summarized in Table I.

<table>
<thead>
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<td>Abdominal pain, diarrhea</td>
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**Discussion**

With the increasing intensification of chemotherapy, toxicity during neutropenic episodes can be expected. Therefore familiarity with the spectrum of diseases encompassing neutropenic enterocolitis is needed to recognize the disease entities. Recognizing clinical signs, pathological changes and inflammatory changes might facilitate early detection, improve the supportive care around this spectrum of diseases and ultimately decrease the morbidity and mortality.

The 2 cases discussed both illustrated damage to the intestinal mucosa. In both cases rectoscopy was done as part of a prospective study gaining insight in the pathological, infectious and immunological causes of this complication. It was performed by the pediatric gastroenterologist with a flexible pediatric scope. Platelets were kept >50 x 10⁹/L and no complications were seen. Both cases were children with solid tumors. Neutropenic enterocolitis used to be an infrequent finding in patients with solid tumors [6].

Now with the intensification of chemotherapy this is no longer the case. It has been proposed that some chemotherapeutic agents cause direct epithelial necrosis in the gastrointestinal tract [5]. Following the damage to the mucosa secondary infections can occur due to enteric or opportunistic organisms like *pseudomonas* or fungal species [3]. The first patient described
developed a \textit{C. difficile} colitis, possibly due to a shift in the normal gastrointestinal microbial flora due to antibiotics, antifungals and nosocomial colonization with hospital flora. [6]. The toxins of \textit{C. difficile} cause direct toxic damage of the actinoskeleton leading to cell rounding, and eventually cell death [8]. The second patient described had ulcerative changes on rectal biopsy with a fibrinous exudate representing neutropenic enterocolitis. No organism was cultured. Both cases were managed conservatively and it was clearly shown that when neutrophils appeared in the blood the clinical picture improved [6].

Neutropenic enterocolitis should be suspected in a neutropenic patient with abdominal pain, fever and diarrhea. To define a definite enterocolitis rectoscopy was helpful in the 2 patients described. However mostly the typhlitis occurs in the cecum or sigmoid area which will not be adequately detected by rectoscopy. In this case the inflammatory parameters might be of use. Interleukin-8 was extremely high in the second patient illustrating the severity of the clinical condition. Interleukin-8 is an inflammatory chemokine which mainly functions as a neutrophil chemoattractant and activating factor [2] IL-6 and IL-8 have been used in neutropenic patients as a predictor of bacteremia in patients with fever during their neutropenic episode [2]. In patients with severe neutropenic enterocolitis, IL-8 release depends on toxic or ischemic bowel injury. The source therefore of IL-8 lies in the endothelial cells and fibroblasts, and not in the myeloid cells [7]. The high level of IL-8 together with the severe ulcerative changes on rectal biopsy in patient B acted as predictor of severity of the enterocolitis. Human neutrophil elastase is low when no neutrophils are present in the peripheral blood. A rise was observed on day 5 of the enterocolitis, soon after neutrophils were detected in the peripheral blood and the clinical picture of the patient improved. It was shown that neutrophil elastase increased just before the neutrophils recovered. Therefore elastase could act as predictor of clinical improvement (manuscript in preparation).

The clinical picture combined with the rectoscopy and the inflammatory parameters improves our understanding of this severe condition and enables us to support the patient in a more appropriate way, at an earlier stage of the disease.

\textbf{Acknowledgements}

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References

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