Typhlitis

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Objective: To provide an overview of the pathophysiological features and management of the clinical entity typhlitis.

Data sources and study selection: The data presented are derived from a review of the English-language literature on typhlitis. The majority of papers analysed were small clinical series.

Data extraction and synthesis: Data derived from the literature review were collated. The major finding was that typhlitis comprises a number of different diseases characterized by the presence of right lower quadrant pain, an immunocompromised host and altered function of the mucosal barrier of the right colon.

Conclusions: Typhlitis should be suspected in any immunocompromised patient presenting with right lower quadrant pain with compatible radiographic findings. Most patients can be treated conservatively with intravenously administered fluids and antibiotics, although surgery may be necessary if complications arise.

Objectif : Présenter un aperçu des caractéristiques pathophysiologiques et de la prise en charge de l'entité clinique typhlite.

Sources de données et sélection d'études : Les données présentées proviennent d'une recension des écrits en anglais sur la typhlite. La majorité des documents analysés étaient de petites séries d'études cliniques.

Extraction et synthèse des données : On a colligé les données tirées de la recension des écrits. On a constaté principalement que la typhlite comporte un certain nombre de maladies différentes caractérisées par la présence d'une douleur au quadrant inférieur droit, un patient dont le système immunitaire est compromis et une altération du fonctionnement de la barrière muqueuse du côlon droit.

Conclusions : Il faudrait soupçonner une typhlite chez tout patient dont le système immunitaire est compromis, qui se plaint de douleurs au quadrant inférieur droit et qui présente des résultats radiographiques compatibles. Il est possible de traiter la plupart des patients de façon conservatrice au moyen de liquides et d'antibiotiques administrés par voie intraveineuse, même si l'intervention chirurgicale peut s'imposer en cas de complications.

Typhlitis, a syndrome of enterocolitis occurring in immunosuppressed patients, has been reported increasingly over the last 3 decades. The initial descriptions of this syndrome, which has also been termed "necrotizing enteropathy,"[1] "neutropenic enterocolitis"[2] and "ileocecal syndrome,"[3] were reported in children who underwent induction chemotherapy for acute leukemia.[4] Subsequently, typhlitis has been observed in adults,[5] associated with such conditions as myelodysplastic syndromes,[6] multiple myeloma,[7] aplastic anemia,[8] solid malignant tumours,[9] cyclic neutropenia,[10] sulfasalazine therapy for rheumatoid arthritis,[11] the acquired immunodeficiency syndrome,[12] and after solid organ[13] and bone marrow[14] transplantation.

Epidemiology and pathogenesis

It is difficult to determine accurate prevalence rates for typhlitis. The nonspecific features of this illness and similarities to other acute abdominal syndromes in immunosuppressed patients limit the accuracy of clinical series that lack pathological confirmation of the diagnosis. An autopsy study in children

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with acute leukemia reported evidence of typhlitis in 24%.[15] A frequency of 33% was reported in a cohort of children treated for acute myelogenous leukemia.[4]

The pathogenesis of typhlitis was originally believed to be a combination of shock, treatment-induced necrosis of intestinal leukemic infiltrates, hemorrhage with subsequent mucosal necrosis and traumatic mucosal erosions.[1] A more current perspective is that typhlitis is a syndrome associated with a number of clinical scenarios rather than a specific disease and that it results from a combination of mucosal injury and impaired host defences to intestinal organisms.[16]

Pathological characteristics

Neutropenic enterocolitis typically involves the terminal ileum and right colon.[2–5] Many gross and microscopic alterations have been described, including edema of the mucosa or entire intestinal wall, mucosal ulceration, focal hemorrhage and mucosal or transmural necrosis.[1,4,7,15,17] Only rarely are leukemic or acute inflammatory infiltrates identified.[17] These changes may be induced by several means. Various chemotherapeutic agents are directly toxic to intestinal mucosa.[7] Cytosine arabinoside, a common antileukemic drug, has been shown to denude colonic mucosa through a variety of mechanisms.[18] In addition, the disappearance of leukemic infiltrates after therapy may disrupt the architecture and blood supply of the intestinal wall.[19] There is evidence that neutropenia itself causes mucosal ulceration.[16]

The lack of a normal granulocytic reaction to infection[7] and reduced blood supply to the distended cecum[5] impair the local immune response, which may promote the persistence of microorganisms in the bowel wall. Electron microscopy has demonstrated submucosal macrophages laden with gram-negative organisms.[17]

Microbiologic features

Various organisms, alone or in combination, have been identified in surgical specimens and peritoneal fluid, including gram-negative rods, gram-positive cocci, enterococci, *Clostridium septicum*, *Candida* and cytomegalovirus.[4,13,15,16] *Clostridium difficile* toxin is occasionally detected in the stools.[13] Bacteremia, often recurrent, is frequently reported.[20]

Clinical presentation

The typical presentation mimics acute appendicitis and is characterized by fever, nausea, vomiting, diarrhea, abdominal distension and diffuse pain or right lower quadrant abdominal pain and tenderness.[13] Occasionally, the boggy cecum is palpable on examination of the abdomen.[5] Symptoms often occur 10 to 14 days after initiation of cytotoxic chemotherapy.[2,4,17] Neutropenia (polymorphonuclear cells less than 1.0×10^9/L) is usually observed but is not an invariable finding.[21]

Radiologic findings

Routine radiologic investigation rarely aids in the diagnosis.[13] Abnormalities are nonspecific and may include an ileus or small-bowel obstruction, paucity of gas in the right lower quadrant or a dilated fluid-filled cecum.[15,22] Pneumatosis intestinalis in the area of the cecum has been observed.[4] Barium enema is contraindicated if intestinal perforation is suspected, but water-soluble contrast enema may demonstrate thickening and rigidity of the cecal wall.[16] Other imaging modalities are more helpful. Abdominal ultrasonography may show an enlarged cecum with characteristic echogenic thickening of the mucosa,[23] with or without fluid collections. Computed tomography reveals thickened bowel and abnormally thickened fascial planes.[22]

Treatment

There have been no randomized trials on the treatment of typhlitis, and there are advocates for both medical[24] and surgical[25] intervention. In a collective review of 178 reported cases of selected patients, 97 were treated medically, with a 48% death rate, and 81 were treated surgically, with a 21% death rate.[16] Many reports have suggested a poor prognosis for typhlitis.[13,19] In general, the outcomes tend to reflect the course of the underlying disease.[13] Conservative management consists of bowel rest, intravenously administered fluids and broad-spectrum antibiotic therapy.[24] Cytopenias and coagulopathy should be corrected. Recombinant granulocyte colony-stimulating factor (G-CSF) has been used to hasten recovery.[26] Sloas and colleagues[13] treated 21 of 24 children without operation, with an 8.3% death rate.

Shamberger and colleagues[4] proposed 4 indications for surgery in typhlitis: gastrointestinal bleeding that persists after improvement of neutropenia, thrombocytopenia and coagulopathy; free intra-abdominal perforation; clinical deterioration during medical therapy; and differentiation from other acute abdominal diseases for which surgery is indicated. The standard resectional therapy is right hemicolectomy, with or without primary anastomosis, depending on the condition of the patient.[2] Defunctioning the colon with a loop ileostomy has been suggested as an alternative.[27] If laparotomy reveals only edematous bowel without severe inflammation or gangrene, a surgeon may opt for nonextirpative treatment, with the caveat that diffuse mucosal necrosis may lurk beneath otherwise unimpressive serosal inflammation.[16]

An algorithm for managing a patient with suspected typhlitis is presented in Fig. 1.

Directions for further investigation

There are recent developments in the management of gastrointestinal diseases that may have an impact on the diagnosis and treatment of typhlitis. Although many of these modalities have not been evaluated specifically in the setting of neutropenic enterocolitis, they represent evolving areas of clinical research. The effectiveness and limitations of novel strategies in the management of typhlitis can only be established by conducting further clinical trials. We propose the following areas in which further investigation is warranted.

Diagnostic laparoscopy

The ultrasonographic and CT features of typhlitis are nonspecific,[22,23] and a clinician may not be able to rule out other surgical diseases solely on the basis of imaging tests. In such cases, diagnostic laparoscopy may be helpful.[28] Several studies have reported the utility of diagnostic laparoscopy for the investigation of the acute abdomen.[29,30] Laparoscopy is particularly useful in confirming the presence of appendicitis and is able to rule out this diagnosis in 20% to 40% of patients with atypical presentations.[29,30]

Although its safety in immunosuppressed or neutropenic patients has not been specifically studied, laparoscopy is a well-tolerated procedure in many other settings.[28] This technique should be reserved for patients with an acute abdomen and suspected typhlitis when the diagnosis is in doubt despite appropriate cross-sectional imaging and when an alternative surgical process such as appendicitis cannot be ruled out.

Selective decontamination of the digestive tract

Colonization of the gastrointestinal tract with pathologic bacteria is associated with the development of nosocomial infections and multiple organ failure in critically ill surgical patients.[31] The role of the gut as a potential microbial reservoir has prompted investigation into strategies to prevent pathologic colonization. The technique of selective decontamination of the digestive tract (SDD) involves the

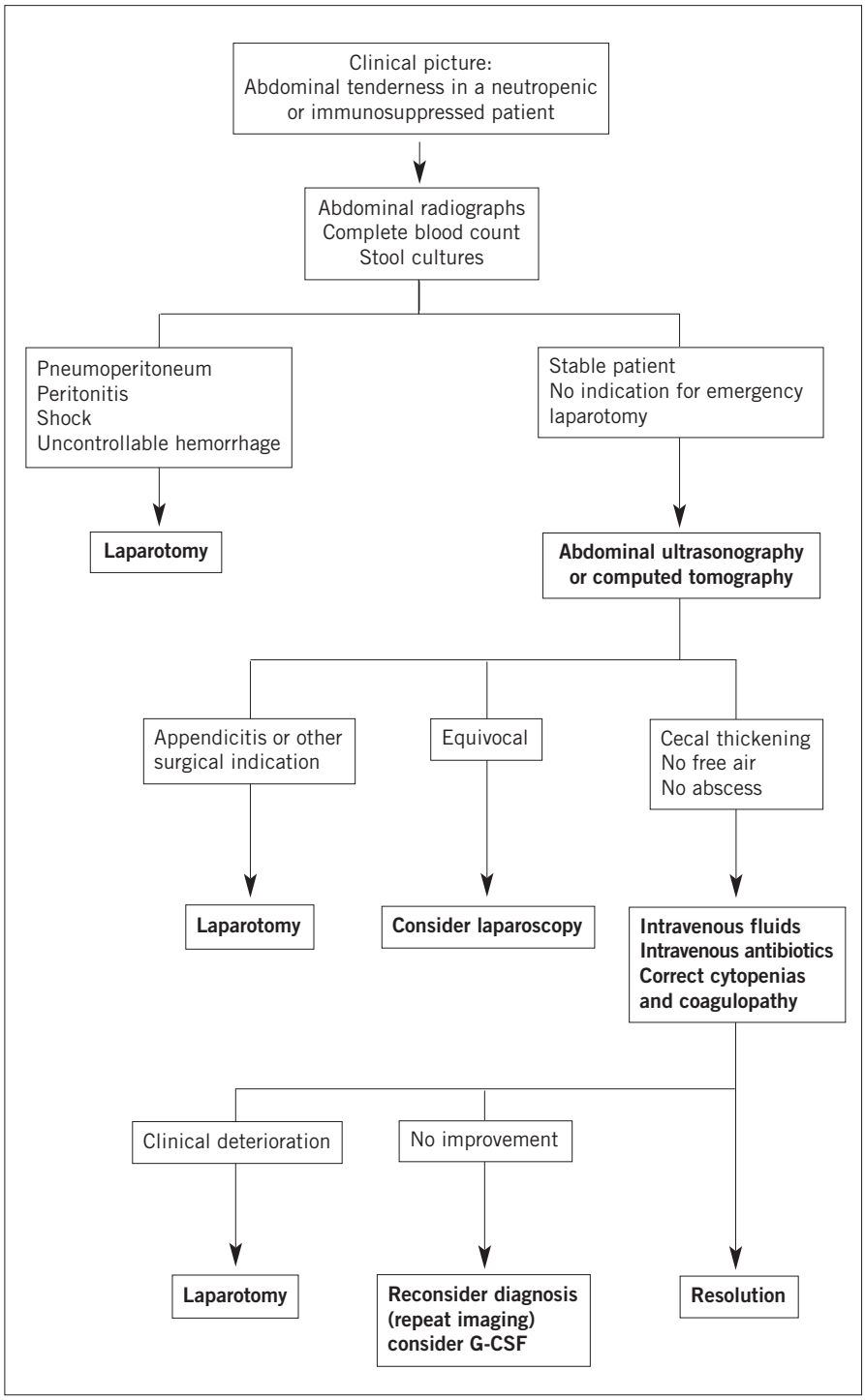

FIG. 1. Recommended approach to the patient with suspected typhlitis. G-CSF = granulocyte colony-stimulating factor.

administration of oral nonabsorbed antibiotics that preferentially eliminate aerobic gram-negative bacteria and fungi while sparing the gram-positive and anaerobic flora.[32] A meta-analysis of 36 trials of SDD demonstrated a significant benefit in reducing the rate of pneumonia but only a marginal improvement in survival when both enteral and parenteral antibiotics were administered.[33]

A role for SDD has already been proposed for infection prophylaxis in leukemic patients during episodes of neutropenia.[34,35] However, it remains speculative whether SDD is effective in reducing the incidence of typhlitis in this population. Further studies evaluating SDD in the setting of leukemia should include typhlitis as an outcome to be considered.

Enteral nutrition

The lack of enteral feeding has been associated with bowel mucosal atrophy and the loss of structural and functional integrity of the gut.[36] As well, nutrient intake via the enteral route is beneficial in maintaining systemic immunocompetence.[37]

Although elimination of oral intake has traditionally been prescribed for patients with typhlitis, a strategy of early enteral nutrition should be explored in those patients who can tolerate it. Many of the pathophysiologic abnormalities observed in typhlitis, such as bowel mucosal injury and persistent infection within the intestinal wall, might be prevented by promoting the continued use of the gastrointestinal tract.

Glutamine

Glutamine, a conditionally essential amino acid, has become the subject of intense interest for its effects on the immune system and gastrointestinal tract.[38] Glutamine therapy has beneficial effects on both systemic immunity[39] and local mucosal immune function of the intestine.[40] Infusions of glutamine can decrease the amount of small-bowel atrophy caused by parenteral nutrition.[41] In addition, animal studies have demonstrated that pathologic increases in intestinal permeability can be prevented by the topical or parenteral administration of glutamine.[42,43]

The ability of glutamine to maintain gut integrity and promote local and systemic immune function strongly suggests that it should be considered for the treatment of typhlitis.

Colony-stimulating factors

CSFs are molecules that can promote hemopoiesis.[44] Two recombinant forms of these molecules are available for clinical use, G-CSF and granulocyte-macrophage CSF. In addition to speeding recovery from episodes of neutropenia occurring during chemotherapy treatment,[45] treatment with G-CSF also decreases the incidence of complications such as mucositis.[46] The ability to improve the neutropenia and intestinal cytotoxic effects of chemotherapy should improve the course of typhlitis. Treatment of typhlitis with G-CSF has already been reported,[26] and formal clinical trials are warranted.

Conclusions

The general surgeon occasionally encounters typhlitis in the assessment of patients with an acute abdomen. The diagnosis is usually suggested by the clinical picture of right lower quadrant pain in a patient with neutropenia and is confirmed by abdominal ultrasonography or CT. Although most patients can be successfully managed with intravenous fluids and antibiotics, those with severe cases of typhlitis may require surgical therapy, especially if complications develop. Newer strategies for the diagnosis and treatment of typhlitis are evolving and will add to the armamentarium of clinicians treating this disease.

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