Management of Neutropenic Colitis

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Abstract

Neutropenic colitis is a potentially life-threatening condition with an incidence of approximately 6% and a prevalence of 1-15%. The precipitating event is likely mucosal injury secondary to factors such as chemotherapeutic agents, antibacterial therapy or steroids. The differential diagnosis is wide and early identification relies on a high index of suspicion.
This review outlines the pathophysiology, clinical signs, diagnostic modalities, histological findings, differential diagnosis and suggested management of neutropenic colitis, and underlines the fact that neutropenic colitis remains a major challenge to both medical and surgical teams.

INTRODUCTION

Neutropenic colitis, also termed typhlitis (Greek typhoon = caecum) or agranulocytic lesion ([1]) is a potentially life-threatening infection that occurs in association with profound neutropenia This complication is also termed the ileocaecal syndrome in patients receiving aggressive chemotherapy for haematological malignancies, leukaemias, anaplastic anaemia and cyclic neutropenia ([2]). Since Cooke described the presence of submucosal haemorrhage and appendiceal perforation in children with leukaemia in 1933 ([3]), the association of this necrotising lesion in immunosupressed patients has become more commonly recognised ([4,5]).

The exact incidence and prevalence rates are unknown because survivors are rarely diagnosed, and patients who die of the condition are diagnosed on a post-mortem examination. A study from India ([6]) has reported an incidence of 6.1% in 180 children undergoing chemotherapy for acute lymphocytic leukaemia. A retrospective study from Turkey ([7]) reported an incidence rate of 6.5% in child acute myeloid leukaemia and 4.6% in adult acute lymphoblastic leukaemia. More recent advanced and detailed studies requiring computered tomography (CT) or ultrasound (US) evidence of bowel thickening to confirm the diagnosis of neutropenic colitis have found a prevalence rate between 1% and 15% ([8,9,10,11]). A prospective study of 36 leukaemic patients who experienced 62 neutropenic episodes found the incidence of this condition to be 6.5% per each neutropenic episode ([8]).

Patients who are immunosupressed for haematological stem cell transplantation and those with cyclic neutropenia are also at risk ([2]). Although neutropenic colitis was initially described in children; it is increasingly reported in adults. No predilection for race or sex is reported in the literature.

PATHOPHYSIOLOGY

Although the exact aetiology and progression are clearly unknown, profound neutropenia appears to be the common dominator. Granulocytopenia resulting from marrow infiltration, aplasia or myelosupression causes a major deficit in the key internal host defence mechanism against intestinal mucosal injury and bacterial invasion. The pathological process appears to have a predisposition for the terminal ileum, appendix and caecum, hence its alternative nomenclature ([12]).

Many factors have been described that may potentially play a role in the development of this condition and include the following:

Mucosal injury caused by chemo-therapeutic agents, which can alter the normal mucosa leading to local ulceration and ischaemia ([1]). Caecal distension, whether primary or secondary to cytotoxic drug therapy, may further compromise the blood supply and lead to local ulceration and ischaemia.

The use of antibiotics and steroids may also contribute to an altered enteric bacterial flora and fungal overgrowth.

Bacterial invasion of the damaged bowel wall may result in

transmural inflammation leading to perforation and generalised peritonitis. Bacteraemia which is often recurrent is a frequent complication.

Ileocaecal mucosal damage is probably the initiation step. The onset of clinical signs immediately following the administration of cytotoxic therapy supports the contention that drug-induced neutropenia leading to mucosal injury plays a significant role in the pathological process ([12]). Among the many cytotoxic agents thought to promote mucosal damage, Cytosine and Arabinoside which are used in combination therapy in the treatment of haematological malignancies appear to be the most potent and toxic combination in causing the spectrum of damage which can range from cellular atypia to frank ulceration ([13]).

There is also evidence to suggest that neutropenic colitis is a toxin-mediated disease and prior use of cytotoxic agents is unnecessary for its pathogenesis ([2]). Clostridia is an element of the normal gut flora, it secretes many toxins and haemolysins, some of which may limit the overgrowth of pathogenic bacteria ([14]). Autopsy study has identified Clostridia septicum, tertium and welchi in the necrotic bowel wall of patients with neutropenic colitis ([5,15,16]). A wide spectrum of bacteria and fungi have been isolated from peripheral blood cultures in patients with neutropenic colitis including E. coli, Klesiella, Pseudomonas, Enterococcus and Candida species ([17,18]). Chemotherapy is hence not the only requirement for the development of neutropenic colitis, partly because of its occurrence in cyclic neutropenia, and as presenting symptom of acute leukaemia ([2]).

SYMPTOMS AND SIGNS

The sudden onset of abdominal pain (often right lower quadrant), fever (temperature >38ºC) and diarrhoea are often the hallmarks of presentation of a patient with neutropenic colitis ([17]) usually 7-10 days after commencing myelosuppressive chemotherapy. If the initial symptoms are followed by peritonitis, haemodynamic instability and septic shock, the prognosis is poor ([2]).

There may be a mass palpable in the right iliac fossa or the lower abdomen; this usually reflects a thickened, dilated, fluid-filled caecum ([12]). It should be noted that in the presence of severe sepsis, physical signs may be minimal. Rapid progression to fulminant septicaemia may precede the development of any abdominal signs. The diagnosis is difficult and a significant number of patients are only diagnosed at post mortem ([19]). A high index of suspicion of the possibility of neutropenic colitis in immunosupressed patients is most important in timely diagnosis ([1]).

DIAGNOSTIC TESTS

LAB STUDIES

Complete blood count is used to confirm the neutropenia. Blood cultures are obtained for aerobic/anaerobic bacteria and fungus to rule out a masking bacterial or fungal sepsis. Stool cultures are obtained to rule out colitis due to Clostridium difficile or other organisms.

IMAGING

A plain abdominal radiograph may show caecal distension, distal small bowel obstruction, thickening of the bowel wall, a right sided soft tissue mass or a gasless abdomen ([20,21]). Ultrasound scans may be still the primary imaging modality at some centres ([22]). It identifies echogenic bowel wall thickening that produces a target or halo sign in patients with neutropenic colitis. This may be also useful as a follow-up tool to assess the gradual decrease in bowel wall thickening. Limitations are fat, bowel gas and ascites, which may modify sound wave transmission causing a decrease in resolution.

Computered tomography (CT) findings are similar to those seen on ultrasonography but CT may be more accurate in determining caecal wall thickening ([21,23]). In a study of 88 patients with neutropenic colitis, caecal thickening of more than 10mm on CT scanning was associated with significantly reduced survival compared to patients with less than 10mm of caecal wall thickening (40% vs 96%) ([24]). The use of ultrasound or CT scanning is usually based on their availability and the patients' body habitus. Avoiding delay in diagnosis is crucial. Therefore, use of the most rapidly accessible tool is prudent. If obesity or ascites potentially limit ultrasound penetration, CT should be the preferred modality ([2]).

Arteriography shows hypervascularity of the caecum, intense mucosal staining, opacification, superficial ulcers and A-V shunting into the mesenteric vein ([1]). Endoscopic procedures are relatively contraindicated due to increased risk of complications, especially in the setting of underlying neutropenia and thrombocytopenia. These procedures are unnecessary except in rare circumstances in which a gentle sigmoidoscopy may aid in the exclusion of pseudomembranous colitis.

HISTOLOGY

Histological findings include mucosal and submucosal bowel wall necrosis, associated with bacterial invasion as well as intramural haemorrhage, oedema and ulceration. Since the mucosa is involved primarily, the serosa may appear normal ([1]). A lack of inflammatory response is noted microscopically. However, mucosal ulceration my progress to full thickness gangrene ([25,26]).

Immunohistochemical studies of the gut in leukaemic patients demonstrated the infiltration of the bowel mucosa by leukaemic cells ([27,28]). These deposits are more likely to result in ulceration following the administration of cytotoxic agents ([12]). By contrast, metastases from a solid non-haematological primary tumour are more likely to involve the serosal surface. This may explain the relative rarity of neutropenic colitis in solid tumours treated with the same cytotoxic chemotherapeutic agents ([12]).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of immunosuppressed patients presenting with fever and abdominal pain includes appendicitis, cholecystitis, pancreatitis, C. difficile colitis, hepatic abscess, other bacterial viral/fungal/parasitic causes of colitis, perforated hollow viscus, volvulus and intussusception ([29]). In patients undergoing haematopoietic stem cell transplantation, differential diagnoses should also include graft versus host disease ([30]).

MANAGEMENT

Due to the small number of patients included in reports already published, it is difficult to establish clear guidelines for the treatment of neutropenic colitis. The optimal strategy in treating patients with this rapidly progressive fatal condition therefore remains controversial.

In all circumstances, patients with neutropenic colitis should be nursed in an intensive care environment. Joint care between medical and surgical teams is critical in the outcome of these patients. Bowel rest by permitting patients nothing by mouth or with nasogastric suction has been uniformly included in the initial management of patients with neutropenic colitis but this recommendation is not evidence-based. However, one might argue that luminal nutrients are useful in preserving intestinal barrier function and prompting colonisation resistance of normal gut flora ([2]).

Treatment that focuses on antibiotics that cover Clostridial organisms and translocating bacteria and fungi, combined with restoration of neutrophil counts, appears highly effective if administered early ([24,31]). A carbapenem (imipenem) or another extended spectrum B-lactam is often used with an aminoglycoside (gentamycin) for additional gram-negative coverage and metronidazole to cover anaerobic bacteria. Anti-fungal coverage is also added (fluconazole) to the initial antibiotics combination if patients remain febrile after 72 hours ([2]). Granulocyte colony-stimulating factor infusion is an emerging therapy; it hastens neutrophil recovery and has been used to shorten the duration of granulocytopenia ([11,17,31]).

Since the development of CT and ultrasound imaging modalities, the literature demonstrated successful non-operative management of neutropenic colitis and has changed the role of surgery from the standard care of all patients with neutropenic colitis to one with specific indications (persistent bleeding, intra-peritoneal perforation, severe clinical deterioration and development of symptoms of an intra-abdominal process, which would normally require surgical intervention in the absence of neutropenia) ([2]).

Most authors agree that a right hemicolectomy is the operation of choice ([26,32,33,34]). Less extensive surgical interventions such as appendicectomy may be inadequate as the extent of mucosal necrosis may often be greater than what is obvious by the naked eye inspection of the serosa ([13,25]). At operation, the surgeon must also decide whether to perform an end-to-end anastomosis or to exteriorise the bowel. If extensive sepsis or significant peritoneal soiling is present, primary anastomosis is inappropriate. In this situation an end ileostomy and a mucous fistula is recommended ([12]).

While non-operative conservative treatment can succeed in the early stages of neutropenic colitis, worsening of the patient's general condition and/or localised or generalised peritonitis are indications for immediate surgical intervention.

No published randomised controlled trials comparing conservative therapy with early surgical intervention exist; however, advocates for both types of treatment exist. The prognosis and outcome appear to reflect the state of underlying disease and other co-morbidities present at the time of diagnosis rather than the treatment modality chosen. Therefore, a uniform management strategy can not be recommended. Guidelines for treatment are not clear and controversy remains regarding indication for immediate

surgical intervention. Each case should be treated individually but prompt recognition of the condition, appropriate and timely therapy with return of neutrophil counts to normal are the key to a possible successful outcome.

CONCLUSION

Neutropenic colitis remains a major medical and surgical challenge. With the wider use of toxic chemotherapeutic agents in the treatment of haematological and solid malignancies, it is likely to be encountered with an increasing frequency. A high index of suspicion is imperative in order to make a prompt diagnosis in order to institute aggressive treatment for this potentially fatal condition.

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