Nevtropenični enterocolitis, povzročen s tirostatikom - poročilo o primeru

Neutropenic enterocolitis caused by antithyroid drug - case report

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Izvleček

Namen: *Nevtropenični enterokolitis (NE) je redka klinična slika, povezana z nevtropenijo in nekrozantnim enterokolitisom. Gre za nevaren zaplet nevtropenije. Čeprav se pogosteje pojavlja pri bolnikih z levkemijo in malignimi tumorji, ga lahko povzroči vsako zdravilo ali strup, ki povzroča nevtropenijo. Predstavljen je primer bolnice z NE, ki je prejemala tirostatik propiltiouracil. Gre za prvi tak primer, povezan z obsežno nekrozo ozkega in debelega črevesja.*

Poročilo o primeru: *Petdesetletna bolnica z neznačilno anamnezo je bila sprejeta zaradi nenadoma nastalih neznosnih bolečin v trebuhu. Imela je diarejo in je bruhala. Klinični pregled trebuha je bil neznačilen. Ultrazvočna preiskava je pokazala prosto tekočino v trebušni votlini. Laboratorijski izvidi so pokazali zvišane*

Abstract

Purpose: *Neutropenic enterocolitis (NE) is rarely reported condition, characterized by necrotizing enterocolitis. It is unusual acute complication of neutropenia. Although it was most often associated with leukemia or cancer patients it can be caused by any drug or poison associated with neutropenia. We present a case of neutropenic enterocolitis in a patient who received antithyroid drug propylthiouracil. To the best of our knowledge, this is the first description of NE associated with antithyroid drug propylthiouracil and extensive necrosis of small bowel.*

Case report: *A 50- year-old woman with no significant past medical history presented to the emergency department of a community hospital complaining of intractable abdominal pain, nausea, vomiting and diarrhea. The onset of symptoms was acute. Physical*

vrednosti CRP in hudo nevtropenijo. Toksikološke preiskave so bile negativne. Zaradi hitrega slabšanja klinične slike, zmedenosti in hude bolečine, ki je ni bilo mogoče nadzorovati z morfijem, je bila opravljena nujna operacija. Med operacijo se je izkazalo, da gre za nekrozo ascendentnega kolona in terminalnega ileuma. Prizadeti deli črevesja so bili resecirani. Po posegu je bila pacientka premeščena na oddelek za intenzivno nego. Po mesecih intenzivne oskrbe in številnih dodatnih kirurških posegih na črevesju je bila odpuščena ozdravljena. Šele kasneje je pacientka lahko povedala, da se je tri mesece pred sprejemom pričela zdraviti zaradi hipertiroze in je prejemala tirostatik propiltiouracil.

Zaključek: *O neželenih učinkih zdravil se redko poroča, čeprav vplivajo na pomemben delež sprejemov na urgenci in bi zdravniki morali biti z njimi bolje seznanjeni. Tirostatiki lahko povzročajo agranulocitozo in NE. Pri bolnikih z nevtropenijo in hudo bolečino v trebuhu je potrebno vedno pomisliti na NE.*

examination of abdomen was unremarkable. Ultrasound examination revealed free liquid in abdominal cavity. Severe neutropenia with elevated CRP was present. Toxicology was negative. As patient was becoming more and more confused and pain could not be controlled by morphine immediate surgery was performed. Surgical exploration of abdomen revealed gangrenous ascendent colon and terminal ileum. Diseased bowel parts were resected. After surgery patient was transferred to intensive care unit. She was discharged from hospital after several month of intensive medical treatment and repeated surgical procedures. Upon later questioning she noticed that three months before emergency admission to hospital she started with antithyroid drug (propylthiouracil).

Conclusion: *Physicians should be aware that antithyroid drugs can be associated with agranulocytosis and NE. Neutropenic patients, presenting with either generalized or focal abdominal pain, along with a fever, should uniformly be considered at a risk for NE.*

INTRODUCTION

Neutropenic enterocolitis is a rare acute complication of neutropenia. It is characterized by segmental enteric lesions that may progress to necrosis and perforation. Affected patients can progress rapidly to the sepsis and multiorgan failure syndrome. Necrotizing enterocolitis has long been acknowledged in the pediatric literature but has been rarely reported in larger series in adult patients (1). In adult patients it is associated with a variety of diseases, including acute leukemia following chemotherapy, chronic leukemia (2), lymphoma, HIV infection (3), colhicin poisoning (4) and agranulocytosis (5).

The presentation is dramatic, treatment is controversial, and the outcome may be devastating with several fatal cases reported (6, 7). Early recognition and treatment are essential for survival. Even with the currently recommended therapy, there is still high mortality rate varying between 20% and 100% (8, 9). As far as we are aware, there has been only one case reported of NE associated with antithyroid drug-induced agranulocytosis (5).As far as we are aware, there has been only one case reported of NE associated with antithyroid-drug-induced agranulocytosis (5). However, antithyroid drugs are widely used to control hyperthyroidism, and various side effects have been reported in large series in up to 40% of patients (10). In the previously reported case enterocolitis was limited to colon and no bowel resection was needed (5).

We present a case of neutropenic enterocolitis with extensive necrosis of small bowel in a woman with hyperthyroidism diagnosed three months before hospitalization, who started treatment with propylthiouracil at the time the disease was diagnosed. To the best of our knowledge, this is the first description of NE associated with antithyroid drug propylthiouracil and extensive bowel necrosis.

Case report

A 50- year-old woman presented with intractable abdominal pain, nausea, vomiting and diarrhea of several hours duration. The onset of symptoms was acute. Abdominal pain was intractable and could not be controlled by morphine. She was confused and no intelligible medical history could be taken. Her abdomen was not distended, no muscular rigidity was de-

tectable, on palpation it was painless but there were no bowel signs on auscultation. She was febrile with temperature 38.7 ^{0}C. Her white cell count was 2.9 x 10^{9}/L with no detectable neutrophils. The hemoglobin level was 110 g/L and was rapidly decreasing. Serum C-reactive protein was 175 nmol/L.

She was immediately taken to the intensive care unit with profound fatigue and confusion. She was found to be severely acidotic and in septic shock. Mechanical ventilation, intravenous pressor support, intra-venous antibiotics and ICU care were performed. Toxicology was negative.

Ultrasound examination revealed free liquid in abdominal cavity with distended small bowel loops with fluid collection. As her clinical picture deteriorated despite ICU care emergency laparatomy was performed. Surgical exploration of abdomen revealed gangrenous terminal ileum, cecum, ascendent colon and proximal half of transverse colon. Diseased bowel parts were resected. Jejunostomy was constructed and remaining part of colon was blindly closed.

Histology of resected parts revealed severe necrotizing enterocolitis. In the most severely affected areas there was full thickness necrosis of the bowel wall with serosal involvement. In less severely affected areas confluent ulcerations were present and involved predominantly mucosa and lamina propria. They had fibrinous base with paucity of active inflammation.

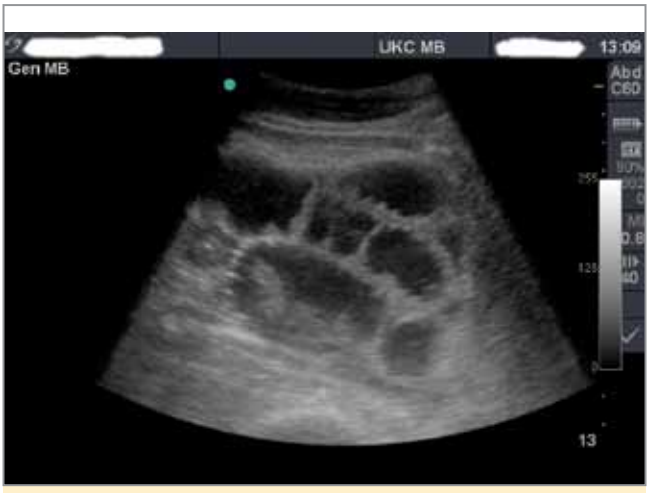

Fig. 1. *Urgent ultrasound examination of abdominal cavity. Typical distended loops of small intestine filled with fluid are seen – paralytic ileus. (Nujna preiskava abdomna z ultrazvokom. Vidne so značilne razširjene vijuge ozkega črevesja, napolnjene s tekočino – paralitični ileus).*

After surgery patient was transferred to an intensive care unit. Severe initial gastrointestinal disorder progressed into bone marrow suppression and multi-organ failure. She developed acute renal failure. In first weeks after first surgical procedure dialysis was needed. She was discharged from hospital after six months of intensive medical treatment and repeated surgical procedures (second look with additional resection of small bowel, drainage of two abdominal abscesses, two reoperations because of ileus and eventually enteral continuity procedure).

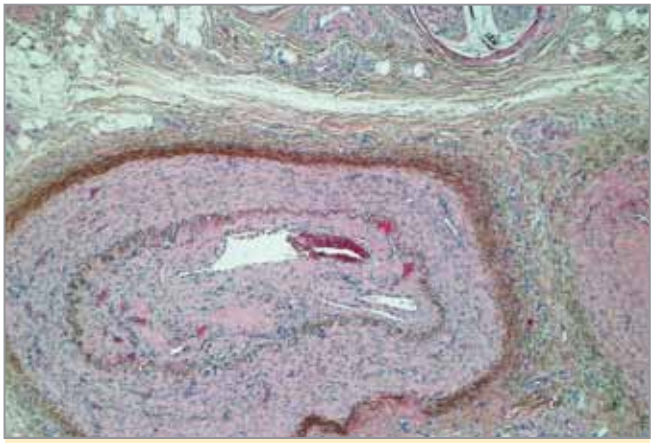

Fig. 2. *Histological picture of small artery. Artery is filled with thrombus, so typical for small vessel vasculitis. (histološka slika majhne arterije. Arterija je zaprta s krvnim strdkom, kar je značilno za vaskulitis majhnih arterij).*

Upon later questioning she noticed that three months before emergency admission to the hospital she started with antithyroid drug (propylthiouracil). Treatment with propylthiouracil was not continued. The disease did not entail any permanent sequellae which was confirmed two years after the patient was considered cured.

DISCUSSION

Neutropenic enterocolitis (NE) is a rare but highly lethal complication of neutropenia. The incidence rate is about 0, 1-26% after receiving chemotherapy and mortality rate 50% or higher (1, 2). In adult patients it is associated with a variety of diseases, including acute

leukemia following chemotherapy, chronic leukemia (2), lymphoma, HIV infection (3), colhicin poisoning (4) and agranulocytosis (5). NE is characterized by a septic or inflammatory intraabdominal process in patients who are neutropenic. The acute inflammatory disease may involve cecum, colon, and terminal part of ileum. The diagnostic criteria are heterogeneous. There are many unanswered questions, and our understanding of the pathophisiology of NE is sparse at best (11). It is believed to be a syndrome that is associated with number of clinical presentations rather than a specific disease, resulting from a combination of mucosal injury and impaired host defenses to intestinal organisms (6).

Official diagnostic criteria do not exist and there are no firm guidelines for treatment (11). Presenting clinical signs and symptoms for patients with NE can be varied and elusive. NE may mimic the presentation of appendicitis and a host of other diagnostic possibilities. Physical examination is usually unremarkable except for mild abdominal tenderness. Song et al. reported in a group of 14 patients, the most common presenting symptom was crampy abdominal pain that occasionally localized to the right lower quadrant. All 13 mentally alert patients complained of abdominal pain. All patients had mild diffuse tenderness, localizing to the lower quadrant in almost one quarter of the patients (12).

Diagnosing neutropenic enterocolitis can be difficult. Although the criterion of the radiologic definition may need more investigation, the systematic analysis of evidence quality of NE suggested that the definitive criteria should include fever, abdominal pain, and bowel wall thickening of more than 4 mm demonstrated by computed tomography or ultrasound in a neutropenic patient (1). The ultrasound examination in our case revealed free liquid in abdominal cavity with thin walled and distended small bowel loops, filled with fluid collection. In connection with the metabolic acidosis and intractable abdominal pain ultrasound examination was interpreted as ileus due to bowel gangrene. Patients who are hemodinamically unstable and are unable to safely tolerate transport to CT scanner may benefit from the rapid detection of bowel changes using ultrasound, which can be performed at the bedside.

Treatment for NE is controversial. 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 (13, 14). Other reports have suggested that the poor prognosis correlates with the patient's underlying disease (15). There is general agreement that in cases, where there are no unequivocal signs of surgical acute abdomen early management should be conservative, consisting of bowel rest, intravenous fluid administration, total parenteral nutrition, broad spectrum of antibiotics and normalization of neutrophil count. Recombinant granulocyte colony-stimulating factor (G-CSF) has been used to hasten recovery (15). In most patients, the symptoms resolve after correction of the neutropenia (1). Surgical intervention for NE is suggested for persistent gastrointestinal bleeding despite correction of neutropenia, thrombocytopenia and coagulopathy, free intraabdominal perforation and clinical deterioration despite aggressive supportive therapy and differentiation from other acute abdominal diseases for which surgery is indicated (13). In our patient urgent surgical intervention was indicated because of rapid clinical deterioration during initial conservative treatment and strong suspicion that intractable abdominal pain is caused by intestinal gangrene.

It remains to be fully understood how neutropenic enterocolitis occurs in response to agranulocytosis, caused by antithyroid drugs. Agranulocytosis is the most feared side effect of antithyroid drug therapy. In the largest series, severe agranulocytosis occurred in 0, 37% of patients receiving propylthiouracil and in 0, 35 percent receiving methimazole (10). Most cases of agranulocytosis occur within the first 90 days of treatment, although this complication can occur even a year or more after starting therapy. Agranulocytosis is thought to be mediated by a variety of mechanisms, including direct toxic effects and immunological reactions (16). Fever and sore throat are the most common presenting symptoms of agranulocytosis, but sepsis should be suspected if there is very rapid onset of fever, chills and prostration. In such cases, antithyroid drugs should be immediately discontinued and the patient should be hospitalized. Conservative therapy for

agranulocytosis does not differ from therapy for NE. After recovery from agranulocytosis, doctors should be cautious about prescribing antithyroid drugs again, even another type of thioamide, due to common cross reactions among thioamides (16). The recognition of adverse drug reaction (ADE) should depend on detailed and rigorous history taking as final diagnosis is usually possible by exclusion of other possible causes only. ADE have been increasingly recognized as the leading cause of medical injury; however few ADE are actually detected and reported (17). An emergency department- based study found that emergency physicians uderappreciate the frequency and significance of ADE (18). Given the increased use of drugs that can affect bone marrow cells physicians should be aware of their ADE and add neutropenic enterocolitis to their list of differential diagnoses in patients receiving potentially dangerous drugs.

CONCLUSION

Physicians should be aware that antithyroid drugs can be associated with agranulocytosis and NE. Neutropenic patients, presenting with either generalized or focal abdominal pain, along with a fever, should uniformly be considered at a risk for NE.

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