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CASE REPORT

Neutropenic enterocolitis in patients with FLT3 mutated acute myeloid leukemia undergoing induction chemotherapy with midostaurin

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Abstract

Neutropenic enterocolitis mostly affects patients with acute myeloid leukemia (AML) who get treated with intensive chemotherapy which is associated with prolonged neutropenia; its pathogenesis is not well understood and the main factors in this life-threatening condition appear to be neutropenia, mucosal injury and a weakened immune system as a consequence of intensive chemotherapeutic agents. Midostaurin in combination with chemotherapy became the standard of care for FLT3 mutant AML since its approval by the United States Food and Drug Administration (FDA) in April 2017. Anecdotally in our institution, we noticed the common occurrence of neutropenic colitis in three out of three patients who were treated with midostaurin as part of induction chemotherapy for AML.

Keywords Neutropenic enterocolitis · AML · Midostaurin

Introduction

Neutropenic enterocolitis, also known as typhlitis, is a necrotizing infection of the bowels which is seen in patients undergoing intensive cytotoxic chemotherapy for AML during periods of severe neutropenia. Typhlitis is a known but uncommon complication in AML [1]. It mainly affects the cecum and right colon but may involve other parts of the small and large bowel as well [2]. Although the pathogenesis is not well understood, it appears to be related to many factors including an impaired host defense due to severe prolonged neutropenia as well as ulcerations in the colonic mucosa, which allow proliferation of mostly gram-negative bacteria and other organisms. Signs and symptoms of neutropenic enterocolitis include fever, nausea and vomiting, diarrhea, abdominal pain and tenderness [2]. Computed tomography (CT) findings include thickening of the cecal wall, or other parts of the colon, along with edema, hemorrhage or pneumatosis. It is usually treated supportively unless perforation occurs. It is known to occur during treatment with cytarabine as part of induction chemotherapy but there are no reported cases of typhlitis with midostaurin use in the literature. Midostaurin is an oral FLT3 inhibitor used in those patients harboring FLT3 mutations during induction chemotherapy [3]. We present three cases of neutropenic enterocolitis during induction cytotoxic chemotherapy with midostaurin for AML.

Case 1

A 35 year-old Caucasian female with no significant past medical history, presented to the emergency room with complaints of persistent sore throat and fever for more than a week. Blood work showed neutrophilic leukocytosis, normocytic anemia and thrombocytopenia with total white blood cells of 64,100 cells/mm^3, hemoglobin 9.2 g/dL and platelet count 100,000 cells/mm^3. It was also significant for 3% circulating blasts in the peripheral blood with rare Auer rods. An infectious work-up including blood cultures, urine culture and chest X-ray were negative. A bone marrow aspirate and biopsy confirmed the diagnosis of acute myeloid leukemia (AML) and was morphologically and phenotypically consistent with monocytic type AML with 80% blasts in the bone marrow. FISH and karyotype showed no abnormalities; however, the molecular studies were positive for NMP1 and FLT3-TKD (tyrosine kinase domain) mutations.

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Accordingly, she was started on a standard induction chemotherapy with a continuous infusion of cytarabine 200 mg/m^2 on days 1–7 and idarubicin 12 mg/m^2 on days 1–3, along with prophylactic antifungal and antiviral medications. On day 6, she was noted to have absolute neutrophil count (ANC) 255 cells/mm^3, along with fever of 102.4 °F. She was promptly started on cefepime and vancomycin. She had no obvious localizing symptoms and infectious work-up was again negative. She was started on oral midostaurin 50 mg every 12 h on days 9–21. She then began to notice abdominal cramping with loose stools 24 h after the administration of midostaurin. On physical exam, she had mild tenderness to palpation in the right lower quadrant. On day 11, she developed a pruritic maculopapular rash over most of the body and her abdominal discomfort continued on day 12 so midostaurin was held. Computed tomography (CT) of the abdomen and pelvis was notable for mural thickening and submucosal edema of the ascending colon and proximal transverse colon with no evidence for bowel obstruction (see Fig. 1). Neutropenic colitis was suspected. Her antibiotics were changed to piperacillin/tazobactam for anaerobic coverage in addition to supportive measures that lead to resolving of her symptoms. Midostaurin was re-initiated on day 15, but again she experienced fevers and abdominal cramping afterwards. Her fevers were thought to be related to midostaurin as no source of infection was apparent and once again her abdominal symptoms resolved after discontinuation of midostaurin.

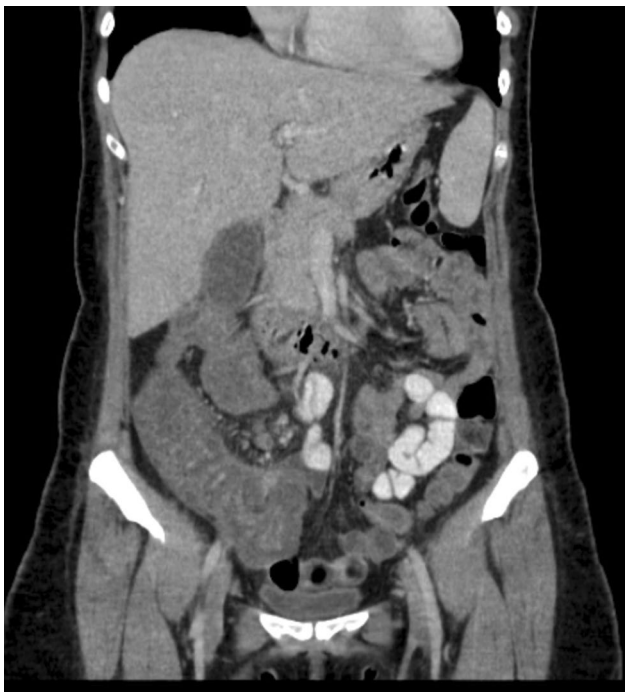

Fig. 1 Computed tomography of the abdomen and pelvis was notable for mural thickening and submucosal edema of the ascending colon and proximal transverse colon with no evidence for bowel obstruction

Post induction bone marrow evaluation on day 22 revealed no evidence for residual leukemic cells. She completed 3 cycles of consolidation chemotherapy with high dose cytarabine and maintenance midostaurin but did not experience any additional gastrointestinal complaints during consolidation therapy. She currently remains in remission from her disease.

Case 2

A 59-year-old Caucasian male with a past medical history significant for hypertension, gastroparesis, chronic obstructive pulmonary disease and hyperlipidemia, who originally presented to our cancer center with pancytopenia found on routine blood work. He had a bone marrow biopsy that showed high-grade myelodysplastic syndrome (MDS) with excess blasts in some areas of his marrow. He began undergoing evaluation for a clinical trial, but in a few weeks his MDS evolved into AML. He was subsequently admitted for induction chemotherapy. Bone marrow biopsy revealed 40% blasts, hypercellular marrow (50%) and erythroid hyperplasia. Cytogenetics and karyotype were normal. Additionally, he was positive for the FLT3-ITD mutation.

The patient was started on induction chemotherapy with cytarabine 200 mg/m^2 continuous infusion (days 1–7) and daunorubicin 60 mg/m^2 (days 1–3), along with prophylactic anti-viral and anti-fungal. Midostaurin 50 mg twice daily was added to the regimen on days 8–21 of induction therapy due to having the FLT3 mutation. On day nine of chemotherapy, the patient developed a pruritic rash. On day 10, the patient developed diarrhea followed by a fever of 101.9 °F on day 12. ANC was 30 cells/mm^3. The patient was started on IV vancomycin and cefepime. Infectious work-up was negative, including stool polymerase chain reaction (PCR). Midostaurin was held on day 13 due to persistent fever, rash and diarrhea. The following day, patient developed new onset abdominal pain and a subsequent CT of the abdomen and pelvis showed inflammatory changes in the right paracolic gutter, suspicious for typhlitis (see Fig. 2). Antibiotics were switched to piperacillin/tazobactam. Midostaurin was restarted on day 21 of therapy, but due to recurrent fever, diarrhea and rash, was again held. Bone marrow biopsy was performed on day 25 of induction, which unfortunately showed persistent blasts at 14%. The patient's gastrointestinal complaints resolved. He then went on to have an unsuccessful response to salvage chemotherapy and currently he is receiving third line therapy with azacytidine.

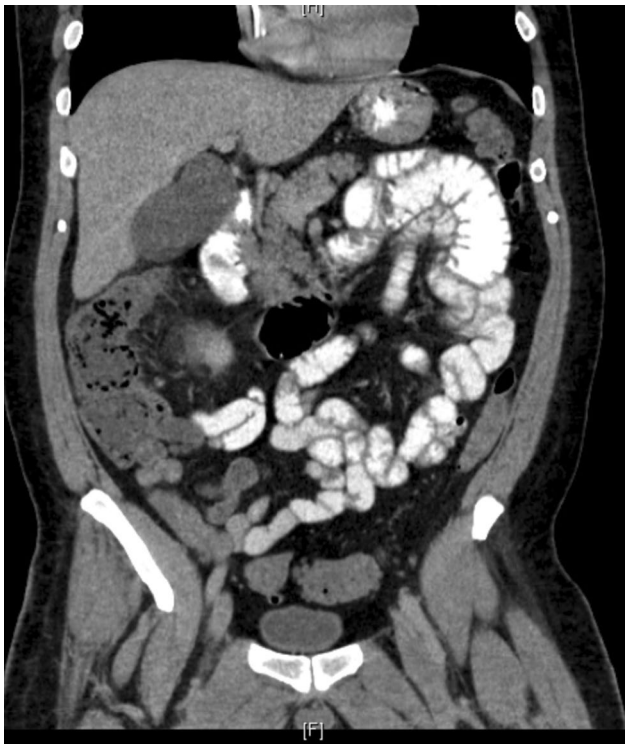

Fig. 2 CT of the abdomen and pelvis showed inflammatory changes in the right paracolic gutter

Case 3

A 73-year-old Caucasian female with no significant medical history initially presented with pancytopenia and found to have severe vitamin B12 deficiency. The pancytopenia failed to improve despite B12 replacement and a subsequent bone marrow biopsy revealed myelodysplastic syndrome with excess blasts-2 (MDS-EB2) with blasts > 15%, in transformation to acute myeloid leukemia. FISH and cytogenetics were normal but next-generation sequencing revealed a FLT3-ITD mutation. She was hospitalized for induction chemotherapy with daunorubicin 60 mg/m^2 on days 1–3, cytarabine 50 mg/m^2 on days 1–7 and midostaurin 50 mg on days 8–21. The evening after administration of midostaurin, she developed an erythematous macular rash on the hands and feet. On day 9, she developed a fever up to 100.8 °F and noted to have ANC of 8 cells/mm^3. She also reported nausea and watery diarrhea. She was started on empiric cefepime along with intravenous and oral vancomycin. Infectious work-up including blood and urine cultures, stool PCR, including testing for *Clostridium difficile*, were negative. Her physical exam was significant only for mild tenderness to palpation in the right lower quadrant. Subsequently, a CT scan of the abdomen revealed mucosal thickening and enhancement involving the rectosigmoid colon, as well as the cecum with sequelae of colitis suspected (see Fig. 3).

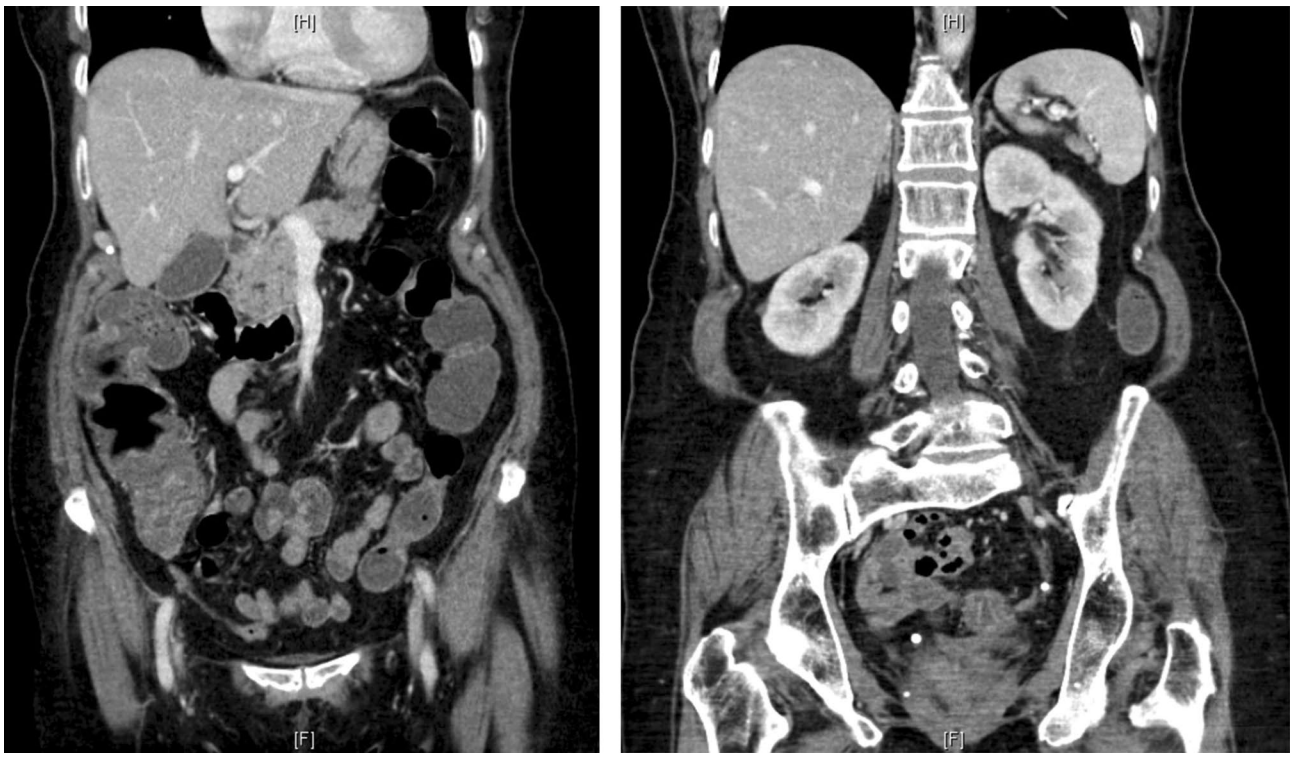

Fig. 3 CT scan of the abdomen revealed mucosal thickening and enhancement involving the rectosigmoid colon, as well as the cecum

Her antibiotics were switched to piperacillin/tazobactam. Her bowel movements improved to normal consistency and she remained on midostaurin. On day 20, she developed another fever of 100.5 °F. She did not have any other systemic symptoms and her diarrhea had mostly resolved at this time. Blood cultures became positive at 14 h for vancomycin-resistant enterococcus (VRE), thought to be secondary to a gastrointestinal source. Antibiotics were switched to daptomycin, ceftriaxone and ampicillin. Peripherally inserted central catheter (PICC) line was removed and cultured, which was negative. Echocardiogram was negative for vegetation and repeat blood cultures were negative. Due to the bacteremia, bone marrow biopsy and aspirate was not performed until day 28 and unfortunately revealed 10% blasts. She was discharged on prolonged antibiotics and was planned to start a salvage regimen with decitabine as an outpatient.

Discussion

Neutropenic enterocolitis is a rare and life-threatening necrotizing infection of the bowel, which has been noted to occur during treatment of AML. The actual incidence is not well known but literature suggests incidences ranging from 2.53% in AML patients to an observed 5.3% in a combined cohort of patients with both solid and hematologic malignancies [2, 4]. Prognosis also varies with estimated mortality between 0 and 50% of patients, which has lessened over the years likely due to rapid recognition and improvement in supportive care. Typhlitis has traditionally been associated with cytarabine and anthracyclines such as idarubicin which are given as induction chemotherapy for AML [4]. This is given as a continuous infusion of cytarabine over 7 days concurrently with an anthracycline over 3 days. Midostaurin, a FLT3 inhibitor, was recently introduced as an adjunct to standard induction treatment [3]. In recent years it has been noted that cytogenetics and somatic mutations play an important role in the prognosis of AML patients. FLT3 mutations in particular often portend a worse prognosis compared to other types of AML. They are seen in around 7.7–20% of patients depending upon the type of mutation, either internal tandem duplication (FLT3-ITD) or tyrosine kinase domain mutations (FLT3-TKD) [3, 5]. Midostaurin was the first targeted therapy approved in the treatment of AML which actually improved overall survival. It is given after completion of cytarabine and an anthracycline on days 8 through 21 and administered at a dose of 50 mg orally twice daily. Side effects of midostaurin most commonly include febrile neutropenia, infection, diarrhea, rash, pneumonitis, gastrointestinal complaints such as nausea and mucositis, in addition to the expected cytopenias. Infections commonly reported with use of midostaurin included upper respiratory tract infections, cellulitis and fungal infections [3]. There are no reported cases in the literature at this time of typhlitis with the use of midostaurin during induction chemotherapy treatment for AML, likely due to its recent onset of use.

Neutropenic enterocolitis most commonly occurs in the cecum but also noted to occur in other areas of the small and large bowel [6]. Pathologic and imaging features are highly varied ranging from mucosal edema and ulceration of the intestine, focal hemorrhages, transmural necrosis to pneumatosis intestinalis and even perforation [6, 7]. The onset of symptoms typically occurs around 10–14 days after the start of cytotoxic chemotherapy and include fever, nausea and vomiting, diarrhea, abdominal pain or tenderness that may be diffuse or limited to the right lower quadrant in the clinical setting of severe neutropenia [6]. Pathologic examination is the gold standard for diagnosis but endoscopic evaluation is usually not recommended due to increased risk of complications. For this reason, the diagnosis is clinical and based upon a constellation of signs, symptoms and imaging findings in the appropriate clinical scenario. Imaging with computed tomography (CT) and ultrasound are the most commonly used modalities for diagnosis and typically show inflammatory changes, such as mucosal wall thickening of the bowel and peri-cecal fluid accumulation.

Anecdotally, in our small academic institution, we noticed an unprecedented incidence of neutropenic colitis in all three out of three patients treated with midostaurin, or 100%. Typhlitis is a known complication of cytarabine treatment but has not yet been associated with midostaurin [4]. It is theorized to occur secondary to multiple factors including direct insult to the colonic mucosa from chemotherapeutic agents, mucosal damage driven by neutropenia and leukemic infiltrates altering the vascular supply, as well as an impaired immune response from the patient [6]. The observation by pathologists in post-mortem studies noted a high incidence of gram-negative bacteria infiltrating the bowel wall and its blood supply in these cases [6]. Because of this, antibiotics directed especially at gram-negative bacteria are recommended. Otherwise, the general consensus for treatment includes conservative measures including bowel rest and supportive care if patients do not have signs of perforation. If medical management fails and the patient is rapidly deteriorating, surgery is indicated [7].

In our series of patients, all three patients were observed to have a combination of signs and symptoms (fever, abdominal pain and gastrointestinal complaints) as well as compelling imaging findings that support the diagnosis of neutropenic enterocolitis. While performing an endoscopy to obtain a biopsy for histopathologic evaluation would be ideal, it is rarely able to be performed due to the high risk of complications from both severe neutropenia and the procedure itself. Infectious causes such as *Clostridium difficile* and other types of infectious diarrhea were investigated and

found to be non-revealing. Two out of three patients experienced rash as well, which was thought to be due to midostaurin and is a known side effect. Withdrawal of midostaurin led to improvement in both their gastrointestinal complaints and rash, but due to its significant impact on overall survival, the drug was restarted in two out of three patients. One patient was not restarted due to VRE bacteremia, which was presumed to be from a gastrointestinal source. The onset of symptoms in our cases is typical of typhlitis secondary to cytarabine. However, due to its uncommon occurrence, the fact that 100% of patients in our institution treated with midostaurin developed clinical symptoms consistent with neutropenic enterocolitis suggests that this drug may somehow contribute to the pathogenesis of this illness. This small case series is by no means a cause for definite association between typhlitis and midostaurin but will hopefully bring awareness and further investigation into incidences of a potentially fatal complication in the treatment of patients with AML.

Conclusion

Typhlitis is a known but uncommon occurrence during induction chemotherapy for AML. It has a known association with cytarabine but only occurs in a small percentage of patients. The temporal relationship between the starting of midostaurin and the development of enterocolitis as well as the exclusion of other etiologies such as infections, lead us to believe that the occurrence of enterocolitis in our patients is very likely related to midostaurin therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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