

Acute Typhlitis: A Rare Complication of FOLFIRINOX Chemotherapy in the Treatment of Advanced Pancreatic Cancer

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Abstract

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Abstract

FOLFIRINOX is a combination of multiple chemotherapeutic agents, commonly used to treat metastatic pancreatic cancer [1]. A less commonly associated side-effect to this chemotherapy regimen is typhlitis, also known as neutropenic enterocolitis (NEC). This is a life-threatening condition that occurs secondary to cytotoxic damage of the gastrointestinal mucosal wall, particularly the cecum [2]. This loss of mucosal wall integrity subsequently leads to infection and inflammation. As such, immunosuppressed patients exposed to highly cytotoxic agents are of higher risk for translocation of gut bacteria and eventually septic shock. Our case report reviews the diagnosis, management and impact of typhlitis secondary to FOLFIRINOX therapy. Typhlitis should always be suspected when a patient undergoing active chemotherapy presents to an acute care facility with Right Lower Quadrant (RLQ) abdominal pain, fever and neutropenia. Nonetheless, this life-threatening diagnosis is often missed.

Introduction

There is unfortunately a wide array of complex and unpleasant side effects that arise when utilizing chemotherapeutic agents for treatment of pancreatic cancer. One of the most common regimens used specifically in metastatic pancreatic cancer is a powerful combination of medications known as FOLFIRINOX, which consists of leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin [1]. Alone, each of these drugs are known to produce side effects that affect all system organs. When used in combination however, the patient might expect a compilation of effects that would certainly require a guided risk-benefit discussion between the patient and their oncologist. One such adverse effect is a gastroenterological condition known as neutropenic enterocolitis, or typhlitis.

Case Presentation

We present a case of a 74-year-old female with a past medical history of hypertension and metastatic pancreatic cancer presenting with abdominal pain, nausea, vomiting and diarrhea. The patient completed her second cycle of FOLFIRINOX one week prior to presentation and had been having diarrhea ever since. Of note, she had presented to a different facility three weeks prior after her first round of FOLFIRINOX. She was admitted for possible colitis at that time, though her stool cultures

returned negative. However, on the day of presentation, she abruptly began to experience sharp, stabbing pain in her right side associated with projectile vomiting and nausea. Upon presentation to a satellite emergency room, she was afebrile with a heart rate of 86, blood pressure of 124/88, saturating appropriately on room air. Her physical exam was pertinent for diffuse abdominal tenderness particularly tender to palpation in the epigastrium and right lower quadrant without guarding or rebound.

The patient's initial laboratory values to include a Complete Blood Count (CBC) with differential revealed a white blood cell (WBC) count of 2.4 with an ANC of 500. A contrast CT scan of the abdomen and pelvis with intravenous contrast demonstrated mild colonic thickening in the ascending and transverse segments (Figure 1). Blood cultures, stool PCR, and *Clostridium difficile* stool cultures were ordered and she was subsequently initiated on broad-spectrum antibiotics with piperacillin-tazobactam. The following day, the patient became intermittently febrile and her oncologist was notified of her admission. The primary team was advised to place the patient on Filgrastim for expected post-chemotherapy pancytopenia. The patient was monitored closely for signs of peritonitis and she continued to improve clinically despite ongoing intractable nausea. Blood cultures remained negative and antibiotics were discontinued after 5 days.

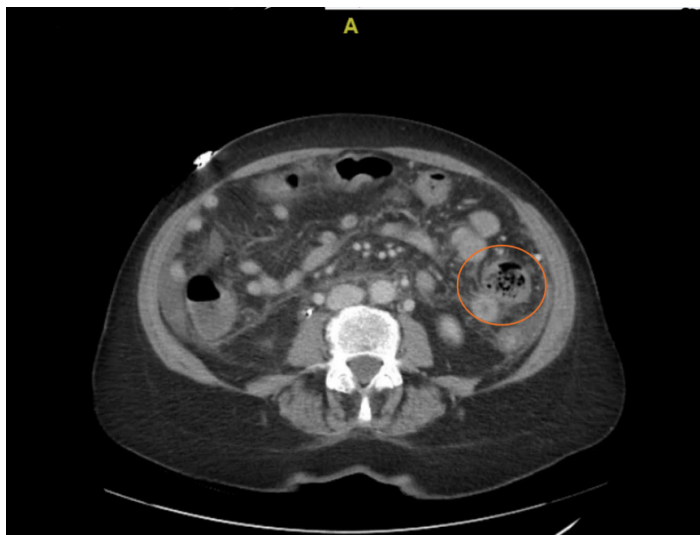


Figure 1: A single view of a Multi-detector CT imaging of the abdomen and pelvis performed using the standard protocol bolus administration of intravenous contrast which showed mild thickening of the mild colonic thickening in the ascending and transverse segments (red circle).

Discussion

Neutropenic Enterocolitis (NEC) was first described as a complication found in pediatric leukemia patients but is now becoming a more common complication among adults undergoing treatment for many different types of cancer [2]. It typically arises when the Absolute Neutrophil Count (ANC) gets below 500, most often for as little as one week [2,3]. There are many pathogens cited to be involved, quite commonly *Clostridium* species and *Candida*, but infiltration of the ascending colon with gram-negative bacteria have also been described [3-5]. Typhlitis more specifically relates to the cecum, which is expected when considering its increased distensibility and diminished vascularization when compared to the rest of the colon [6,7]. However, migration to ascending colon and even pancolonic involvement is common [2,6].

Recurrence is not uncommon; however, diagnosis is commonly missed. Diagnosis is made with a combination of history, physical examination, and Ultrasound or CT imaging findings that support inflammation of the colon, although definitive diagnosis is histological [2]. There has been debate or lack of consensus on the diagnostic criteria. The following criteria are generally accepted in diagnosing patients, especially when all 5 are met [6-8].

1. An immunosuppressed patient with an ANC < 500
2. The presence of fever or temperature > 99.5°F
3. Abdominal pain, especially in the RLQ
4. Imaging evidence of bowel wall thickening or inflammation, especially in the cecum
5. Recent exposure to cytotoxic agents.

Conclusion

Although the diagnosis of neutropenic enterocolitis is important, it is far more important to risk stratify patients with fever and neutropenia as these patients are at baseline more likely to become septic. In immunosuppressed patients with abdominal pain, diarrhea or generalized gastrointestinal upset, imaging modality such as a CT of the abdomen should be done to rule out an abscess, fistula, abdominal perforation or typhlitis. Once the diagnosis of typhlitis is established, treatment is typically supportive and guided by the disease severity. Initiation of empiric antibiotics is reasonable, with narrowing based on detection of pathogens in the blood, especially in cases of bacteremia. Prompt detection and treatment is paramount as typhlitis is a condition that is life-threatening and can eventually lead to death. We particularly hope to enhance research and literature related to Folfurinox-associated typhlitis in order to improve early detection and suspicion of this life-threatening condition.

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