

First reported case of afatinib-associated toxic megacolon

Wang Chun Kwok , Terence Chi Chun Tam & David Chi Leung Lam

Department of Medicine, Queen Mary Hospital, Hong Kong, China.

Keywords

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Correspondence

Wang Chun Kwok, Department of Medicine, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong Special Administrative Region, China.
E-mail: herbert728@gmail.com

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Introduction

We report the first case of toxic megacolon associated with afatinib use. It is a potentially fatal complication, and a high index of suspicion is needed.

Case Report

A 59-year-old non-smoker was diagnosed with Stage IV adenocarcinoma of the lung in February 2018. She presented with cough and dyspnoea for two months. Positron emission tomography-computed tomography (PET-CT) showed a right middle lobe primary tumour with multiple bilateral intra-pulmonary metastases. Computed tomography-guided biopsy was performed, and histology was consistent with adenocarcinoma of the lung. An epidermal growth factor receptor (EGFR) mutation test identified a 15-nucleotide deletion in exon 19 of the EGFR gene. She was started on Afatinib 40 mg daily in late April 2018.

She was admitted 10 days later for high fever, central abdominal pain, and severe diarrhoea, with bowel opening up to six times per day. On admission, her body temperature was 40.5 °C, and she was clinically dehydrated and hypotensive with a blood pressure of 107/67 mmHg and heart rate of 120 beats/min. Abdominal examination demonstrated paraumbilical tenderness. Blood tests showed a

Abstract

We report the first case of toxic megacolon associated with afatinib use, which is a potentially fatal complication, with risks of colonic perforation. In this case, the condition improved on stopping afatinib. Clinicians need to be alert of this rare but fatal adverse effect and to avoid anti-diarrhoeal agents, which can worsen toxic megacolon. Anti-diarrhoeal agents are routinely given if diarrhoea occurs on afatinib. These should be stopped and avoided if toxic megacolon occurs.

white cell count of $1.99 \times 10^9/L$ (Normal: $3.89-9.93 \times 10^9/L$), neutrophil count of $1.50 \times 10^9/L$ (Normal: $2.01-7.42 \times 10^9/L$), haemoglobin of 12.5 g/dL, and creatinine of 52 $\mu\text{mol/L}$ (Normal: 49–82 $\mu\text{mol/L}$). Potassium level was low at 3.1 mmol/L (Normal: 3.6–5.0 mmol/L). There was mild hepatic changes in liver function, with alanine aminotransferase of 178 unit/L (Normal: 8–45 unit/L) and aspartate aminotransferase of 131 unit/L (Normal: 15–37 unit/L).

Abdominal radiograph (AXR) shows marked transverse colon dilatation, with maximum width at 8.1 cm (Fig. 1). Afatinib was withheld, and she was rehydrated with intravenous fluid. Empirical intravenous ciprofloxacin of 400 mg every 12 h was started, and the antibiotics were later stepped up to intravenous ceftriaxone 1 g every 12 h in view of a persistent fever and diarrhoea. Bacterial, fungal, and viral culture of the stool, along with *Clostridium difficile* toxin and culture, turned out to be negative, as was the blood culture and cytomegalovirus pp65 antigen level. Infectious cause is considered to be unlikely, and the antibiotics were stopped.

After cessation of afatinib, her symptoms gradually improved. Repeat AXR showed resolution of colonic dilatation. Liver function also subsequently improved. Overall, the clinical course is compatible with toxic megacolon and hepatitis caused by afatinib use, which improved with withdrawal of afatinib. She was switched to gefitinib



Figure 1. Abdominal radiograph showing transverse colon is dilated to 8.1 cm.

250 mg daily afterwards. She tolerated gefitinib well without significant gastrointestinal or hepatic toxicity.

Discussion

To the best of our knowledge, this is the first reported case of afatinib-associated toxic megacolon. Afatinib is known to cause gastrointestinal side effects, with Grades 3–4 diarrhoea occurring in 697 (16%) of the 4257 patients across 44 clinical trials. In LUX-Lung 3, diarrhoea occurred in 96% of patients, while 15% were Grade 3 in severity and occurred within the first six weeks [1]. Toxic megacolon is defined as segmental or total colonic distension of more than 6 cm in the presence of acute colitis and signs of systemic toxicity. One of the proposed diagnostic criteria for toxic megacolon include the following:

- Radiographic evidence of colonic distension, with transverse colon measuring more than 6 cm
- Plus at least three of the following:
 - Fever of more than 38 °C
 - Heart rate more than 120 beats/min
 - Neutrophilic leukocytosis of more than $10.5 \times 10^9/L$
 - Anaemia plus at least one of the following
 - Dehydration
 - Altered sensorium
 - Electrolyte disturbances

- Hypotension [2]

Our patient fulfilled most of the diagnostic criteria for toxic megacolon except for the cell count, but the leucopaenia can indeed reflect a severe systemic inflammatory response syndrome, much akin to neutrophilia required in the diagnostic criteria. Toxic megacolon is a potentially fatal condition with colonic perforation as one of the complications. Mortality is reported to be 19% [3]. Common causes of toxic megacolon include inflammatory bowel disease and infectious colitis, especially *C. difficile* infection. Other infective agents include *Salmonella*, *Shigella*, *Campylobacter*, and *Entamoeba*. Ischemic colitis is another cause for toxic megacolon. Cytomegalovirus colitis, *Cryptosporidia* infection, and Kaposi's sarcoma have also been reported to cause toxic megacolon in patients with human immunodeficiency virus infection [4]. Drugs that slow colonic motion, including anti-diarrhoeal and anti-cholinergics, has been reported to be associated with development of toxic megacolon.

Medical therapy is the first line of treatment for toxic megacolon associated with inflammatory bowel disease and *C. difficile* infection. Surgical treatment, including subtotal colectomy with end-ileostomy, may be needed in patients who do not improve on medical management.

Clinicians need to be alert of this rare but fatal adverse effect. Instead of only prescribing anti-diarrhoeal agents to patients with gastrointestinal side effects associated with afatinib use, assessment for any systemic toxicity and AXR can help identify toxic megacolon, in which anti-diarrhoeal agents should be stopped or avoided. On encountering afatinib-associated toxic megacolon, withdrawal of afatinib, rehydration, extensive microbiological examination, empirical antimicrobials, and radiological monitoring for colonic dilatation is recommended.

Disclosure Statement

Appropriate written informed consent was obtained for the publication of this case report and accompanying images.

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