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PALBOCICLIB-INDUCED APOPTOTIC COLOPATHY: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Background: Cyclin-dependent kinase (CDK) 4/6 inhibitors (ribociclib, abemaciclib, and palbociclib) are standard first-line therapy for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. While diarrhoea is a known adverse effect, severe gastrointestinal toxicity, particularly colitis, is rare and its histopathologic features are not well-characterized.

Case report: We report the case of a 65-year-old woman with HR-positive, HER2-negative metastatic breast cancer who developed severe diarrhoea and significant weight loss during palbociclib treatment. Her prior treatment included adjuvant chemotherapy, radiotherapy, and letrozole, followed by first-line treatment for metastatic disease with fulvestrant and abemaciclib. Due to recurrent grade II diarrhoea on abemaciclib, she was switched to palbociclib. One year after initiating palbociclib, she presented with 6–10 daily bowel movements, 11 kg weight loss, anaemia, and hypoalbuminemia. Infectious aetiologies were excluded. Imaging revealed pancolitis, and a colonoscopy showed multiple deep ulcers. A rectal biopsy demonstrated chronic proctitis with increased epithelial apoptosis. Palbociclib was discontinued, and oral budesonide was initiated, which led to clinical and endoscopic remission. She remained asymptomatic on fulvestrant monotherapy for over 6 months.

Conclusion: This rare case describes palbociclib-induced colitis with characteristic histopathologic findings of increased epithelial apoptosis, consistent with drug-induced apoptotic colopathy. To our knowledge, this is the first report of palbociclib-associated colitis with histological confirmation of apoptotic changes and successful treatment with budesonide. Clinicians should consider CDK4/6 inhibitors as a potential cause of severe gastrointestinal symptoms and recommend biopsy when the diagnosis is uncertain.

KEYWORDS

Palbociclib, cyclin-dependent kinase inhibitors, drug-induced colitis, apoptotic colopathy, breast cancer

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LEARNING POINTS

- Although diarrhoea is a common side effect, palbociclib can, in rare cases, cause severe colitis with deep ulcers at video colonoscopy; internists should be aware of this underrecognized adverse effect.
- Histologic findings of increased epithelial apoptosis can support the diagnosis of drug-induced apoptotic colopathy.
- Oral budesonide, commonly used in microscopic colitis, may be an effective treatment for CDK4/6 inhibitor-induced colitis, offering a well-tolerated therapeutic option.

INTRODUCTION

Cyclin-dependent kinase (CDK) 4/6 inhibitors (ribociclib, abemaciclib, and palbociclib) are a standard of care for metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer. While their mechanism of action and efficacy are similar, there are some differences in their safety profiles[1].

The most common gastrointestinal adverse effect is grade I-II diarrhoea, which is more frequent with abemaciclib. The absolute risk for grade III-IV diarrhoea is higher with abemaciclib compared to palbociclib, at 0.135 (95% CI 0.092–0.192) and 0.011 (95% CI 0.007–0.018), respectively[1]. Little is known about the histopathological changes associated with severe gastrointestinal side effects of CDK 4/6 inhibitors[2,3].

Here, we describe the clinical, endoscopic, and histopathological features of a patient who developed severe colitis during palbociclib treatment, which resolved with drug withdrawal and oral budesonide.

CASE DESCRIPTION

A 65-year-old woman with metastatic breast cancer was admitted due to diarrhoea and weight loss.

Five years before she was diagnosed with an early HR-positive HER2-negative breast cancer. She underwent adjuvant therapy consisting of 4 cycles of doxorubicin and cyclophosphamide, 12 weeks of paclitaxel, and whole breast radiation therapy; followed by treatment with letrozole. She had a history of hypothyroidism treated with levothyroxine (75 µg/d).

Approximately 3 years after cancer diagnosis, she developed an adrenal mass, which was surgically resected. Histological examination confirmed HR-positive HER2-negative metastatic breast cancer. She was started on first-line therapy with fulvestrant (500 mg on days 1, 15, 29, and then every 28 days intramuscular) and abemaciclib (150 mg twice daily orally).

Around 5 months after starting the first-line therapy, she developed diarrhoea, which led to a dose reduction of abemaciclib to 100 mg twice daily and symptomatic treatment with loperamide. Diarrhoea improved during the next 5 months when it recurred, leading to another interruption of abemaciclib. After one month without abemaciclib, she was switched to palbociclib (125 mg daily for 21 days, followed by 7 days off) in addition to fulvestrant. One year after initiating palbociclib, she developed diarrhoea (6-10 bowel movements per day). Stool cultures and Clostridia toxin tests were negative. She received ambulatory treatment with loperamide, rifaximin, trimebutine and probiotics without improvement. Palbociclib was interrupted. Despite this, diarrhoea persisted, and the patient was admitted.

At admission, the patient reported a weight loss of 11 kg. On physical examination she had abdominal tenderness. Laboratory tests revealed anaemia (haemoglobin: 8.9 g/dl); hypoproteinaemia (5.4 g/dl - normal range: 6.4-8.3 g/dl); hypoalbuminemia (2.1 g/dl -normal range: 3.2-4.6 g/dl). Erythrocyte sedimentation rate (90 mm/1st hour) and C-reactive protein (112.7 mg/dl; normal: < 5 mg/dl) were markedly elevated.

Clostridioides difficile antigen and toxin A/B were negative. A stool multiplex polymerase chain reaction (BioFire FilmArray®) was negative *(Table 1)*.

An abdominal computed tomography (CT) scan showed diffuse, non-stenosing thickening with submucosal oedema in the rectum, sigmoid, descending, and proximal transverse colon. Loss of the colonic haustra was noted, along with accentuation of adjacent fat and peripheral vascular congestion *(Fig. 1)*.

A video colonoscopy (VC) showed multiple deep ulcers, one larger (approximately 25 mm) with raised edges and



Figure 1. Contrast-enhanced abdominal computed tomography (CT) scan demonstrated diffuse, non-obstructive wall thickening with submucosal edema involving the rectum, sigmoid, descending, and proximal transverse colon. Additional findings included loss of colonic haustra, increased pericolic fat attenuation, and peripheral vascular congestion—radiologic features suggestive of an acute inflammatory process.

Target
Campylobacter
Clostridium difficile A/B toxin
Plesiomonas shigelloides
Salmonella
Vibrio spp.
Yersinia enterocolitica
Enteroaggregative *Escherichia coli*
Enteropathogenic *E. coli*
Enterotoxigenic *E. coli*
Shiga toxin (stx1/stx2) *E. coli*
Enteroinvasive Shigella/*E. coli*
Cryptosporidium
Cyclospora cayetanensis
Entamoeba histolytica
Giardia lamblia
Adenovirus F 40/41
Astrovirus
Norovirus GI/GII
Rotavirus A
Sapovirus

Table 1. Gastrointestinal multiplex molecular panel targets.

smaller punched-out ulcers *(Fig. 2)*. A rectal biopsy was performed. The histopathological diagnosis was chronic proctitis with increased apoptotic bodies *(Fig. 3)*. No viral cytopathic changes were noted, and immunohistochemistry for cytomegalovirus was negative.

The patient was treated with oral budesonide (9 mg daily modified release capsules, single dose) for 8 weeks, which led to symptomatic improvement. Serum protein and albumin levels normalized, and both erythrocyte sedimentation rate and C-reactive protein decreased. Follow-up CT scan and VC showed significant improvement.

The patient continued treatment with fulvestrant monotherapy and has remained stable for 6 months after the discontinuation of budesonide.

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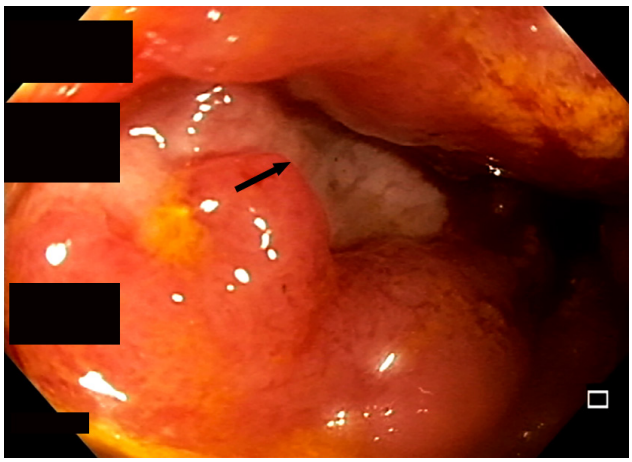


Figure 2. Video colonoscopy (VC) showed multiple deep colonic ulcers, including one larger ulcer (arrow) approximately 25 mm in diameter with raised edges, and several smaller, punched-out ulcers—findings suggestive of severe mucosal injury.

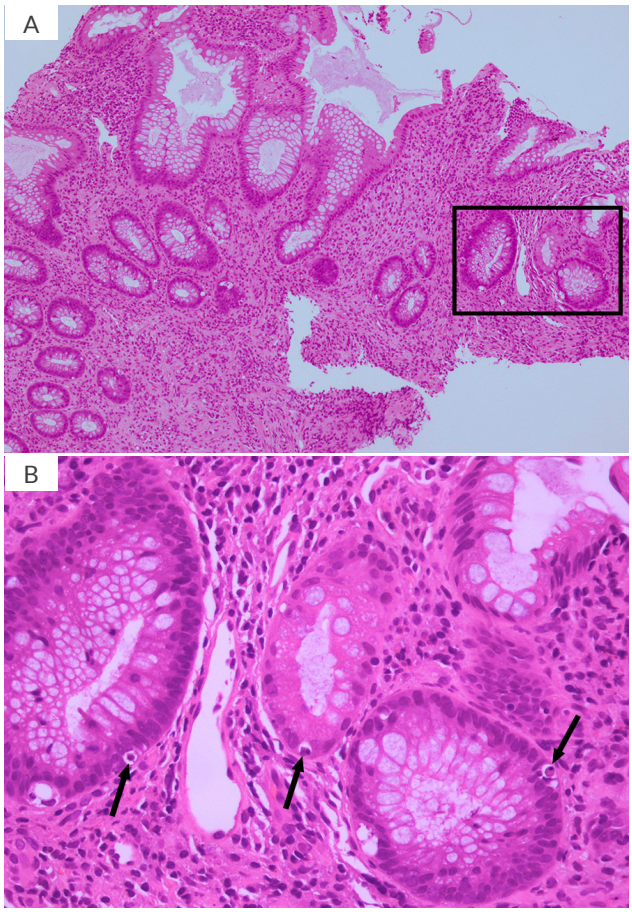


Figure 3. Rectal biopsy, hematoxylin and eosin staining: A) 100×. B) 400×. Histological section of rectal mucosa showed distorted glandular architecture, reduced mucin production, and areas of surface epithelial sloughing. Frequent apoptotic bodies (arrows) and focal glandular loss were evident. A moderate inflammatory infiltrate composed of lymphocytes, plasma cells, and polymorphonuclear leukocytes was present in the lamina propria.

DISCUSSION

Three different CDK4/6 inhibitors are approved for first-line treatment of HR-positive, HER2-negative metastatic breast cancer. Although they offer comparable therapeutic benefits, their safety profiles differ[1]. Diarrhoea, particularly grade I–II, is a common adverse effect, but severe colitis is extremely rare[1].

To date, we found only two published reports of palbociclib-associated colitis. Gomez et al. described a patient who developed abdominal pain, diarrhoea, and haematochezia after two months of treatment with letrozole and palbociclib. VC revealed ileocolonic ulcers, and histopathology showed nonspecific ileitis and colitis. The patient's condition resolved after treatment with prednisone and drug withdrawal[3]. Van Aken et al. reported a patient who developed severe enterocolitis after 2 months of palbociclib and letrozole, following concurrent pelvic radiotherapy; CT imaging showed swollen bowel loops. No histopathological diagnosis was reported[4]. In another case, Malik et al. described a patient on ribociclib who presented with gastrointestinal bleeding, pancolitis on CT scan, and colonic ulceration. Histopathology was consistent with colitis, and the patient improved with hydrocortisone[2].

In our case, the patient, who had previously experienced diarrhoea with abemaciclib, developed severe, persistent diarrhoea, weight loss, and hypoalbuminemia after switching to palbociclib, leading to hospitalization. Imaging and endoscopy revealed colitis with deep ulcers. A rectal biopsy showed chronic proctitis with increased apoptotic bodies.

The effects of CDK4/6 inhibitors on the gastrointestinal tract are not fully understood. Publications have primarily focused on abemaciclib, which is the CDK4/6 inhibitor most frequently associated with diarrhoea. Non-clinical studies suggest that diarrhoea is not due to the primary pharmacological activity (CDK4/6 inhibition) but to activity on secondary pharmacological targets[5]. Rats treated with abemaciclib showed a dose-related proliferative enteropathy in the small and large intestine[5]. Unlike the other drugs in this class, abemaciclib also targets CDK9, a crucial regulator of intestinal cell proliferation. CDK9 inhibition can potentially alter the glycogen synthase kinase-3β cascade, leading to intestinal toxicity. Furthermore, the activation of the Wnt/β-catenin pathway can contribute to cell proliferation and gastrointestinal toxicity. Lastly, abemaciclib inhibits Ca2+/calmodulin-dependent protein kinase, which plays a role in gut motility and may partially explain the increased bowel movements observed with abemaciclib, but not the proliferative effects observed in rats after abemaciclib treatment[5].

In our report, the histopathological changes were consistent with drug-induced inflammatory colitis with increased epithelial apoptosis, known as apoptotic colopathy[6-8]. Drug-induced mucosal injury associated with increased epithelial apoptosis was described with the administration of mycophenolate, immune checkpoint inhibitors, idelalisib, brentuximab, tumour necrosis factor α inhibitors (etanercept, infliximab), antimetabolites (methotrexate, capecitabine), non-steroidal anti-inflammatory drugs, sodium phosphate, taxanes and colchicine [6-9].

Our patient was successfully treated with oral budesonide (9 mg daily) for eight weeks, a therapeutic approach similar to that used for inflammatory bowel diseases like microscopic colitis[10]. This led to clinical, tomographic, and endoscopic improvement. She continued on fulvestrant monotherapy and remains free of colitis symptoms 6 months after discontinuing steroids. Given the resolution of symptoms after palbociclib withdrawal and the absence of other identifiable aetiologies, the diagnosis of drug-induced apoptotic colopathy secondary to palbociclib is highly suggested.

When asked for her perspective, the patient considered it important to report the side effects experienced during specific medical treatments, especially when such effects had not been previously documented or adequately communicated. She believes that promoting the dissemination of those experiences can contribute to scientific research, clinical practice, and the well-being of other patients who may then have the knowledge to recognize the origin of symptoms emerging during the course of therapy.

To our knowledge, this is the first report of palbociclib-induced colitis with increased epithelial apoptosis and also the first one successfully treated with oral budesonide.

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