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Case Report

Erlotinib Induced Ischemic Colitis

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Abstract

Ischemic Colitis (IC) is a clinical entity that includes all secondary lesions due to circulatory anoxia of the wall of the colon and/or rectum. This complication may occur in connection with the use of many drugs. Rare forms were described in combination with chemotherapy are rather secondary to neutropenia than to chemotherapy itself. Ischemic colitis induced by Erlotinib use is an exceptional form. We describe in this report a case of ischemic colitis during treatment with Erlotinib.

Introduction

Ischemic Colitis (IC) is a clinical entity that includes all secondary lesions due to circulatory anoxia of the wall of the colon and/or rectum. This complication may occur in connection with the use of many drugs. Rare forms were described in combination with chemotherapy are rather secondary to neutropenia than to chemotherapy itself. Ischemic colitis induced by Erlotinib use is an exceptional form. We describe in this report a case of ischemic colitis during treatment with Erlotinib.

Case Presentation

A 60 years old woman, with no history of smoking or particular digestive problems is followed for an initially metastatic lung adenocarcinoma. All conducted investigations confirmed the diagnosis of non small cells lung adenocarcinoma without activating mutations Epidermal Growth Factor (EGFR), Anaplastic Lymphoma Kinase (ALK) os Ras) and showed lymphangitis carcinomatosis, a metabolically active pleural and pericardial effusion as well as multiple bone metastasis.

The patient received successively following therapeutic lines

A first protocol by Carboplatin-Paclitaxel-Bevacizuamb showing after four cycles a partial response at the price of persistent peripheral neuropathy grade 2 of CTCAE.

Maintenance by Bevacizumab with progressive disease in bones and lungs after 8 cycles.

Pemetrexed as second line with stable disease for 13 cycles.

After disease progression Erlotinib has been started. One week after the patient was admitted to hospital for abdominal pain; mucoid-bloody diarrhea and fever. On admission a diffuse abdominal tenderness was noted. Laboratory tests were normal (amylase, lipase, liver function tests, and lactate). Toxins clostridium difficile were negative. Abdominal CT scan showed a consistent appearance with colitis (Figure 1, 2). Colonoscopy showed ischemic colitis (Figure 3) aspect confirmed by histological examination of biopsies. Therapeutic management consisted in stopping Erlotinib, intravenous hydration and analgesics. The evolution was rapidly favorable with amendment of the digestive symptoms after few days and almost completes healing of colonic lesions in the control colonoscopy performed after three weeks. Chemotherapy was continued by Vinorelbine and no recurrence of colitis was detected.

Discussion

There are three forms of Ischemic Colitis (IC) depending on the extent of tissue necrosis: non gangrenous transient and reversible acute IC (65%); acute gangrenous IC which includes irreversible damages and can lead to perforation (20%); IC stenosed which has a more pronounced necrosis leading to fibrosis (15%) [1]. The ICs are often multifactorial and two mechanisms of ischemic lesions are described: obstructive and hemodynamic. The most common mechanisms are hemodynamic non obstructive due to decreased blood flow. Physiopathological causes can be multiple (hypovolemic cardiac or septic shock, dehydration, drugs, cocaine, and prolonged physical effort). Less frequently, obstructive mechanisms are described with acute or chronic perturbation of macro or microcirculation [2]. The gastrointestinal toxicity of cancer drugs has long been known

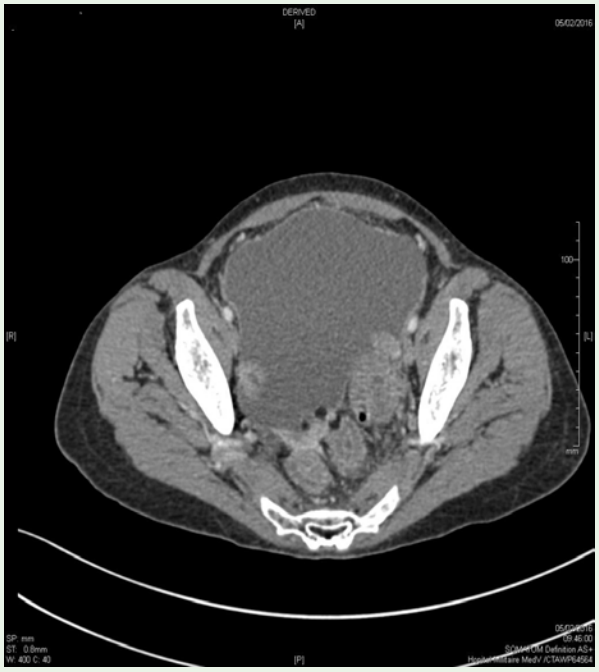

Figure 1: Coronal CT scan aspect of circumferential colorectal thickening with mucosa taking contrast and submucosal edema giving an aspect of target and infiltration of the adjacent fat.

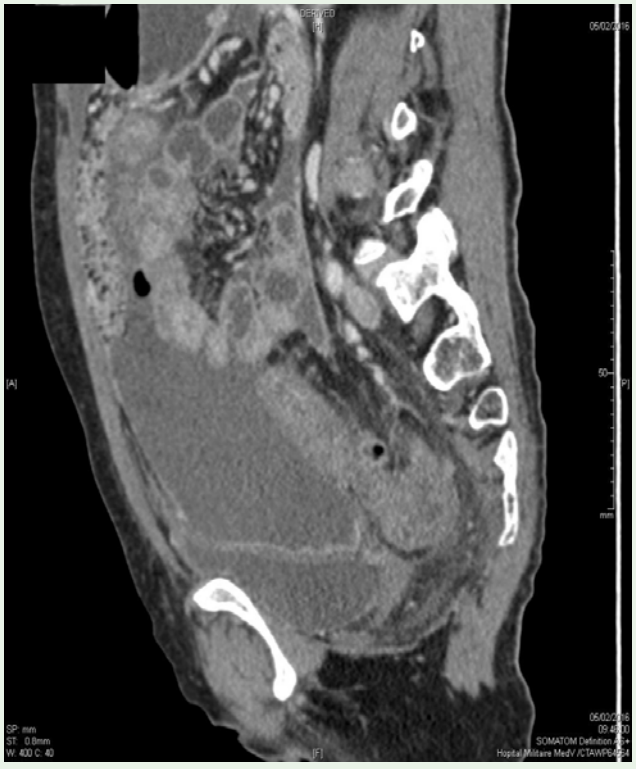

Figure 2: Sagittal CT scan aspect of circumferential colorectal thickening with mucosa taking contrast and submucosal edema giving an aspect of target and infiltration of the adjacent fat.

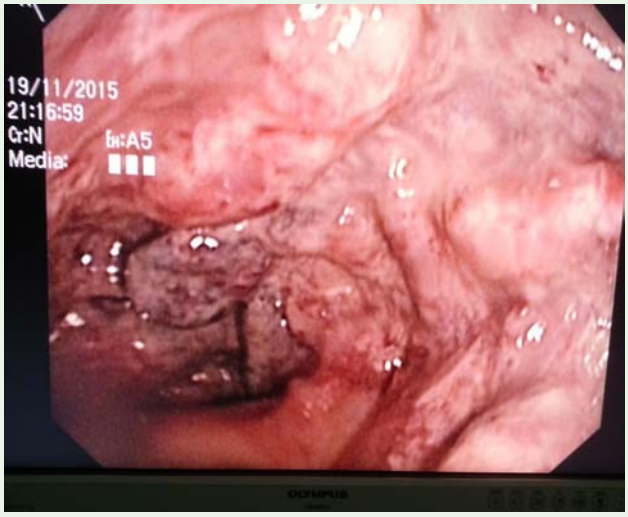

Figure 3: Endoscopic aspect of ischemic colitis with petechial hemorrhages, edematous and fragile mucosa, segmental erythema, scattered erosion and sharply defined segment of involvement.

and can take various forms. Several antimitotic agents have been implicated in development of IC. The clinical presentation and the pathophysiology of recent cancer drugs induced IC do not necessarily obeys to the classical neutropenic mechanism. Taxans induced pseudomembranous colitis have been described [3,4]. Description of colitis induced by other commonly used cytotoxic agents include reports of cases caused by vinorelbine [5], capecitabine [6] rituximab [7]. Colitis secondary to cancer immunotherapy have been described with sometimes severe forms resistant to steroids [8,9]. However an IC induced by Erlotinib remains exceptional and was only reported in some case-reports. [10,11] The pathophysiologic mechanism of this IC is not well known and not be related to direct toxicity of this molecule on the gastrointestinal mucosa as is assumed for the all diarrhea induced by erlotinib. Diarrhea can be a major cause of treatment discontinuation and of decreased drug efficacy because it represents a dose limiting toxic event. The pathophysiological mechanism of diarrhea induced by targeted therapies remains unclear [12]. EGFR is frequently overexpressed in gastrointestinal normal mucosa. There is evidence that EGFR is a negative regulator of chloride secretion [13]. EGFR inhibitors could, therefore, increase chloride secretion and thereby inducing secretory diarrhea. No correlation was observed between plasmatic exposure and diarrhea, whereas frequency of diarrhea is known to be dose-related [14]. These results suggest direct damage from erlotinib. In a phase II trial, 1 case out of 41 patients with vulval squamous cell carcinoma treated by Erlotinib developed IC [11].

Treatment of the patient is dictated by the severity of the ischemia. The absence of colonic gangrene or perforation, supportive care is appropriate (bowel rest, intravenous fluids, Empiric broad-spectrum antibiotics…). Approximately 20% of patients with ischemic colitis will require surgery because of peritonitis or clinical deterioration despite conservative management. Despite resection, the mortality rates exceed 50% in those with infracted bowel [15]. This highlights the need of collaboration with other medical specialties (e.g. surgeon) in order to avoid an unnecessary and possible lethal surgical procedure.

Conclusion

Given the increasingly frequent use of chemotherapeutic agents capable of causing colitis, clinicians and oncologists should be knowledgeable of this complex condition and its various pathogeneses, risk factors, and prognoses to enhance patient care.

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