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Case Report

Complete Response of an Iraqi Patient with Multiple Liver Metastasis, Colon Cancer and Deep Vein Thrombosis to XELOX/Bevacizumab Treatment

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Abstract

Background: The incidence of colon cancer is rising globally, and several therapeutic techniques, such as surgery, radiation, and systemic therapy, are used to control this illness. Patients with initially treatable metastatic colorectal cancer and unresectable metastases receive preoperative chemotherapy. In patients with rapidly progressing cancer, this strategy aims to shrink the tumor, manage any micro-metastases, and avoid liver surgery. ***Case presentation***: We present a rare case of an Iraqi patient with metastatic colon cancer and initially unresectable liver metastasis. The patient initially experienced a partial response to chemotherapy with capecitabine, oxaliplatin (XELOX), and Bevacizumab, but after a few days, we observed deep venous thrombosis (DVT). We stopped the oxaliplatin and administered Capecitabine with bevacizumab as a chemotherapy treatment, observing no adverse effects during the therapy period and achieving a complete response with Capecitabine and bevacizumab. ***Conclusions***: The full response in the liver and colon after treatment, which reduced the patients' treatment burden, was the case's unique result. Additionally, this study highlights deep vein thrombosis as a critical problem that can arise with the use of oxaliplatin.

Keywords: Bevacizumab, Colon cancer, DVT, Metastasis, XELOX.

استجابة كاملة لمريض عراقي مصاب بورم خبيث متعدد في الكبد وسرطان القولون وتجلط الأوردة العميقة لعلاج زيلوكس/بيفاسيزوماب

الخلاصة

الخلفية: يرتفع معدل الإصابة بسرطان القولون على مستوى العالم، وتستخدم العديد من التقنيات العلاجية، مثل الجراحة والإشعاع والعلاج الجهازي للسيطرة على هذا المرض. المرضى الذين يعانون من سرطان القولون والمستقيم النقيلي القابل للعلاج في البداية والنقائل غير القابلة للاستئصال يتلقون العلاج الكيميائي قبل الجراحة. في المرضى الذين يعانون من السرطان سريع التقدم، تهدف هذه الاستراتيجية إلى تقليص الورم، وإدارة أي نقائل دقيقة، وتجنب جراحة الكبد. **عرض الحالة**: نقدم حالة نادرة لمريض عراقي مصاب بسرطان القولون النقيلي وورم خبيث في الكبد غير قابل للاستئصال في البداية. عانى المريض في البداية من استجابة جزئية للعلاج الكيميائي باستخدام كابسيتابين وأوكساليبلاتين (زيلوكس) وبيفاسيزوماب، ولكن بعد بضعة أيام ، لاحظنا تجلط وريدي عميق. أوقفنا أوكساليبلاتين وتم استخدام كابسيتابين مع بيفاسيزوماب كعلاج كيميائي، ولم نلاحظ أي آثار ضارة خلال فترة العلاج وحققنا استجابة كاملة مع كابسيتابين و بيفاسيزوماب. **الاستنتاجات**: كانت الاستجابة الكاملة في الكبد والقولون بعد العلاج، والتي قللت من عبء علاج المريض، وهي النتيجة الفريدة للحالة. بالإضافة إلى ذلك، تسلط هذه الحالة الضوء على تجلط الأوردة العميقة كمشكلة حرجة يمكن أن تنشأ مع استخدام أوكساليبلاتين.

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INTRODUCTION

According to the WHO, in 2020, colon cancer will rank as the second most common cause of death. Colon cancer ranks as the third-most common type of cancer globally [1]. In Iraq, CRC prevalence and mortality are rising across all age groups [2]. The CRC mortality rate ascended from 1.25 to 1.77 deaths per 100,000 people in 2010 and 2019, respectively [3]. In recent years, there has been a significant advancement in (stage IV) colon cancer systemic chemotherapy treatment in addition to targeted therapy [4]. Although there is still controversy over the use of chemotherapy in patients with initially resectable metastatic CRC, the goals of this strategy include shrinking the tumor, managing any micro-metastases, and staying away from liver surgery in patients with quickly progressing cancer. After receiving multidrug chemotherapy, 13 percent of people whose metastases are initially unresectable can eventually be resectable. [5]. Patients with pathological complete remission have a better prognosis than those who do not [6]. Recently, adding monoclonal antibodies to cytotoxic chemotherapy has increased the rate of tumor response [7]. We report herein one of the rare cases of a mCRC Iraqi patient with

initially unresectable liver metastasis for which chemotherapy with XELOX/Bevacizumab resulted in a partial response initially, then a complete response with Capecitabine and Bevacizumab and we will discuss a rare incidence case with the most common sequela that was observed with the use of Oxaliplatin that is usually used with Capecitabine or 5-FU, which is DVT.

CASE PRESENTATION

A healthy 44-year-old woman was accidentally presented with abdominal pain. Colonoscopy showed that up until the ascending colon, there is a cauliflower mass circulating most of the lumen scope (Figure 1A). Histopathology tests showed adenocarcinoma of the colon (hepatic flexure) was moderately differentiated (Figure 1B).

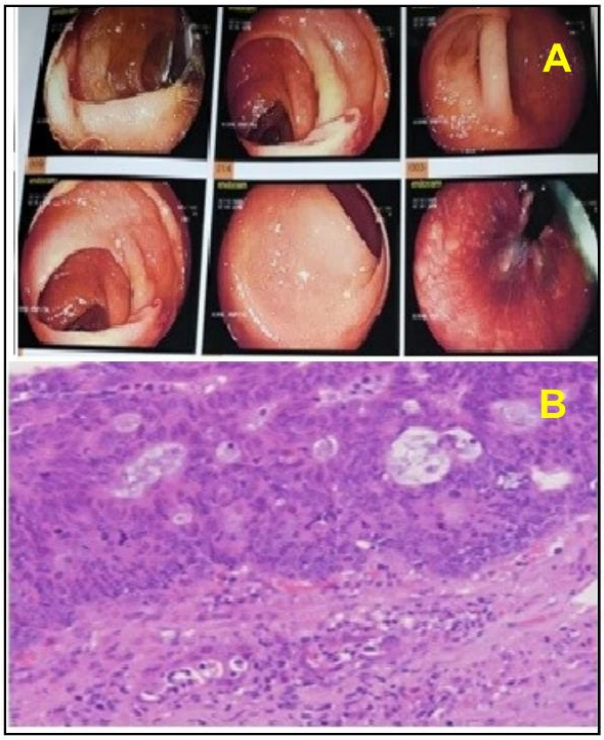

Figure 1: **A**) Colonoscopy showing a cauliflower mass circulating most of the lumen scope; **B**) Moderately differentiated adenocarcinoma of colorectal cancer by digital pathological imager at 40 times magnification.

A positron emission tomography (PET) scan showed circumferential thickening of the colon wall measuring 2.1 cm with local narrowing of the lumen (Figure 2A). There are two suspiciously enlarged lymph nodes near the lesion: one is 1.5*1.2 cm and the other is 1.9*1.2 cm. The appearance is suspicious of colon cancer. The ascending colon proximal to the lesion is slightly dilated, measuring 65 mm in diameter. The liver exhibits numerous hypodense areas in both lobes, the largest of which measures 4.0* 4.0 cm. This appearance is consistent with liver metastasis (Figure 2B). The level of carcinoembryonic antigen (CEA) was 4.2 ng/ml; (0.0 to 5.0) ng/ml is considered normal. We also reported a complete blood count (CBC), plasma electrolyte levels, coagulation tests, kidney and liver function assessments, and a urinalysis as normal. The Eastern Cooperative Oncology Group's (ECOG) performance status was zero. She has no family history of cancer.

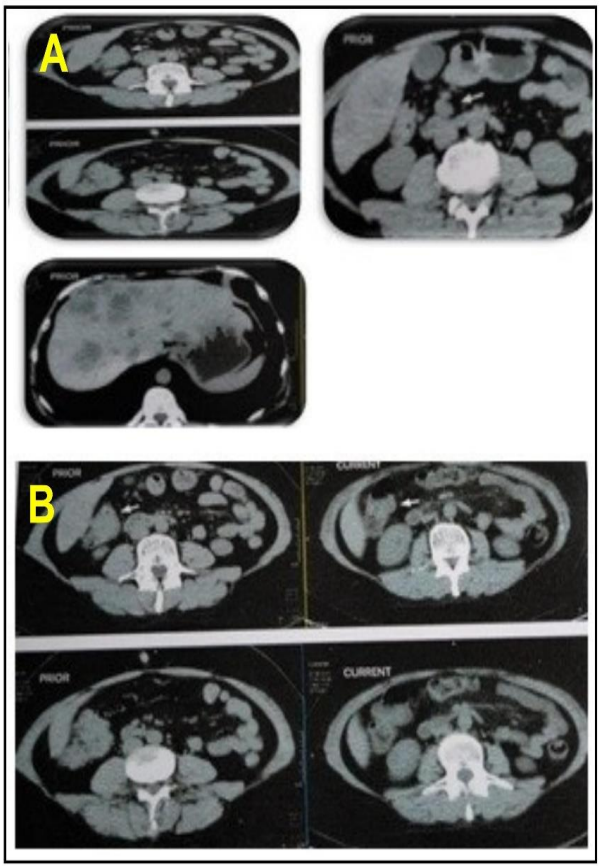

Figure 2: **A**) Positron emission tomography (PET) scan before neoadjuvant chemotherapy; **B**) PET scan showing partial favorable therapy response reduction in size extent of primary lesion in hepatic flexure of colon.

Immunohistochemical analysis of four mismatch-repair genes' (MLH1, MSH2, MSH6 and PMS2) showed a positive result. , Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome (Lynch syndrome) is one of the things that can lead to colon cancer. It is caused by changes in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes. Examining tumor tissue revealed the presence of a predominant somatic mutation. We identified only one mutation in the Exon 2 KRAS gene. A) In the hepatic flexure segment, the colon wall thickened; B) There were two suspiciously enlarged lymph nodes near the lesion; and C) There were numerous hypodense areas in both lobes. The multidisciplinary team chose to initiate chemotherapy with XELOX/bevacizumab. Every 21 days, the patient initially received 5 cycles of oral capecitabine plus IV oxaliplatin (XELOX) and bevacizumab (Table 1).

Table 1: Patient's Treatment Protocol

Drug	Dosage	Route	Frequency	Diluent and Rate
Oxaliplatin	130 mg/m^2	IV	Every 21 days	500 ml Glucose 5% infusion over 2 hours
Capecitabine	1000 mg/m^2 BD	PO	Every 21 days	Twice daily, morning and evening for 14 days followed by 7 days off.
Bevacizumab	7.5 mg/kg	IV	Every 21 days	500 ml sodium chloride 0.9% infusion over 1 hour

We saw a big change in the liver metastasis after the fifth cycle of XELOX and bevacizumab using a PET scan. This was based on the Response Evaluation Criteria in Solid Tumors (RECIST). Overall features indicate a partially favorable therapy response in the colon's hepatic flexure. The lesion measures approximately 2.3 cm in length (previously 3.9 cm) and has a maximum wall thickness of 1.6 cm (previously 2.1 cm) (Figure 2B). The largest possible metastatic peri-lesion and pericolic lymph nodes are now 0.8*1.4 cm (they used to be 1.9*1.2 cm) (Figure 3A), and the largest residual lesion in liver segments IV and VI is now 2.4*2.4 cm (it used to be 4.0*4.0 cm) (Figure 3B).

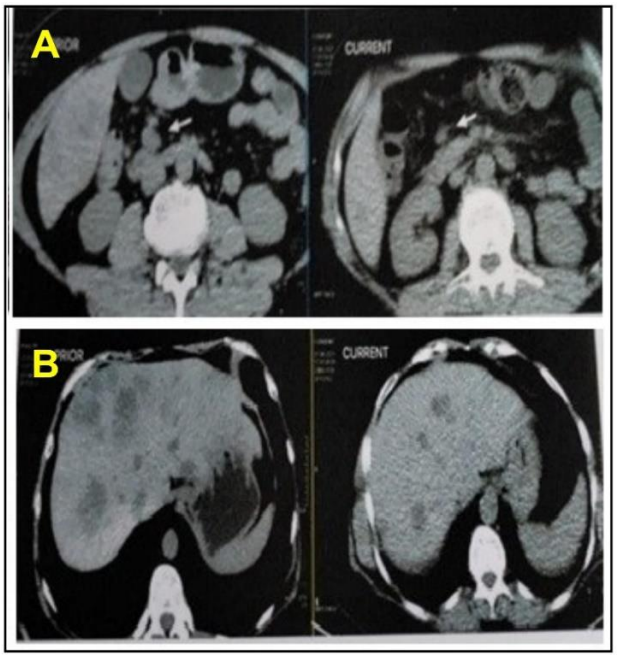

Figure 3: **A**) PET scan showing reduction in size of metastatic peri-lesion pericolic lymph nodes; **B**) PET scan showing remission of hypodense areas in both lobes with low grade residual tumor activity.

Ten days into the fifth cycle of chemotherapy, the patient complained of swelling and severe pain in the left lower limb. Doppler ultrasound showed deep vein thrombosis; DVT findings suggest 20% blood flow insufficiency. The patient received a therapeutic dose of low molecular weight heparin (LMWH) S.C. Due to the patient's DVT, the physician decided to add an additional 3 cycles of capecitabine. However, after these three cycles, the patient's CEA was 6.7, prompting the physician to initiate another 6 cycles of capecitabine and bevacizumab. Following a reassessment, we used PET to document the response of the liver metastases after 6 months of therapy. The results showed an overall excellent therapy response, stable disease, residual ill-defined hypodense lesions in both liver lobes, and a CEA of 2.3. A repeat of the Doppler ultrasound revealed a stable case with 10% blood flow insufficiency. The patient underwent a right hemicolectomy, surgical resection, and a liver biopsy. At present, the patient's CEA stands at 0.95 U/ml, all other investigations are normal, and the PET scan shows a remission of the disease, with no recurrent disease (Figure 4A), resolution of all previously observed hypodense areas in the liver (Figure 4B), and no evidence of other pathological hypermetabolic lesions in the rest of the body (Figures 5A and B).

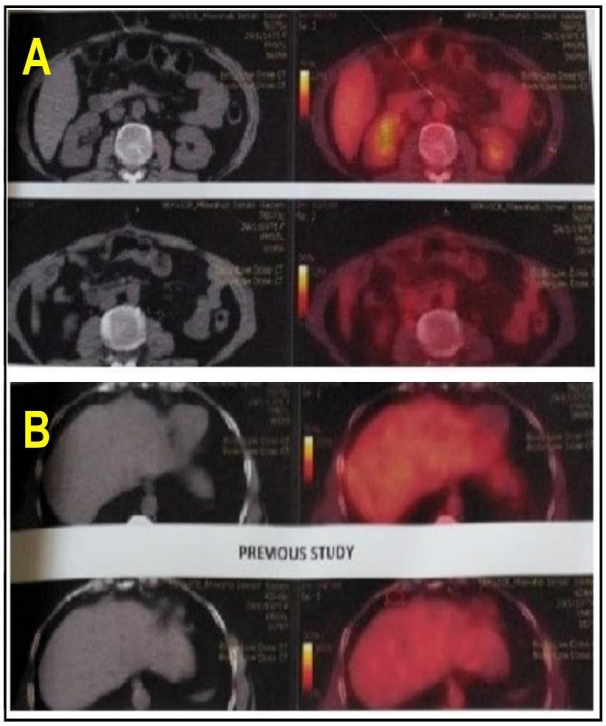

Figure 4: **A**) PET scan showing disease remission with no evidence of hypermetabolic pathological abdominal lymph nodes; **B**) Positron emission tomography (PET) scan showing resolution of all previously seen hypodense area in liver.

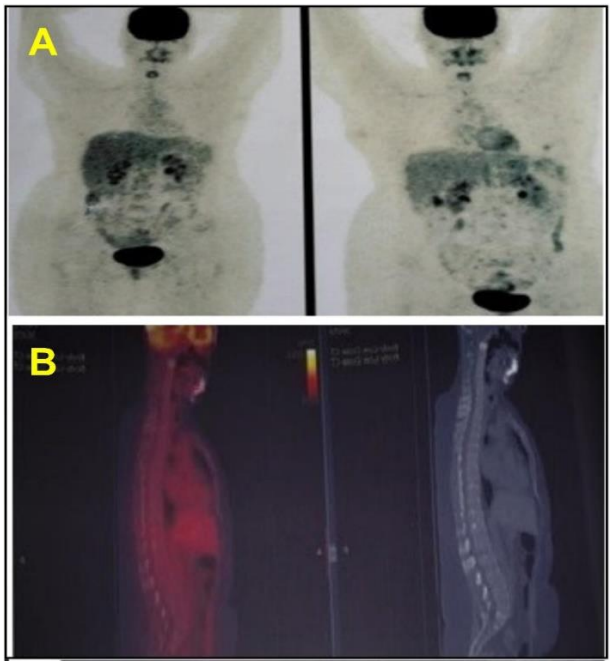

Figure 5: PET scan showing no evidence of other pathological hypermetabolic lesion in the rest of the whole-body, **A**) Previous, **B**) Current.

After surgery, the patient will continue on capecitabine and bevacizumab to prevent the recurrence of the tumor for up to 22 months. The patient is stable.

DISCUSSION

Optimal systemic and localized chemotherapeutic, biological, and radiotherapies for unresectable patients

increase survival and may make previously unresectable patients resectable [9]. The use of highly effective chemotherapy regimens in patients with liver metastasis and colon cancer has resulted in an increased frequency of complete response and is associated with a higher survival rate [10]. Few cases documented the use of Oxaliplatin with Capecitabine. In one such case, XELOX managed a 50-year-old Caucasian patient with mCRC who noticed temporary haziness and impaired vision in his right eye, a condition he had not previously reported and later discovered. Five days after the second cycle of chemotherapy, retinal vein thrombosis began. Another case involved a 75-year-old man who had liver metastasis (CRC). The patient received capecitabine, oxaliplatin, and bevacizumab; however, the treatment was stopped in the midst of the second session due to oxaliplatin-related DVT [12]. The phase 3 CAIRO3 research revealed that patients with metastatic colorectal cancer (mCRC) benefit from an effective maintenance treatment of capecitabine with bevacizumab (CAP-B) without affecting quality of life. [13]. Previous metastatic colon cancer cases, including those involving the liver, lymph node metastases, bone, urinary system, lung, and various other conditions, also responded effectively to bevacizumab treatment [14,15]. Bevacizumab use may increase the risk of arterial thromboembolism in older individuals [16]. Capecitabine may cause systemic toxicity, including neutropenia, stomatitis, and diarrhea and hand-foot syndrome, which may need a dosage adjustment or stop depending on the grade [17]. One of the most common adverse effects of oxaliplatin is peripheral neuropathy: hyperesthesia, while documented cases of thrombotic thrombocytopenic purpura (TTP) are rare [18]. While cancer is a hypercoagulable condition associated with a 7-fold increase in venous thromboembolism, its association with arterial thromboembolism (ATE) is less clear [19]. We treated our patient, who had no prior history of vascular illness, with Bevacizumab, Oxaliplatin, and Capecitabine. Overall features indicated a partial favorable therapy response, but DVT symptoms developed after the fifth cycle of treatment. Using biological medicines like bevacizumab in conjunction with doublet chemotherapy regimens has demonstrated the ability to increase patients' progression-free survival (PFS), decrease their treatment burden, and maintain a successful treatment outcome [20]. Thrombosis linked to oxaliplatin use is a problem with long-term therapy in individuals with CRC. The results of this case study show that treatment with capecitabine and bevacizumab is at least as effective as bevacizumab and XELOX in reducing treatment burden and achieving a significant complete response to therapy. This further supports the effectiveness of the maintenance therapy, capecitabine plus bevacizumab (CAP-B). This case presented a unique problem because the patient was unable to obtain oxaliplatin for more than five months due to the DVT side effect. Therefore, the physicians felt obliged to change the course of treatment from oxaliplatin to capecitabine and bevacizumab. The patient could afford the treatment. It's fascinating that the patient remained stable for as long as 22 months. These results show how important it is for people with CRC who have metastases in the liver to take Capecitabine and Bevacizumab by mouth together to avoid serious side effects and get long-term disease control.

Conclusion

In our case study, there was a significant full response to treatment with bevacizumab and capecitabine, resulting in long-term disease control. This provides more evidence in favor of the use of capecitabine and bevacizumab (CAP-B) maintenance therapy in metastatic CRC. The development of a full response in the liver after treatment, which reduced the patients' treatment burden, was the case's unique result. Additionally, by highlighting this case with such an uncommon complication, we hope to raise awareness of these ischemia symptoms within the medical field and among patients, while encouraging them to be more aware of any vascular symptoms that their patients may experience.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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