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Two Cases of Colon Cancer Patients Who Were Treated with Cetuximab and Presented with Superior Vena Cava Syndrome

Bala Basak Oven Ustaalioglu[1,*], Recep Ustaalioglu MD[2], Mehmet Yildirim[2]

[1]Medical Oncology, Haydarpasa Numune Educatio and Research Hospital
[2]ThoracicSurgery Siyami Ersek Education and Research Hospital, Istanbul, Turkey
*Corresponding author: basakoven@yahoo.com

Abstract **Objectives:** Venous port catheter has been currently used in chemotherapy especially for colon cancer patients. Venous thrombosis related with venous device is frequently reported but superior vena cava syndrome(svc) with high mortality rate is rarely seen as a port catheter related thrombosis. Cetuximab which has been used in metastatic colon cancer is an anti-EGFR agent has shown to be risk factor for venous thromboembolic events. **Patients:** Inhere we reported 2 metastatic colon cancer patients who had been treated with chemotherapy combined with cetuximab via venous port catheter. Svc was detected in both of them during therapy with cetuximab. None of them had any co-morbidity or tendency for thrombosis. Cetuximab is thought to be increase thrombosis and may cause the svc syndrome. **Conclusion:** When metastatic colon cancer patients presented with redness and swelling of face while they receiving cetuximab via venous port catheter, other than allergic reaction, **s**uperior vena cava syndrome also should keep in mind.

Keywords: *superior vena cava syndrome, port catheter, cetuximab, thrombosis, cancer*

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1. Introduction

Cancer patients tend to acquire thromboembolic conditions that increase mortality and morbidity [1]. Cancer patients have several nonspecific risk factors for thrombosis, such as age, histopathological type of cancer, bed rest and chemotherapy type [2]. Venous thrombosis has been reported in 4%–20% of cancer patients [3]. Deep venous thrombosis, pulmonary embolism and superficial thrombophlebitis are the most often seen events in cancer patients; catheter-related thrombosis is also seen frequently [1].

Venous access port systems have been used in chemotherapy since 1982 [4]. The central venous route is useful for cancer patients because it avoids venous toxicity and allows patients daily activity [4]. The subcutaneously inserted venous port is standard to obtain long-term venous access for continuous chemotherapy infusion without hospitalization [5]. Jugular or subclavian veins have been used generally for port catheter insertion [5]. Although central venous port systems have a lower risk of complications, infection, catheter fracture, thrombosis or extravasation can be reported [4,6]. The aetiology of port catheter thrombosis may be endothelial injury caused by chronic mechanical trauma or chemotherapy toxicity [4]. Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select, high-risk patients [7]. Prophylactic low-molecular-weight heparin (LMWH) after 6 weeks of catheter insertion did not reduce the risk of deep venous thrombosis [2].

Drug exposure can increase the risk of thromboembolism. There is limited knowledge about the risk of thromboembolism for anticancer drugs. An anti-EGFR (epithelial growth factor) agent was shown to be a risk factor for venous thromboembolic events (VTE) [1]. Cetuximab is an anti-EGFR monoclonal antibody that binds to the extracellular part of EGFR and inhibits EGFR signalling activity [9]. It was shown to be effective in the treatment of several lines of metastatic colorectal cancer, which were of the RAS wild type, with or without the combination oxaliplatin or irinotecan-based regimen [8,9].

Superior vena cava (svc) syndrome is characterised by stenosis or occlusion of the svc with venous outflow obstruction of the head and upper extremities [10]. The main causes of this syndrome are malignancies, mediastinal fibrosis, an indwelling catheter of the svc or pacemaker wires [10]. Central venous catheter occlusion was reported as 2%–4%, but symptomatic svc syndrome related to a central venous catheter are not common. Upper limp, facial oedema, shoulder and neck pain, dyspnea, dizziness, blurred vision and chest pain are the symptoms of svc syndrome [11]. Port catheter thrombosis presenting with svc syndrome has been reported in a few case studies in the literature. Here we reported two cases of metastatic colon cancer treated with FOLFIRI-cetuximab

by continuous infusion via a central venous port catheter presenting with svc syndrome due to port catheter thrombosis.

2. Cases

Case 1: A 55-year-old man was referred to the Department of Thoracic Surgery because of swelling in the face and upper half of the body, discoloration of the trunk, cyanosis and plethora in December 2014. He complained of headaches, redness and swelling of his eyes, dizziness and dyspnea. Colon carcinoma with multiple liver metastasis was diagnosed in August 2014. Colonoscopic biopsy revealed RAS wild-type adenocarcinoma grade 2 in the transverse colon. After left subclavian port catheter insertion, FOLFIRI-cetuximab (after induction of 400 mg/m^2 cetuximab, 250 mg/m^2 weekly combined with 180 mg/m^2 irinotecan, 200 mg/m^2 calcium leucovorin and 400 mg/m^2 5-Fluorouracil (5FU) iv bolus, continuing with a 46-h infusion of 5FU 2600 mg/m^2 for 2-week cycles) was administered for 4 months. Other than grade 2 hand-foot syndrome, he tolerated this regimen well. He had no history of chronic disease, smoking or drug usage. After thoracic computerized tomography (CT) was performed, thrombosis, which caused complete obstruction of the lumen of the svc, was detected. CT revealed signs of venous collateralization. The patient was treated with LMWH, and the port catheter was immediately surgically removed under local anaesthesia. After he was discharged a week later, symptoms began to resolve, step-by-step, over 1 month. The patient continued his therapy with iv irinotecan and cetuximab combined with LMWH for 15 months until progression.

Case 2: A 73-year-old woman presented to the emergency room with dyspnea and swelling of the face, neck and upper trunk in August 2016. Physical examination revealed a purple-coloured face with watery eyes and significant collaterals in the upper trunk. Laboratory findings were normal except for prerenal azotaemia. A thoracic CT without contrast in the emergency room did not reveal any abnormalities and an allergic reaction was suspected. Despite antihistaminic and steroid therapy, the patient's symptoms progressed and she was admitted to the Department of Thoracic Surgery with a diagnosis of svc syndrome. She underwent right colon resection in January 2015 for colon cancer and received 12 cycles of a FOLFOX regimen for stage III disease. During follow up, liver metastasis and pelvic implants were detected in February 2016 and RAS analysis revealed a wild-type tumour. FOLFIRI-cetuximab was applied for 9 cycles after a right jugular venous port was placed. When thoracic CT angiography was performed, svc thrombosis was detected (Figure 1). The port catheter was removed surgically, and LMWH was started immediately. Chemotherapy with cetuximab and irinotecan was continued.

3. Discussion

Port system thrombosis is a serious complication that causes morbidity and interrupts the infusion of chemotherapy [12]. Although many cases are asymptomatic, catheter-related thrombosis (CRT) can cause serious morbidity, including pulmonary embolism [12]. Catheter- related thrombosis was reported in 4.3% of cancer patients in another prospective study (19 of 444 cancer patients) [12]. Eleven percent of the 444 catheter-related thrombosis cases were patients with colorectal cancer, and they did not report any life-threatening symptoms. Furthermore, they did not mention a relationship with chemotherapy type or frequency of catheter thrombosis. Here we reported on two metastatic colon cancer patients with port thrombosis who presented with life-threatening svc syndrome. Both had received cetuximab combined with FOLFIRI and had no known comorbidities, which regiment might be a tendency for thromboembolism.

Ma et al. reviewed the complications of port catheterization in 2996 breast cancer patients [4]. The most common complication was fibrin formation (1.84%), followed by bacteraemia (1.44%) and deep venous thrombosis (0.63%). Although deep venous thrombosis was reported, only eight ports required removal; also, no svc syndrome was seen among them. Yukisawa et al. prospectively reviewed 92 port catheters of colorectal cancer patients with respect to thrombosis by USG and detected 10 (11%) with venous obstruction needing anticoagulation therapy [13].

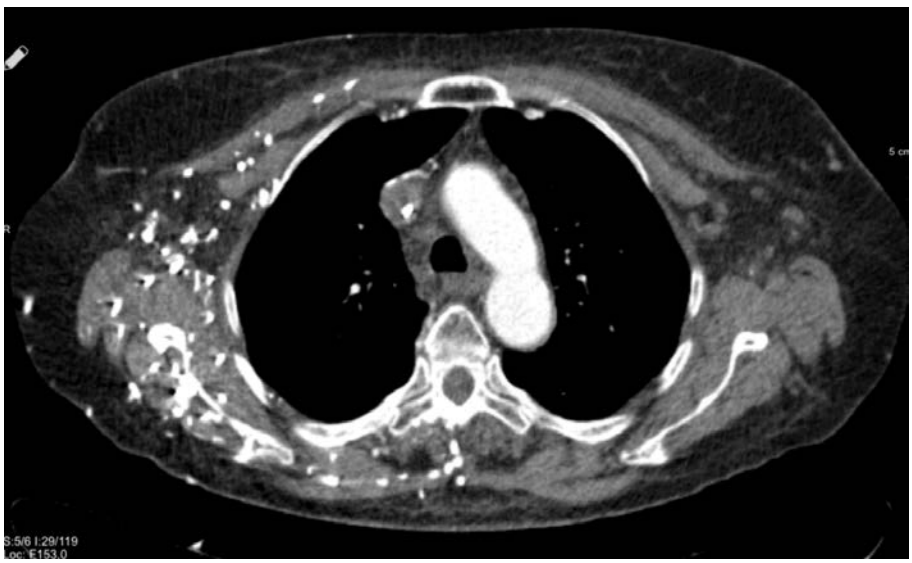

Figure 1. Computarized Tomography image of the patient with superior vena cava syndrome

Although venous thrombosis is an important complication of venous catheterization, symptomatic patients, especially those with central venous thrombosis causing svc syndrome among cancer patients are uncommon, and only few case reports exist [14,15,16]. Dağdelen reported thrombotic occlusion of the entire svc after placement of the subclavian vein port [15]. The patient had metastatic gastric cancer and the aetiology of the thrombosis may be cancer related. Both of our patients had limited liver metastatic colon cancer without any comorbidity or drug usage that might have caused thromboembolism.

Miroddi et al. analysed 15 randomized clinical trials to evaluate the thromboembolism risk of anti-EGFR. Four of them included metastatic colon cancer that was treated with cetuximab [1]. Regimens including cetuximab were shown to be associated with a higher risk of venous thromboembolism compared with chemotherapy not combined with anti-EGFR [1]. In this study, pulmonary embolism and venous thromboembolism were reported as thromboembolic events, but svc syndrome was not. Petrelli et al. carried out a meta-analysis to determine the risk of both venous and arterial thromboembolism associated with an anti-EGFR agent [17]. The incidence of venous thromboembolism was higher in patients receiving anti-EGFR monoclonal antibody (5.9% vs 3.7%) compared with the control arm [17]. There is no information about the aetiology of catheter-related venous thromboembolism. Several causes can predispose to port thrombosis in cancer patients, such as the hypercoagulability state, chemotherapy type, trauma, surgery and age. However, anti-EGFR monoclonal antibody has been shown as a risk factor for venous thromboembolism. Therefore, clinicians should keep in mind the increased risk of life-threatening thromboembolism presenting with svc syndrome while adding cetuximab to chemotherapy so that antithrombotic prophylaxis might benefit patients at high risk.

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