



Deep vein and artery thrombosis associated with cetuximab-based chemoradiotherapy

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Abstract

Molecular targeted agents have lower hematological toxicity. However, specific side-effects such as allergic rashes, skin reactions and high cost limit their use. We report a case of 35-year-old male patient with carcinoma of left tonsil treated with concurrent cetuximab and radiotherapy. After four weeks of treatment, the patient developed sudden onset of pain in the left calf region radiating to the left foot. Doppler study of the left lower limb revealed complete thrombosis of superficial femoral, popliteal and proximal tibial arteries and veins and no flow in anterior tibial artery and lower posterior tibial artery. Emergency embolectomy was done. After 48 h of observation, no improvement was noted. A repeat Doppler examination showed similar finding. Ultimately a left lower limb amputation was done. We report simultaneous arterio-venous thrombosis associated with cetuximab-based chemoradiotherapy. Oncologists should be aware of this possible complication to undertake early intervention.

Keywords: Cetuximab, chemoradiotherapy, thrombosis

Introduction

An increasing evidence supports the concomitant use of cetuximab (a monoclonal antibody against the epidermal growth factor receptor [EGFR]), along with high-dose radiotherapy in the primary treatment of head and neck cancer.[1] When compared to conventional chemotherapy, molecularly targeted agents have lower hematological toxicity. However, their therapeutic use is limited because of side-effects such as allergic rashes and skin reactions that may have a serious bearing on the patient's compliance.[2]

Solid tumors often express epidermal growth factor receptor (EGFR). Therapy aimed at targeting the EGFR-mediated signalling pathway has become a routine practice in the treatment of lung, pancreatic, head and neck, and colon carcinomas.[1] US FDA has approved cetuximab for metastatic colorectal carcinoma and more recently for head and neck squamous cell carcinoma. Although the safety profile for this drug is unique, with virtually no hematological toxicity, frequent cutaneous side-effects associated with its use may cause serious discomfort.[1,3]

Case Report

We report a case of 35-year-old male presented to the outpatient department of Radiotherapy, CSSMU, Lucknow with chief complaints of sore throat and dysphagia for one month. On clinical examination, there was no palpable neck node. On oral cavity examination, an ulceroproliferative growth was visible over the left tonsil. On palpation, it was found to be extending up to the base of the tongue. On video laryngoscopy, extensive growth involving left tonsil, tonsil lingual sulcus extending to the base of tongue was seen. His routine hematological/biochemical investigations, blood sugar and X-ray of chest were normal. There was no history of smoking and recent trauma /surgery. Complete coagulation profile including the PT, aPTT, and international normalized ratio (INR) were found to be normal. After detailed workup, the disease was staged as carcinoma of left tonsil.

After obtaining informed written consent for treatment, the patient was planned for radical dose of radiotherapy concurrently with weekly cetuximab therapy. The dose of cetuximab administered was 400 mg/m² in the first week followed by 250 mg/m² weekly thereafter.[1] Radiotherapy was planned for a dose of 70Gy in 35# @200cGy/#; 5#/week by parallel and opposing lateral fields to the whole neck and primary with sparing of cord after 46Gy. From the second week onwards, the patient developed skin reactions on the cheek. After receiving four doses of cetuximab and 40Gy of radiation, the patient developed sudden onset of pain in the left calf region which was found to radiate to the left foot. There was loss of sensation below the ankle joint. Color Doppler study of the left lower limb revealed complete thrombosis of lower superficial femoral, popliteal and proximal tibial arteries and veins with few collateral channels and no flow in anterior tibial artery and lower posterior tibial artery [Figure 1a–c]. The tests for antiphospholipid antibodies were negative. Emergency embolectomy was done and low molecular weight heparin was started and the patient was put under observation for 48 h. No improvement was observed after 48 h. There was a change in the color of the skin of the foot [Figure 2]. A repeat color Doppler examination showed complete thrombosis of lower superficial femoral, popliteal and proximal half of posterior tibial arteries and veins with few collateral channels and no flow in anterior tibial artery and lower posterior tibial artery. The patient had to ultimately undergo a left lower limb amputation. After three weeks of radiation therapy break, treatment was restarted with radiotherapy alone, omitting concurrent cetuximab. On first follow up, at six weeks after completion of radiotherapy, the patient was disease free at local site.

Discussion

Cetuximab, a humanized monoclonal antibody, is approved for the treatment of advanced colorectal carcinoma and squamous cell carcinoma of head and neck. It acts by binding and blocking the EGFR protein on the surface of the cancer cells.[1] The resultant blocking of phosphorylation and activation of receptor-associated kinases result in the inhibition of cell growth, induction of apoptosis, and decreased vascular endothelial growth factor production.[4] VEGF is a major endothelial mitogen and its antagonism leads to a decrease in the renewal capacity of endothelial cells in response to trauma.[5] This causes endothelial dysfunction and defects in the interior vascular lining, exposing subendothelial collagen, causing a decreased matrix deposition in the supporting layers of vessels.[6] Therefore, there is not only an increased tendency to bleed, due to decreased renewal capacity of endothelial cells, but also an increased frequency of thrombotic events, as a result of tissue factor secondary to the exposure of the subendothelial collagen. Cetuximab EGFR/HER monoclonal antibodies possess antiangiogenic activity or inhibit angiogenesis as a secondary function.[7]

Thromboembolic phenomena in cancer patients have a multifactorial pathogenesis. Both local and (endothelial lesions) systemic factors (coagulation abnormalities) are involved. Malignancy in itself is an important risk factor for thrombosis. Several genetic risk factors for thrombophilia have been described and they occur in 40% patients with recurrent venous thrombosis. The most common genetic defect is the factor V leiden mutation which interferes with cleavage and inactivation of factor Va thus reducing the clearance and increasing risk of thrombus formation by several folds. Another common thrombophilic mutation is Prothrombin G20210A mutation which causes coagulation disturbances in both arterial and venous system.[8]

Bonner *et al.*, compared radiotherapy with radiotherapy plus cetuximab in the treatment of advanced squamous-cell carcinoma of the head and neck and had not reported any thromboembolic event.[1] There have been reports of cetuximab being associated with hypomagnesemia and dehydration. Hypomagnesemia causes muscle weakness and lethargy which may predispose to thrombosis and dehydration is a known predisposing factor for thrombosis. The onset of dyselectrolytemia and its associated complications occur days to months after initiation of cetuximab. Therefore, patients need to be monitored periodically for hypomagnesemia, hypocalcemia and hypokalemia, during and for at least eight weeks following the completion of cetuximab.[9] There have been reports of cetuximab-induced thrombotic thrombocytopenic purpura in head and neck malignancy. Out of the 7,589 people reported to have side effects when taking Erbitux, 60 people (0.79%) have had thrombosis. The majority of thrombosis (69.57%) had occurred within one month of its administration.[10] There is also an increased incidence of thrombosis with Panitumumab, an anti EGFR receptor antibody.[11]

However, to the best of our knowledge, there is no documented case of simultaneous deep artery and vein thrombosis with the concurrent use of cetuximab with radiotherapy. With the increasing use of cetuximab in head and neck cancer patients along with radiotherapy, this previously unreported finding is important. Pre-therapy coagulation profile should be done in patients being planned for concurrent cetuximab and radiotherapy. Oncologists should also be aware of this possible complication so that early recognition and intervention can be undertaken.

Footnotes

Source of Support: Nil.

Conflict of Interest: None declared.

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Figures and Tables

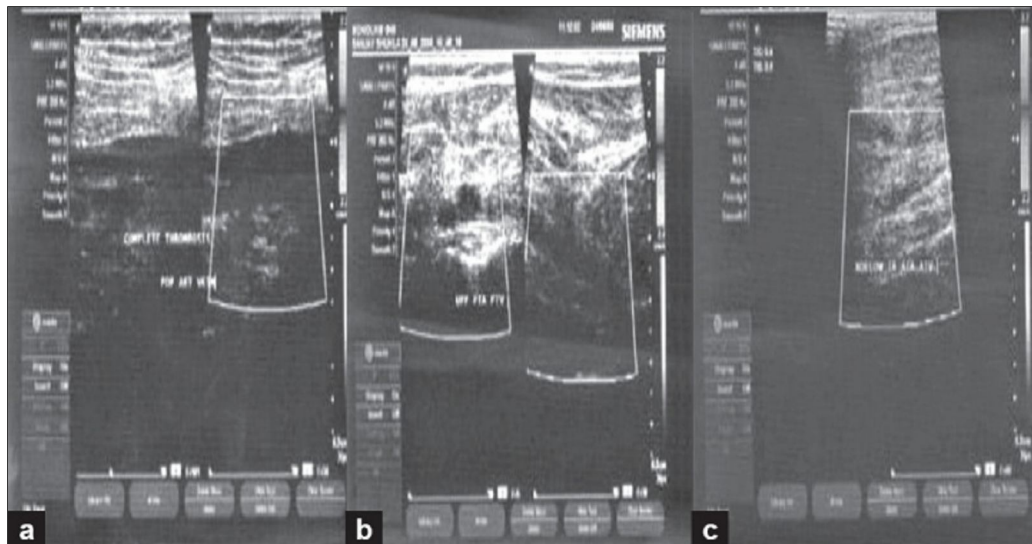


Figure 1

a) Color Doppler showing complete thrombosis of popliteal arteries and veins. b) Complete thrombosis of proximal tibial arteries and veins with few collateral channels. c) No flow in anterior tibial artery and veins



Figure 2

Acneform rash evident on the patient's face. Also seen are the color changes in the foot