



## Adverse drug reaction of Ramucirumab in patients with gastroesophageal junction cancer

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### Abstract

Ramucirumab is the first recombinant human IgG1 monoclonal antibody developed for the treatment of solid cancers and is given as a single drug. Studies have demonstrated that it has survival benefits in patients with advanced gastric or gastro esophageal junction (GEJ) adeno-carcinoma progressing after first-line chemotherapy. Common side effects of Inj. Ramucirumab include Diarrhea, Epistaxis, leucopenia, hypertension or lethargy/malaise. Detailed case reports on adverse drug reactions of Inj. Ramucirumab are lacking, and we hereby present a case report of a patient with GEJ cancer who developed symptoms that mimicked cardiac toxicity immediately after starting Inj. Ramucirumab.

**Keywords:** Ramucirumab, Ramucirumab induced hypersensitivity, Ramucirumab and Cardio toxicity, Ramucirumab and thrombo-embolic disease.

### Introduction

Incidences of arterial thrombosis (1.7%) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia are reported in patients on management with Inj. Ramucirumab. Others common side effects include diarrhea, Epistaxis, Leucopenia, hypertension or fatigue.

Ramucirumab in combination with FOLFIRI (Irinotecan, Folinic acid and 5-FluoroUracil) is indicated in the treatment of metastatic colorectal cancer (mCRC) with disease progression, or after prior therapy with Bevacizumab, Oxaliplatin, and Fluoropyrimidine.

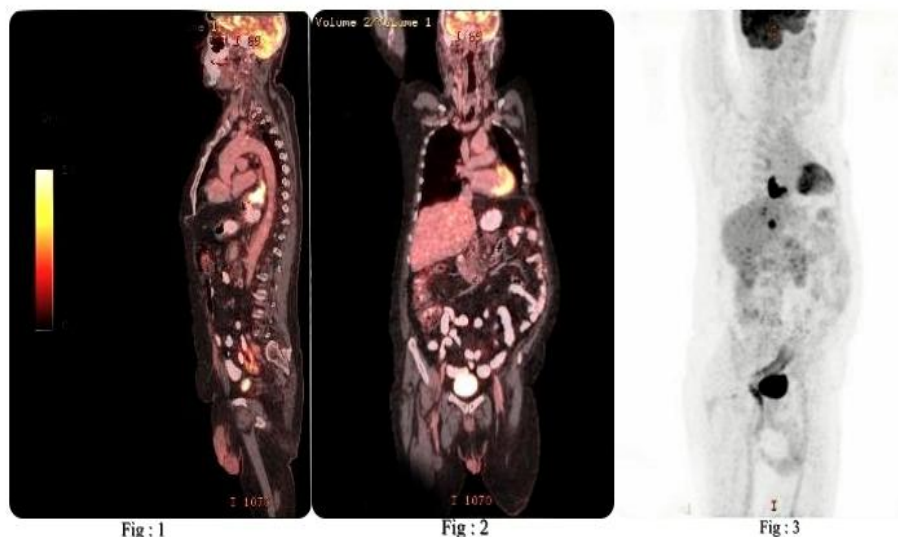
We hereby report a rare case of 77 years old gentleman, previously diagnosed and a treated case of GEJ cancer. He developed symptoms that mimicked myocardial infarction immediately after starting Inj. Ramucirumab. Hence we recommend a complete cardiac evaluation before initiation of such drug to avoid any future complications.

### Case Report

A 77 years old, normotensive and diabetic patient was electively admitted for chemotherapy with Inj. Ramucirumab and Inj. Paclitaxel for gastro-esophageal (GEJ) carcinoma with metastasis to regional lymph nodes and liver.

Earlier PET CT (Fig: 1-3) had revealed metabolically active lesions in distal esophagus, GE junction, stomach (cardia), para-esophageal lymph nodes (LN) and liver. He was treated with FOLFOX-V1 (5-FU, Leucovorin, Oxaliplatin) chemotherapy regime twice weekly for 6 weeks. Surveillance CT scan after 4 months revealed interval disease progression, peritoneal carcinomatosis and a 1cm nodule in the right abdominal wall. Thereafter he was further started

on Inj. Irinotecan and 5 FU based chemotherapy for 4 cycles and was now planned for chemotherapy with Inj. Ramucirumab and Inj. Paclitaxel.



***PET CT (Fig 1-3) - active lesions in distal esophagus, GE junction & cardia of stomach, Para- Esophageal LN and liver***

He was diagnosed to have carcinoma sigmoid colon in 1993, for which he had undergone anterior resection with end-to-end anastomosis in 1994. Serial CT from 1994 to 1998 showed no significant disease progression. However, in 1999 CT scan revealed liver metastasis, for which he had to undergo left lateral hepatectomy, and biopsy was reported as adeno-carcinoma.

Surveillance CT scan in 2012 and 2013 showed no recurrence of disease, although PET CT in 2014-revealed a hyper metabolic thick walled cavitary lesion in the posterior segment of left upper lobe and underwent robotic assisted left upper bisegmentectomy with mediastinal LN dissection in the same year. Biopsy of the lesion revealed moderately differentiated squamous cell carcinoma. Repeat PET CT in 2015 reported a Fluorodeoxyglucose (FDG) avid lesion in left lateral chest wall, and subsequently underwent

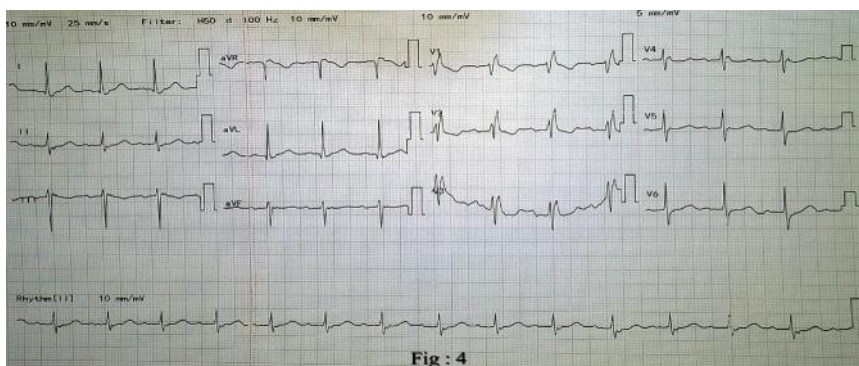
wide local excision and rib dissection for the same.

On admission, he had no complaints of fever, headache, confusion, vision loss, seizure, abdominal pain, vomiting, diarrhea, painful mouth sores, dysphagia, skin sores, cold or flu symptoms, dyspnea, bloody or tarry stools, hemoptysis or nausea. He had no past history of chest pain, palpitation, breathlessness or any thromboembolic events (stroke, MI, pulmonary embolism, DVT) in any systems. He abstained from smoking for 20 years and had no history of bronchial asthma, or COPD.

At admission the general examination of the patient had revealed a conscious, oriented and afebrile patient with heart rate 102/min, B.P (130/80 mmHg), R.R (14/min) and SpO2 – 99%. Other systemic examinations were unremarkable.

As per treatment plan, he was initially started on Inj. Fosaprepitant 150mg, Inj. Dexamethasone 8mg, Inj. Granisetron 1mg, Inj. Pheniramine 22.75mg, Inj. Ranitidine 50 mg and Inj. Hydrocortisone 100mg, followed by Inj. Ramucirumab 584mg in 250ml NS (weight adjusted dose of 8mg/kg). By the 7<sup>th</sup> minute of Inj. Ramucirumab infusion, patient suddenly developed chest discomfort, central chest pain (non-radiating), breathing difficulties, cough and

itching over the nape of neck; hence infusion of Inj. Ramucirumab was discontinued immediately. General examination showed an agitated patient with tachycardia (125/min), B.P (150/80 mmHg), tachypnea (26/min) and hypoxia (oxygen saturation on room air 75%). Chest examination and other systemic examination were unremarkable. ECG revealed left axis deviation and Right Bundle Branch Block (RBBB) with bifascicular block (Fig: 4)



**Fig: 4 - ECG revealed left axis deviation, RBBB with bi fascicular block**

The patient was then started on Inj. Pheniramine, Inj. Hydrocortisone, Nebulization with Duolin, Budecort, and other supportive care, to which he responded well. After stabilization of the patient, Inj. Ramucirumab was re-initiated with standard desensitization (Dana-Farber) technique. The remaining calculated dose of Ramucirumab was further continued, with no similar complications observed.

## Discussion

Inj. Ramucirumab (CYRAMZA) is classified as a recombinant human IgG1 monoclonal antibody, which is a newly FDA approved drug for cancer therapy. Vascular endothelial growth factor A (VEGF-A) is a proangiogenic factor, which promotes blood-vessel dilation and permeability along with new blood-vessel formations. (1) Cancers that express VEGF are ones, which usually grow and metastasize. Mechanism of action of Ramucirumab (CYRAMZA) is to target and bind with the vascular endothelial growth factor receptor-2 (VEGFR-2), by blocking the activation of VEGF and hence controlling or slowing down the tumor growth by decreasing the blood supply of the tumor.(2,3) Currently, there is

no single standard first-line regimen for metastatic or locally advanced unresectable gastric cancer. Ramucirumab is the only FDA approved single agent, or in combination with paclitaxel, for the treatment of advanced or metastatic gastric or GEJ cancer (5). It is also being approved for non-small-cell lung cancer (NSCLC) and colorectal cancer (3). Most commonly documented adverse drug reactions after exposure to Ramucirumab in the phase III *REGARD* trial includes hypertension (16%), diarrhea (14%), anemia (3.8%) and intestinal obstruction (2.1%). Other clinically relevant adverse reactions were headache (9%), proteinuria (8%), hyponatremia (6%), neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), and arterial thrombosis (1.7%) which included myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia. (4)

Bifascicular block on ECG is defined as the combination of a right bundle branch block and a left anterior or posterior fascicular block. If this significant conduction disease is already present, there is an increased risk for higher degrees of atrioventricular block, which may need a PPI in future (6).

The ECG changes associated with Inj. Ramucirumab include non-specific changes in ST segment and T wave. Acute or sub acute form of cardio toxicity may occur immediately after initiation of Inj. Ramucirumab (4) and ECG is one of the most highly recommended diagnostic methods for detection.

In this case the patient had complaints of chest pain and breathing difficulties. ECG done (Fig: 4) showed Bifascicular block, which recovered spontaneously after discontinuation of the drug. In accordance to “Naranjo” adverse drug reaction analysis (7) this case would fall under *Type B Reaction*, as it was immediate in onset, with moderate severity, uncommon in nature, probable ADR (5 scoring) that is not predictable. However this could be due to a pre-existing heart condition which was not evaluated before.

### Conclusion

We aimed to point out that hypersensitivity reaction induced by Inj. Ramucirumab could be seen even with recommended doses. Therefore it should be used and prescribed for correct indications, adjusted dose along with pre-medications and close vital monitoring during administration of the drug. We also highlight the significance of complete cardiac evaluation before initiation of Inj. Ramucirumab, in order to decrease cardiac morbidity and mortality.

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