Case report

Chronic total occlusion of coronary left main artery supplied by right collaterals under vascular endothelial growth factor inhibitor therapy : a rare case report

Abstract

We report a rare case of a patient who despite being under anti VEGF : Bevacizumab , developed a large coronary collateral circulation completely supplying the chronic total occlusion of left main coronary artery

Bevacizumab, a monoclonal antibody was the first potent angiogenic inhibitor , targeting vascular endothelial growth factor (VEGF)-A

Some of it's important cardiovascular adverse events include arterial and venous thrombotic events, coronary artery disease and heart failure resulting from inhibition of endothelial regeneration.

Our patient developed dyspnea after 1 year of receiving bevacizumab with a chronic total occlusion of the left main coronary artery with the particularity of developing extensive collaterals despite the anti VEGF treatment she received.

Introduction:

The progression of a solid tumor requires an adequate blood supply through the formation of new vessels, which depends, among other things, on humoral factors such as VEGF (vascular endothelial growth factor).

VEGF plays an important role in cardiovascular biology by modulating vascular tone, protecting endothelial cells and stimulating collateral circulation during ischemia [1]. Angiogenesis inhibitors either selectively neutralize VEGF (antibodies) or inhibit its receptors (tyrosine kinase inhibitors).

Therefore, all angiogenesis inhibitors such as bevacizumab have cardiovascular adverse effects, including hypertension, thromboembolism and in some circumstances also myocardial dysfunction.

We report a rare case of a patient who despite being under anti VEGF : Bevacizumab , developed a large coronary collateral circulation completely supplying the chronic total occlusion of left main coronary artery .

Case report:

We report the case of a 54 year- old-female patient with past medical history of diabetes mellitus managed by metformin, and rectal adenocarcinoma metastatic to liver managed initially by radiation to control local symptoms and rectal bleeding and then was started on a chemotherapy regimen including at first 2 cures of **Capecitabine** 1000mg/m² + **oxaliplatin**

130 mg/m² then a total of 8 cures of Capecitabine 1000mg/m² + **Bevacizumab** 7,5mg/kg over a period of 1 year.

During the treatment period, the patient had a quarterly cardiac examination and transthoracic echocardiography in the cardio-oncology unit with no abnormalities noted previously.

Upon last cardiac consult , the patient expressed the new onset of progressive exertional dyspnea along with intermittant chest pain , her vital sign were within normal ranges as respiratory rate of 20/min, oxygen saturation of 95% on ambient air, blood pressure of 110/73 mmHg, and pulse rate of 85bpm.

Physical examination revealed no wheezing or jugular venous distension or pedal edema.

EKG tracing displayed sinus rhythm, a slow progression of R wave in anterior leads along with no significant ST segment depression (Figure 1)

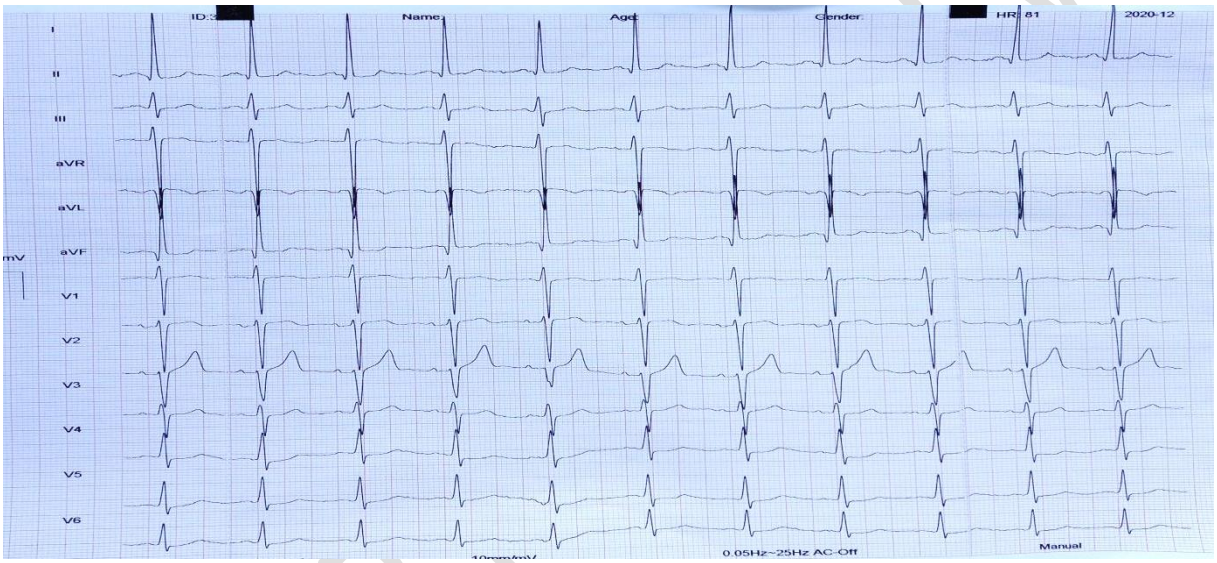


Figure 1 : EKG tracing displayed sinus rhythm, a slow progression of R wave in anterior leads along with 0.5 mm ST segment depression in apical and lateral leads

Transthoracic echocardiography showed a reduced left ventricular ejection fraction of 42% versus 62% (3 months before) with an impairment of regional systolic contractility interesting apical and anterior segments , associated with intense intracavitary contrast (figure 2).

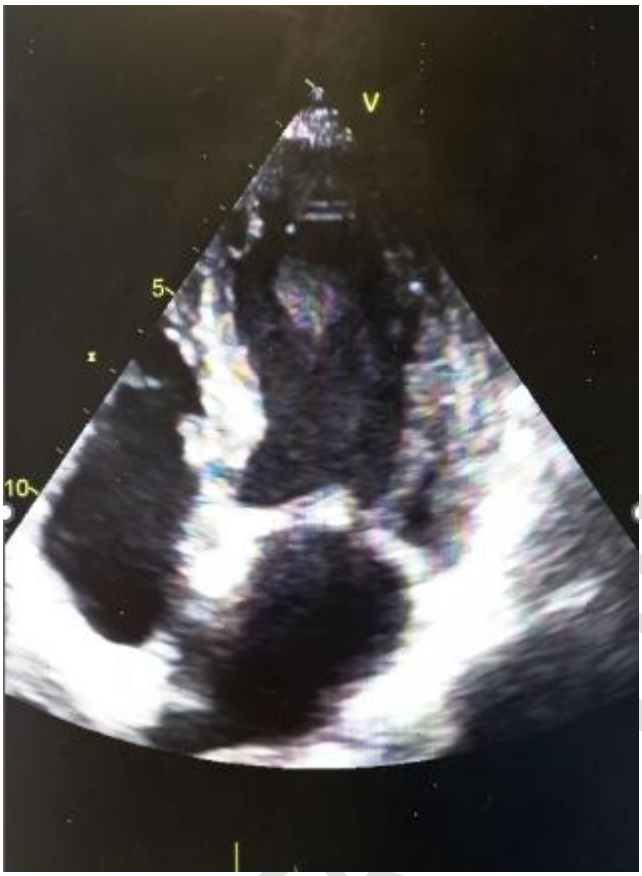
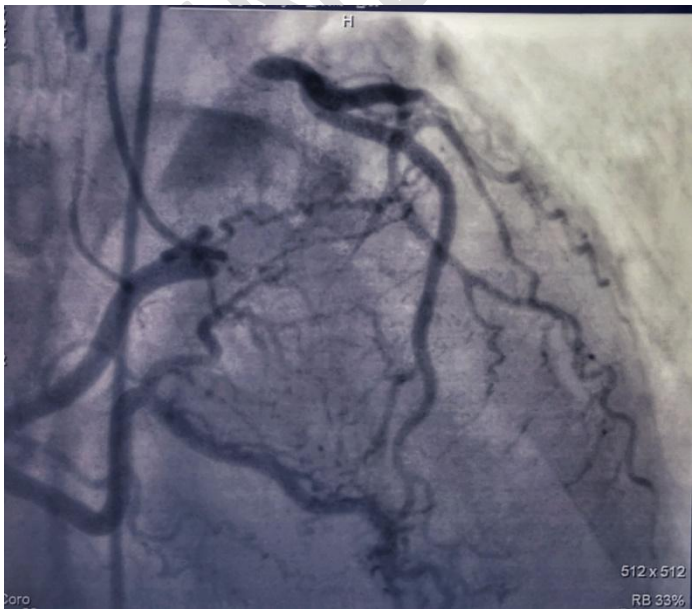


Figure 2 : Transthoracic echocardiography showing a reduced left ventricular ejection fraction of 42% with impairment of regional systolic contractility interesting apical and anterior segments associated with an intense intracavitary contrast

Laboratory tests revealed markedly elevated brain natriuretic peptide (BNP) of 1697 pg/ml (normal 0–100 pg./ml) with initial troponin of 0.05 ng/ml (normal < 0.04 ng/ml)

Faced with this clinical situation, a coronary angiography was performed showing a chronic occlusion of the left main coronary artery , demonstrated by the complete refilling of the left coronary system from the right coronary artery based on extensive collateral development . (figure 3)



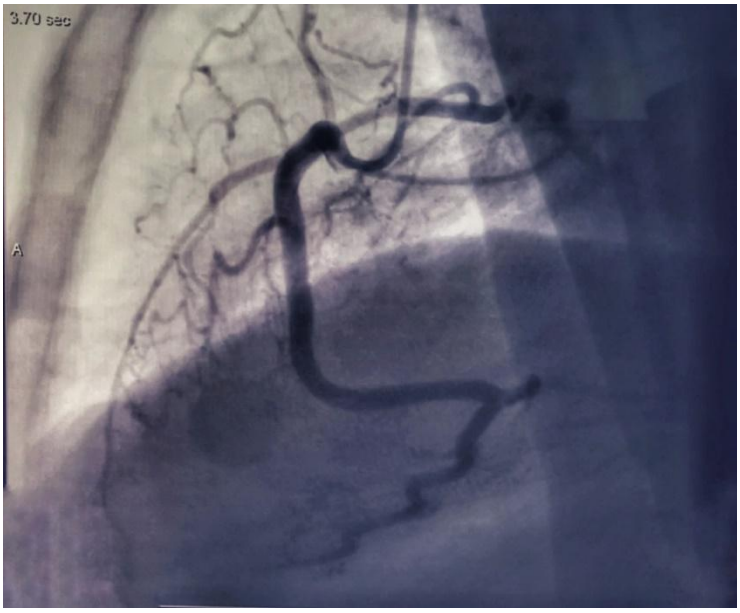


Figure 3: Chronic total occlusion of the left main coronary artery with complete refilling of the left coronary system from the right coronary artery from extensive collateral development

The management of the patient was discussed in an pluridisciplinary team including oncologists , cardiologists , interventional cardiologists , and concluded to change the chemotherapy regimen by stopping capecitabine and bevacizumab and keep oxaliplatine solely , besides antiplatelet therapy and cardioprotective therapy based on Angiotensin-converting enzyme (ACE) inhibitors and betablockers .

An anticoagulation based on low molecular heparin was introduced for 3 months , to reduce risk of thromboembolism in the context of intense intraventricular contrast .

The 3 and 6 moths follow up revealed symptoms control and improvement of dyspnea , with mild improvement of LVEF to 50%.

Discussion:

Bevacizumab, a monoclonal antibody was the first potent angiogenic inhibitor , targeting vascular endothelial growth factor (VEGF)-A , became widely used in colorectal cancer , non-squamous cell lung cancer and metastatic renal cell carcinoma , and played a key role in chemotherapy regimen for increasing survival[2].

However, cardiovascular toxicities have raised some concerns about the safety of its use, especially in the elderly population.

The first cardiovascular bevacizumab side effect is hypertension that occurs shortly after the start of treatment and may lead to decompensation, adequate control of blood pressure can usually be achieved by the administration of antihypertensive drugs (calcium antagonists, ACE inhibitors ...) but it may be necessary to discontinue bevacizumab [3].

Other important cardiovascular adverse events of bevacizumab include arterial and venous thrombotic events, coronary artery disease and heart failure resulting from inhibition of endothelial regeneration.

In 5 randomized trials including 1,745 patients with metastatic colon cancer, lung cancer and metastatic breast cancer, the incidence of coronary syndromes was 1.5% in the bevacizumab group and 1% in the control group [4]. These events can occur at any time, however, the median time of occurrence was approximately 3 months, and are not dose or cumulative dose related. All of this is thought to be related to a decrease in endothelial cell regenerative capacity, exposure of sub endothelial collagen and activation of tissue factor. [4].

Our patient developed dyspnea after 1 year of receiving bevacizumab with a chronic total occlusion of the left main coronary artery with the particularity of developing extensive collaterals despite the anti VEGF treatment she received to the point where the right coronary network had taken over .

Despite our finding, it is still unclear whether VEGF inhibition is a detriment to vascular adaptation in coronary ischemia [5] or whether bevacizumab has a direct effect on myocardial contractility. The VEGF family interferes with humans in a complicated way because it presents duality in it's functions and the outcomes in target tissues can also be opposite with the stimulation of an identical factor. Concretely, a certain degree of angiogenesis conduces to cardiac recovery from hypoxia, while an excessive amount of it may push AS plaques to an unstable state.[6]

Therefore there is currently no argument that antiplatelet agents or anticoagulants should be used for their prophylaxis, and their therapeutic indication may be limited by a risk of bleeding associated with bevacizumab. [3].

Conclusion:

Some anti-angiogenic therapies such as bevacizumab have been shown to have a deleterious effect on the cardiovascular system. Even a large increase in the relative risk of cardiovascular side effects represents a small excess risk compared to that of the tumor process itself. This risk must therefore be estimated and weighed against the expected benefit of these molecules in the context of interdisciplinary collaboration between cardiologists and oncologists for better prevention, screening and management of this toxicity.

References:

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