Case

A 26-year-old male nonsmoker, nondiabetic, non-hypertensive, and normolipidemic presented to the emergency department with history of retrosternal chest discomfort squeezing in nature and radiating to both arms like a flower base with shortness of breath and diaphoresis since last 4 h without any history of palpitation, presyncope, or syncope. During presentation, he had blood pressure of 110/70 mm Hg in right arm supine position with heart rate of 80 beats per minute. Cardiovascular system examination revealed the presence of left ventricular fourth heart sound (LVS4). Base line electrocardiogram (ECG) revealed lateral wall ST elevation myocardial infarction [Figure 1] with reciprocal changes in the inferior leads, high sensitive Troponin (hs-Troponin) level was moderately raised (146 ng/ml), and all other serum chemistries were within normal limit. The gentleman was completely vegetarian from early childhood, even he had never consumed curd since early childhood due to personal dislike. Echocardiography revealed the presence of mild hypokinesia of the lateral wall with borderline left ventricular systolic dysfunction (EF-54%). He was taken for immediate right transradial coronary angiogram and primary percutaneous intervention (primary PCI). He was administered loading dose of aspirin 325 mg with Ticagrelor 180 mg and atorvastatin 80 mg immediately. Prior to transradial coronary angiogram unfractionated heparin 100 IU/kg was administered intravenously and right transradial coronary angiogram was done which revealed focal critical occlusion of the first diagonal branch [Figures 2 and 3] having occlusive luminal thrombus. The lesion was directly stented with a small drug eluting stent of 2.25 × 15 mm size and we achieved distal TIMI III flow [Figures 4 and 5] and patient was discharged in a stable condition the very next day. The patient's lipid profile was absolutely normal with low density lipoprotein (LDL) of 63 mg/dl. We sent

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for serum homocysteine, Lipoprotein little a (Lp a), and Factor V Leiden. Serum homocysteine was quite high with value of 108 µmol/L suggestive of hyperhomocysteinemia and serum Lp a and Factor V Leiden were within normal limit. His serum Vit B12 level was quite low with a value of 43 pg/ml (normal 180–1000 pg/ml) and his serum folate was normal with a value of 6.2 ng/ml (3–20 ng/ml). Vit B12 deficiency is diagnosed when the serum Vit B12 level is below 150 pg/ml and serum Vit B12 level <100 pg/ml is known to be defined as severe form of Vit B12 deficiency. His serum Vit B12 was quite low due to his strict vegetarian nature from early childhood. Our case is the first literature description of exclusive small vessel coronary artery disease in a case of hyperhomocystinemia in a young. We supplemented the patient with oral Vit B12 1000 mcg daily along with Folic acid 1 mg daily with advice to continue the antiplatelets and statins along with regular intake of curd which is a good source of Vit B12 along with adequate intake of fresh fruits and vegetables to maintain the serum folate level. He was advised to repeat serum B12 during routine regular follow-up in the outpatient department after 1 month.

**Discussion**

Elevated level of plasma homocysteine level is definitely associated with increased risk of coronary artery disease and it is also commonly observed across Asians. Hyperhomocystinemia is associated with major form of coronary artery disease as it involves the major coronary vessels; it involves either the left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery. But hyperhomocystinemia exclusively involving small vessel coronaries like diagonals, obtuse marginals, or acute marginal branches has not been described so far in the literature. Our case is a unique and first description of the exclusive involvement of a small coronary vessel that is the first diagonal branch and other coronaries being absolutely normal in a case of hyperhomocystinemia in a young male without conventional cardiac risk factors. Schnyder et al.\[1\] analyzed 549 patients with elevated levels of plasma homocysteine and observed poor outcome in those patients post coronary intervention in the form of major adverse cardiac events (MACE) either in the form of recurrent myocardial infarction, stroke, or death. In their study, homocysteinemia involved the major vessels in the form of either left main coronary artery, left anterior descending coronary artery, left circumflex artery, or right

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**Figure 1:** ECG showing ST elevation in I and aVL (Blue arrows) with reciprocal ST depression (Purple arrows) with T wave inversion in III and aVF suggestive of high lateral wall MI

**Figure 2:** AP cranial view showing critical focal lesion in first diagonal branch

**Figure 3:** LAO caudal or spider view showing critical occlusion in first diagonal branch

**Figure 4:** Recanalized first diagonal post stenting with drug eluting stent (DES) in AP cranial view
coronary artery. Across their observation in 549 patients, exclusive involvement of a small coronary vessel in the form of diagonal, obtuse marginal, or an acute marginal branch was not observed. Shanshan et al[2] described small coronary artery involvement in about 9.1% of patients with coronary artery disease across 667 patients with hyperhomocystinemia. But exclusive involvement of one small vessel sparing major coronaries was not reported in their series. Shah et al[3] in their study across 118 patients with homocystinemia noted single major vessel coronary artery disease in 108 (92.2%) patients, whereas 10 (7.8%) had more than one major coronary artery involvement; there was no description of exclusive involvement of a small coronary artery sparing the major coronary vessel in patients with hyperhomocystinemia. Across their study, mean plasma homocysteine concentration was 44.5 µmol/L, but in our case, it was almost more than two-fold noted across their study. Paradoxically inspite of too high level of homocysteine, patient had coronary artery disease sparing the major coronary vessels and it was limited to a small vessel diagonal only. Contradictory to our observation, Sun et al[4] described the presence of hyperhomocystinemia (>15 µmol/L) in young patients less than 35 years is more commonly associated with multivessel coronary artery disease and left ventricular systolic dysfunction. Karadeniz et al[5] observed a high level of serum homocysteine >18 µmol/L is associated with a high angiographic SYNTAX score but in our patient, although the serum homocysteine level was more than 100 µmol/L, patient had only one diagonal branch coronary artery disease sparing the major ones (SYNTAX score was too low <22). The mechanism of development of coronary artery disease in hyperhomocystinemia includes toxic effect of hyperhomocystinemia impairing endothelial production of nitric oxide and vessel stiffening by increasing proliferation of smooth muscle cells with adventitial inflammation which lead to development of atherosclerosis.[6] Incorporation of homocysteine into the tissue proteins is the principal mechanism behind toxicity. Yun et al[7] described in the presence of homocystinemia LDL particle size becomes smaller, they become more prone to get oxidative modification and they turn more atherogenic. Bianca et al[8] suggested homocystinemia exerts a prothrombotic effect by enhancing platelet aggregation. Those above three described mechanisms of action make young patients more prone to develop coronary artery disease in the presence of hyperhomocystinemia. Since obesity, alcohol, caffeine consumption, smoking, low level of folate, and Vit B12 increase the level of serum homocysteine, young patients are advised to maintain a healthy life style with healthy diet. In our patient, serum Vit B12 level was quite low, we orally supplemented it and advised the patient to have one cup of curd daily with lunch and dinner with adequate intake of fresh fruits and green leafy vegetables as persistently high homocysteine level post coronary intervention carries a high risk of MACE in the form of high risk of recurrent myocardial infarction, stroke or death. Chizynski et al[9] described a homocysteine level >17.17 µmol/L is associated with increased risk of double vessel or triple vessel coronary artery disease. But the index patient having very high level of homocysteine (>100 µmol/L) had coronary artery disease confined to the diagonal branch only, also it was also focal in nature not a diffuse one. Mirbolouk et al[10] described a positive association between serum homocysteine level and severity of coronary artery disease quantified by angiographic Gensini score. Our case is a paradoxic presentation of hyperhomocystinemia in a young with a very high level of serum homocysteine being more than 100 µmol/L presenting as a focal small vessel diagonal disease sparing the major coronary vessels which has not yet been described in the literature. Singh et al[11] described a case of triple vessel coronary artery disease in a patient with familial hyperhomocystinemia with serum homocysteine level of 149 µmol/L (normal 4–15 µmol/L) emphasizing the fact that a very high level of serum homocysteine is associated with major form of coronary artery disease involving the major vessels. But very high level of serum homocysteine presenting as a small vessel coronary artery disease has not yet been described. Kazemi et al[12] described a linear relationship between the level of serum homocysteine and the number of major coronary vessels involved. Normal plasma homocysteine level is 5–15 µmol/L and homocysteine level in the range of 16–30 µmol/l is described as mildly increased, level of 31–100 µmol/l is regarded as moderately increased, and homocysteine level more than 100 µmol/l is regarded as very high level of plasma homocysteine.[13] Therapeutic paradox in treating homocystinemia remains as lowering the serum homocysteine by Vit B12 supplementation failed to demonstrate beneficial effect in cardiovascular disease[14] but folate supplementation is associated with improvement in vascular reactivity.[15–18] Our case is first description of exclusive small vessel coronary artery disease sparing major coronary arteries in a young patient with hyperhomocystinemia with very high level of serum homocysteine being more than 100 µmol/L. Vegetarians should be encouraged to take Vitamin B6 rich food like potatoes, bananas, and garbanzo beans to decrease the likelihood of having severe coronary artery disease secondary to hyperhomocystinemia. Nonuniformity is the rule of nature.
Conclusion

Our case is the first literature description of exclusive small vessel coronary artery disease sparing the major coronary vessels in a case of hyperhomocystinemia with serum homocysteine more than 100 µmol/l in a young male without the presence of conventional coronary risk factors. Although level of serum homocysteine linearly correlates with the severity of coronary artery disease, our case is paradoxic to the same hypothesis and a unique illustration that hyperhomocystinemia can present as an exclusive small vessel coronary artery disease with bles in disguise. Vegetarians should be encouraged to take Vitamin B6 rich food like potatoes, bananas, and garbanzo beans to decrease the likelihood of having severe coronary artery disease secondary to hyperhomocysteinemia. A healthy diet compromising a serve including a cup of curd, a fresh fruit, and a cup of green leafy vegetable can save us from the dangerous consequence of coronary atherosclerosis.

Patient consent

Informed patient consent has been obtained.

Ethical clearance

Institutional Ethical Committee (IEC) clearance has been obtained.

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Conflicts of interest

There are no conflicts of interest.

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