Hypermethionemia with Anticoagulant-related Acute Kidney Injury

Kshitija G Gadekar, Nilrohit Paike, Nilesh Bhange, Sudhir Kulkarni

ABSTRACT

A case of 40-year-old young woman with an extensive, acute thrombosis of left distal brachial artery following an elective laparoscopic cholecystectomy was reported. The patient underwent urgent surgical intervention for brachial artery thrombosis and was started on oral anticoagulant. Within a week, the patient presented with bleeding diathesis and acute renal insufficiency with sepsis. She was found to have markedly increased serum homocysteine level. No other thrombophilic factors could be found. On investigation, a genetic defect of homocysteine metabolism was found to be the underlying cause. The patient recovered completely on treatment with pyridoxine, cyanocobalamin, and folate.

Keywords: Acute kidney injury, Anticoagulant, Heterozygous methylenetetrahydrofolate reductase gene mutation, Thromboembolic event.

INTRODUCTION

Thrombophilias, inherited or acquired, are conditions associated with hypercoagulable state and increased risk of arterial and venous thrombosis, which represent a significant cause of mortality and morbidity worldwide. There may be interaction of genetic and environmental factors. Investigating for thrombophilia requires an initial evaluation of classical prothrombotic risk factors, such as smoking, dyslipidemias, arterial hypertension, or diabetes mellitus. Extended profile of investigations is necessary in patients with arterial or venous thrombosis, which occurs repeatedly in unusual sites or at young age, also when family aggregation of thrombotic events is identified, as well as in women with recurrent idioopathic pregnancy loss. It must include a complete blood count and erythrocyte sedimentation rate, blood film examination, prothrombin time (PT) and activated partial thromboplastin time, factor V Leiden, antithrombin and fibrinogen levels, protein C and S, prothrombin gene mutations, homocysteinemia, methylenetetrahydrofolate reductase (MTHFR) gene mutations, and antiphospholipid antibodies.

Mild to moderate hyperhomocysteinemia (HHC), meaning mildly to moderately increased plasma homocysteine (15–50 μmol/L), is uncommon in the general population. This condition is caused by either genetic factors (mutations of homocysteine metabolism enzymes) or acquired conditions, such as deficiencies in B vitamins, renal insufficiency, and some medications. Two common mutations involving the MTHFR gene have been identified: C677T and A1298C.

CASE REPORT

The case of a 40-year-old nondiabetic and nonhypertensive female admitted with clinical picture of acute kidney injury (AKI) has been presented. Her medical history started 2 weeks prior to her admission, when she underwent an elective laparoscopic cholecystectomy. On the second postoperative day, she developed painful swelling of the left arm with clawing of the hand and ischemia of the fingers. Color Doppler study of left upper limb revealed acute thrombosis in left distal brachial, radial, ulnar, and median arteries with absent flow. She underwent urgent vascular intervention with left brachial artery embolectomy. She was heparinized and started on oral anticoagulant Acenocoumarol 3 mg twice a day. 1 week after embolectomy, she developed generalized swelling involving the face, arms and lower limbs, oliguria, hematuria, bleeding gums, hematemesis, shortness of breath, and fever.

On examination, she was febrile, conscious, oriented with pulse rate 124/minute, blood pressure 120/70 mm Hg, and relative risk 28/minute. She was pale, with facial and pedal edema. She had bleeding gums and left upper limb swelling. Her systemic examination was normal except bilateral fine crepitations on chest auscultation. Her investigations revealed hemoglobin (Hb) 2.9 gm/dL, total leukocyte count (TLC) 28,100/mm$^3$, platelets 600,000/mm$^3$, urea 124 mg/dL, creatinine 6.6 mg/dL, Na 118 mEq/L, K 4.4 mEq/L, PT 120 seconds, international

1. Assistant Professor, 2, 3. Resident, 4. Professor and Head
1-4. Department of Nephrology, MGM Medical College, Aurangabad, Maharashtra, India
Corresponding Author: Kshitija G Gadekar, Assistant Professor, Department of Nephrology, MGM Medical College Aurangabad, Maharashtra, India, Phone: +919422206548 e-mail: kshitij4444@gmail.com

Source of support: MGIHS
Conflict of interest: None


10.5005/jp-journals-10036-1137
normalized ratio (INR) 7.5, total serum proteins 5.2 gm/dL, serum albumin 1.8 gm/dL, Ca 9.5 mg/dL, PO₄ 7.2 mg/dL, and uric acid 9.7 mg/dL. Urine analysis showed 4+ proteinuria, plenty of red blood cells (RBCs), and 30 to 40 pus cells/hpf. Liver function test, lipid profile, electrocardiogram, and two-dimensional echocardiogram were normal. Anticardioplin antibodies and lupus anticoagulant tests were negative. Thrombophilia tests showed that protein C, protein S, and antithrombin III levels were within normal limits. Serum C3 complement was normal. Her homocysteine level was 43.08 μmol/L (normal 3.36 to 20.44 μmol/L in females).

The patient was negative for factor V Leiden and prothrombin gene mutation. However, she was found to have MTHFR gene polymorphism in the form of compound heterozygous for C677T and A1298C. Abdominal ultrasound found both normal-sized kidneys with increased echogenicity. Kidney biopsy was not performed due to risk of bleeding. She was treated conservatively with five packed cell volume (PCV) and eight fresh frozen plasma transfusions, intravenous vitamin K, injection Meropenem, injection Tranexamic acid, pyridoxine, cyanocobalamin, and folate supplements. Anticoagulants were discontinued. She did not need hemodialysis. At the end of 2 weeks, patient showed gradual improvement and was discharged with normal clinical and biochemical parameters. At the time of discharge, her laboratory tests showed PT 27.5 seconds, INR 2.29, normal renal functions, Hb 8.7 gm/dL, TLC 12,600/mm³, PCV 26%, mean corpuscular volume 70 fL, mean corpuscular hemoglobin 18 pg, mean corpuscular hemoglobin concentration 26 gm/dL, and normal urinalysis.

**DISCUSSION**

The mechanism by which MTHFR gene mutations produce prothrombotic states is represented by elevated levels of plasma homocysteine due to decreased enzymatic activity of MTHFR that participates in regulating homocysteine metabolism, and a mutation of MTHFR may be a marker for possible elevated homocysteine levels. At present, HHC is considered to represent a risk factor for deep vein thrombosis and a common risk factor for recurrent venous thrombosis. The prothrombotic state for two polymorphisms of the MTHFR gene, the C677T and A1298C, was found in our case. There are studies which suggest supplementation with folic acid; vitamin B6 and B12 may help in lowering the homocysteine concentrations, and even in reversing endothelial dysfunction regardless of the underlying cause of HHC.

Acute kidney injury resulting from glomerular hemorrhage has been described in patients with glomerular lesions in the absence and presence of coagulopathy (INR 6–9 range). A biopsy study in patients who developed otherwise unexplained AKI in association with anticoagulant overdose revealed the predominant lesion of distal tubular injury and obstruction with RBCs and RBC casts. The glomeruli show little or no abnormalities by light, immunofluorescence, or electron microscopy. The recognition of a characteristic histologic lesion that was associated with the clinical presentation of otherwise unexplained AKI in the setting of overanticoagulation led to the term “anticoagulant-related nephropathy.”

The pathogenesis event appears to be glomerular hemorrhage resulting in the formation of obstructing RBC casts within renal tubules, which is the most conspicuous histologic feature of anticoagulant-related nephropathy. The diagnosis of anticoagulant-related nephropathy should be suspected among patients who present with AKI in the setting of excessive anticoagulation. A definitive diagnosis is made by renal biopsy. However, biopsies are usually not performed, at least initially, among patients who are anticoagulated because the risk of bleeding is high.

Among patients who develop AKI and are on anticoagulant therapy, a presumptive diagnosis of anticoagulant-related nephropathy may be made if a severe warfarin coagulopathy is present and if other causes of AKI have been excluded by clinical features and serologic tests. Restoration of a therapeutic INR may limit the extent of AKI and chronic kidney injury that results from glomerular hemorrhage. The patient was discharged from the hospital with folie acid, vitamin B6, and vitamin B12 supplements. The peculiarities of the present case were the thrombotic events and the extensive arterial thrombosis in a young patient with HHC due to two heterozygotic mutations in the MTHFR gene. Anticoagulant nephrotoxicity presented as AKI, which was successfully treated conservatively.

**CONCLUSION**

In patients with unexplained arterial or venous thrombosis, it is appropriate to investigate for the possible coexistence of multiple predisposing factors for thrombosis, including measurement of the serum homocysteine level, in addition to investigations for mutations of the MTHFR, the prothrombin, and the factor V genes.

**ACKNOWLEDGMENT**

Authors would like to thank the Dean, Dr Ajit Shroff, MGM Medical College and Hospital, Aurangabad, for giving permission to publish this case report.
REFERENCES