IJKD KIDNEY DISEASES

Segmental Renal Artery Thrombosis Secondary to Methylene Tetrahydrofolate Reductase Mutation
An Unusual Presentation

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Methylene tetrahydrofolate reductase (MTHFR) is an enzyme involved in the metabolism of homocysteine to methionine, and folic acid is an essential cofactor. Mutations in the *MTHFR* gene lead to hyperhomocysteinemia and vascular thrombosis. Heterozygous mutation involving a single nucleotide polymorphism in the *MTHFR* gene leading to vascular thrombosis is very rare. We present a case of segmental renal artery thrombosis secondary to this mutation and to the best of our knowledge, it is the first case to be reported. Though easily treatable, this is a condition which is seldom investigated in the workup of thrombotic disorders.

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Case Report

INTRODUCTION

Methylene tetrahydrofolate reductase (MTHFR) is an enzyme which converts methylene tetrahydrofolate to 5-methyl tetrahydrofolate by reduction, which in turn transfers its methyl group to homocysteine, forming methionine. This is a folate-dependent pathway and nicotinamide adenine dinucleotide phosphate-oxidase is used for reduction.[1] The absence or dysfunction of MTHFR leads to hyperhomocysteinemia, a well-known atherogenic factor, also implicated in vascular thrombosis.[2]

The gene encoding for MTHFR is located on chromosome 1. There are 24 genetic polymorphisms associated with this gene and two of the most investigated forms are *C677T* and *A1298C* single nucleotide polymorphisms (SNPs).[3] In *C677T* SNP, the nucleotide in position 677 normally has cytosine coding for alanine. When cytosine is replaced by thymidine, it codes for valine at position 222.[4] This gene expresses a thermolabile MTHFR, which has reduced activity compared to the normal variant and in the presence of low folate levels precipitates hyperhomocysteinemia. Individuals with homozygous *677TT* mutation are more susceptible to vascular thrombosis than those with a heterozygous trait that is *677CT*.

Hyperhomocysteinemia precipitates atherosclerosis and most studies of thrombosis have been done in relation to coronary atherosclerosis and thrombosis.[5] Vascular thrombosis, especially arterial, is rare in heterozygous mutations. Even when combined with folic acid deficiency, most cases documented are with homozygous mutations and a majority is seen with venous thrombosis.[6,7] We present a rare case of heterozygous mutation of the *C677T* gene, along with low folate levels leading to hyperhomocysteinemia and segmental renal artery thrombosis.

CASE REPORT

A 42-year-old man presented to the emergency

room with right-sided loin pain of sudden onset. It was dull aching, nonradiating, and associated with sweating and vomiting. There was no history of hematuria, dysuria, loose stools, or trauma. His blood pressure was 160/100 mm Hg. There was no renal angle tenderness. There was no history of any chronic illness. With a clinical suspicion of renal colic, he was prescribed an antispasmodic agent and was sent home. He continued to have pain and reported the next morning with the same complaints. Clinical examination was unremarkable other than hypertension.

Investigations done revealed a hemoglobin of 12.5 g/dL, leukocyte count of 11.3×10^3/L, platelet count of 120×10^3/L, erythrocyte sedimentation rate of 30 mm/h. Urine microscopy showed no proteins, zero to 2 erythrocytes per high-power field, and 2 to 4 leukocytes per high-power field. Coagulation profile was normal. Electrocardiography and chest radiography showed no abnormality. Urgent ultrasonography of the abdomen done showed no abnrmality. His function functions was marginally deranged, with a serum creatinine of 1.3 mg/dL (reference range, 0.8 mg/dL to 1.0 mg/dL). Liver function tests, serum calcium, and phosphate were in normal ranges.

Since most of the investigations done were inconclusive and he continued to have pain, a contrast computerized tomography scan of the abdomen was done with adequate hydration, which revealed normal-sized kidneys with a well-demarcated nonenhancing wedge-shaped hypodense area involving the right kidney suggestive of a vascular infarct (Figure 1). A gadolinium contrast-enhanced magnetic resonance angiography showed a full-thickness perfusion defect affecting a large part of the right renal parenchyma. Further workup was done to evaluate underlying prothrombotic disorder. Peripheral blood smear was normal, serum lactate dehydrogenase was 1429 IU/L (reference range, 100 IU/L to 350 IU/L), and proteins C and S levels were normal. The antinuclear antibody, antineutrophil cytoplasmic antibody, and antiphospholipid antibodies were negative.

Genetic studies using a line prob assay for Factor V Leiden and Cambridge (Arg306Thr) mutation, and Factor II prothrombin gene *20210A* mutation were negative. He was found to be a heterozygous carrier for *MTHFR C677T* mutation. Further evaluation

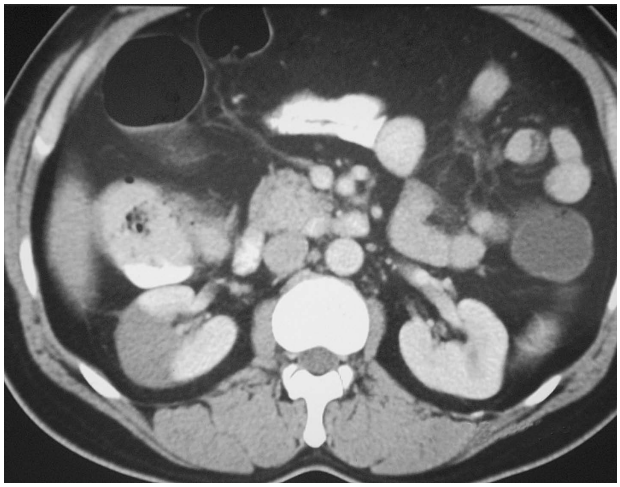

Figure 1. Contrast computerized tomography scan of the abdomen showing normal sized kidneys with a well-demarcated nonenhancing wedge-shaped hypodense area involving the right kidney suggestive of a vascular infarct.

showed that he had low folate levels of 1.4 ng/mL (reference range, < 2 ng/mL) with normal serum vitamin B12 levels. Homocysteine levels were increased to 22 IU/mL (reference range, 7 IU/mL to 15 IU/mL). In view of hyperhomocysteinemia and low folate levels secondary to *MHTFR* gene mutation, he was treated with folate supplements and oral anticoagulants for a few days. His kidney function recovered completely; however, a technetium Tc 99m diethylenetriaminepentaacetic acid renal scintigraphy done 2 weeks later revealed a compromised cortical function with a perfusion defect in the right kidney. The split glomerular filtration rate was 74% (56.3 mL/min) of the left kidney and 26% (19.8 mL/min) of the right kidney with a global rate of 76.1 mL/min/m^2 (Figure 2).

DISCUSSION

The *MTHR* gene mutation leading to vascular thrombosis is rare, and most cases documented are with homozygous mutations.[5,8] Heterozygous SNP mutations leading to hyperhomocysteinemia is not seen as there is adequate functional enzyme for the conversion of homocysteine to methionine. There are a few case reports of renal venous thrombosis,[9] but there are no case reports of arterial thrombosis.

Why the renal artery was the victim is a question unanswered. The initial kidney dysfunction observed may be due to vasoconstriction of the contralateral renal artery, which is a well-known fact,[10] and this must have recovered after a few days leading to normalization of the kidney functions.

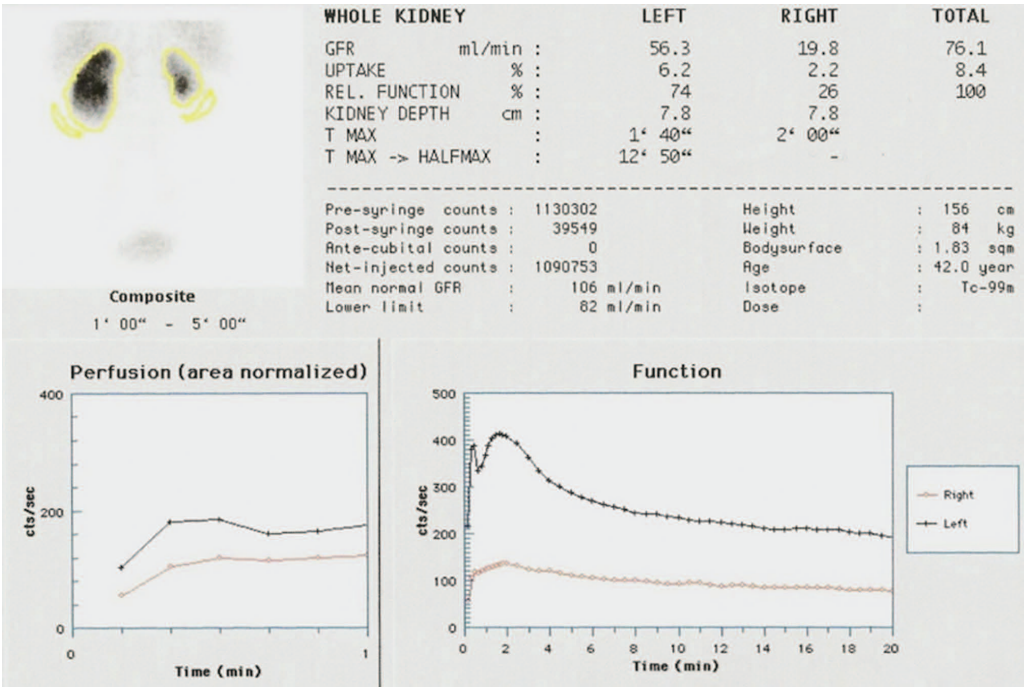

Figure 2. Renal dynamic scan showing reduced function of the right kidney.

This case is the first report of the renal artery being involved. It is essential to screen for *MTHFR* gene mutations in the evaluation for prothrombotic disorders. The patient might be mismanaged with oral anticoagulants alone though the actual treatment is folic acid. It is also important that a strong clinical suspicion of renal artery thrombosis should be entertained in a patient presenting with loin pain rather than just think of it as renal colic. Renal care physicians should be aware of this potentially treatable entity.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. den Heijer M, Keijzer MB. Hyperhomocysteinemia as a risk factor for venous thrombosis. Clin Chem Lab Med. 2001;39:710-3.
2. Eldibany MM, Caprini JA. Hyperhomocysteinemia and thrombosis: an overview. Arch Pathol Lab Med. 2007;131:872-84.
3. Goyette P, Sumner JS, Milos R, et al. Human methylenetetrahydrofolate reductase: isolation of cDNA mapping and mutation identification. Nat Genet.1994;7: 551.
4. Frosst P, Blom HJ, Milos R, Goyette P, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet. 1995;10:111.
5. U.S. Preventive Services Task Force. Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151:474-82.
6. Queffeulou G, Michel C, Vrtovsnik F, Philit JB, Dupuis E, Mignon F. Hyperhomocysteinemia, low folate status, homozygous C677T mutation of the methylene tetrahydrofolate reductase and renal arterial thrombosis. Clin Nephrol. 2002;57:158-62.
7. de Franchis R, Mancini FP, D'Angelo A, et al. Elevated total plasma homocysteine and 677CT mutation of the 5,10-methylenetetrahydrofolate reductase gene in thrombotic vascular disease. Am J Hum Genet. 1996;59:262-4.
8. Cinemre H, Bilir C, Akdemir N. Isolated renal vein thrombosis associated with MTHFR-1298 and PAI-1 4G gene mutations. Clin Appl Thromb Hemost. 2010;16: 708-10.
9. Brophy DF, Bukaveckas BL, Ferreira-Gonzalez A, Archer KJ, Martin EJ, Gehr TW. A pilot study of genetic polymorphisms and hemodialysis vascular access thrombosis. Hemodial Int. 2009;13:19-26.
10. Levin M, Nakhoul F, Keidar Z, Green J. Acute oliguric renal failure associated with unilateral renal embolism: a successful treatment with iloprost. Am J Nephrol. 1998;18:444-7.

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