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## CASE REPORT

# HYPERHOMOCYSTEINEMIA AND INHERITED THROMBOPHILIA AS UNDERLYING RARE CAUSES OF SUBCLAVIAN ARTERY THROMBOSIS: A DIAGNOSTIC CONSIDERATION IN ARTERIAL THROMBOTIC EVENTS

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**Abstract:**
*Subclavian artery thrombosis is a rare but clinically significant condition that can present with upper limb ischemia and neurological symptoms. While atherosclerosis remains the most common cause, hypercoagulable states such as hyperhomocysteinemia are increasingly being recognized as potential contributors.We report the case of a 40-year-old chronic smoker who presented with progressive pain, numbness, and weakness in the left upper limb. Clinical examination revealed absent pulses and a significant blood pressure discrepancy between the arms. CT angiography demonstrated thrombotic occlusion in the proximal segment of the left subclavian artery. Laboratory workup showed a markedly elevated serum homocysteine level (43 µmol/L), reduced protein C (65%) and protein S (51%) levels, and a positive Factor V Leiden test. Antithrombin III was within normal range (111%). Interestingly, fasting serum vitamin B12 and folate levels were elevated (980 pg/mL and 120 ng/mL, respectively). The patient was managed with anticoagulation, antiplatelets, and vitamin supplementation, and showed clinical improvement.This case underscores the importance of evaluating metabolic and thrombophilic risk factors, including hyperhomocysteinemia and inherited thrombophilia, in patients with arterial thrombosis at uncommon sites or in the absence of conventional risk factors. Early identification and correction can guide targeted therapy and potentially prevent recurrence.*

**Keywords:** *Subclavian Artery Thrombosis, Hyperhomocysteinemia, Thrombophilia, Arterial Thrombosis*

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**Introduction:**

Subclavian artery thrombosis is an uncommon clinical entity that presents with a spectrum of symptoms ranging from asymptomatic cases to severe limb ischemia, depending on the extent and location of the occlusion and collateral circulation. The subclavian arteries supply blood to the upper limbs, brain, and thoracic structures. Thrombosis in this vessel can lead to ischemic symptoms in the upper extremity, as well as neurologic deficits if the vertebral artery flow is compromised, potentially resulting in subclavian steal syndrome.[1,2]

Most cases of subclavian artery thrombosis are attributed to atherosclerotic disease, particularly in elderly populations or those with classical cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidaemia, and smoking.[3] Other potential causes include thoracic outlet syndrome

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(TOS), trauma, catheter-induced injury, embolism from cardiac sources, and hypercoagulable states.[4] Among the less common etiologies, hyperhomocysteinemia has emerged as an independent risk factor for both arterial and venous thrombosis and deserves attention due to its under-recognition in clinical practice.[5]

Homocysteine is a non-proteinogenic sulfur-containing amino acid derived from methionine metabolism. Elevated plasma homocysteine levels, termed hyperhomocysteinemia, are classified as moderate (15–30 μmol/L), intermediate (30–100 μmol/L), and severe (>100 μmol/L).[6] It may result from genetic mutations, such as methylenetetrahydrofolate reductase (MTHFR) polymorphism, or acquired causes including deficiencies of folate, vitamin B12, and pyridoxine, chronic kidney disease, hypothyroidism, and certain drugs.[7,8] Lifestyle factors, particularly cigarette smoking and excessive alcohol intake, also contribute to increased homocysteine levels.

Pathophysiologically, homocysteine exerts its prothrombotic effects through multiple mechanisms: inducing endothelial dysfunction, enhancing oxidative stress, promoting smooth muscle proliferation, reducing nitric oxide bioavailability, increasing thromboxane A2 activity, and upregulating tissue factor expression. Additionally, it impairs anticoagulant mechanisms by downregulating thrombomodulin and activating factor V, ultimately creating a hypercoagulable milieu.[9,10,11]

While venous thromboembolism and coronary or cerebral artery thrombosis are more commonly reported in hyperhomocysteinemia, peripheral arterial occlusions, including those of the upper extremity, are rare but increasingly being recognized.[12] This case report illustrates a rare but clinically significant manifestation of subclavian artery thrombosis in a smoker, associated with markedly elevated homocysteine levels and other thrombophilic abnormalities. It underscores the importance of considering metabolic and inherited risk factors in patients presenting with atypical or unexplained arterial thrombosis.

**Case report:**

A 40-year-old right-handed male, chronic smoker with a 20-pack-year history, presented to the emergency department with complaints of progressive pain, tingling, and numbness in both upper limbs-more pronounced on the left side-for the past three days. He also reported heaviness, coldness, and fatigue in the left arm during minimal exertion, with difficulty in gripping objects. There were no associated symptoms of fever, recent trauma, chest pain, palpitations, syncope, visual disturbances, or dizziness. He denied any history of claudication, weight loss, joint pains, rashes, Raynaud's phenomenon, or recent immobilization. There was no history suggestive of recent infection, connective tissue disease, or malignancy.

His past medical history was unremarkable. He had no known history of hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease, or ischemic heart disease. He denied any history of deep vein thrombosis, pulmonary embolism, or previous thrombotic episodes. Family history was negative for premature cardiovascular disease, hypercoagulable disorders, or autoimmune conditions. He was not taking any medications, herbal products, oral contraceptives (inapplicable), or vitamin supplements.

On physical examination, he was afebrile with a blood pressure of 130/85 mmHg in the right arm and unrecordable pressure in the left arm. Pulse rate was 82 bpm, regular, and oxygen saturation was 98% on room air. Inspection of the left upper limb revealed mild pallor and coolness, but no swelling, cyanosis, skin discoloration, ulceration, or muscle wasting. Capillary refill was delayed (>3 seconds) in the left fingers. Radial and brachial pulses were absent in the left upper limb, while the right radial pulse was reduced. Bilateral femoral, popliteal, and dorsalis pedis pulses were palpable, and no carotid or subclavian bruits were appreciated. There was no evidence of asymmetry in limb length or diameter.

Neurological examination showed reduced grip strength and hypoesthesia in the left hand, especially in the distal digits, but no motor weakness or sensory deficits in the lower limbs. Deep tendon reflexes were intact and symmetrical. There was no Horner's syndrome, cranial nerve palsy, cerebellar signs, or gait abnormalities. Cardiovascular, respiratory, and abdominal examinations were unremarkable.

Given the clinical picture of acute-onset upper limb ischemia, with absent pulses, temperature change, and inter-arm BP difference, a vascular cause was strongly suspected.

CT angiography of both upper limbs revealed a thrombotic occlusion in the S1 segment of the proximal left subclavian artery, measuring approximately 16 mm in length. There was reconstitution of flow distal to the thrombus, including the axillary, brachial, and radial arteries-suggestive of collateral circulation. On the right side, a mild (around 40%) luminal narrowing was noted in the S2 segment of the subclavian artery without thrombus (Figure 1 & 2). Bilateral vertebral arteries were patent, ruling out subclavian steal syndrome.

Echocardiogram was normal, without any evidence of mural thrombus, valvular vegetation, or cardiac shunt. No thrombi were detected in the aorta or other large arteries, excluding embolic causes.

Extensive laboratory workup was performed to evaluate underlying hypercoagulable states: Protein C and S levels were reduced (65% and 51% respectively), Antithrombin III was within normal range (111%), Factor V Leiden mutation was positive, aPTT was prolonged to 106 seconds, Serum homocysteine level was significantly elevated at 43 µmol/L, Fasting serum vitamin B12 and folate levels were paradoxically elevated (980 pg/mL and 120 ng/mL, respectively), MTHFR genotyping could not be performed due to unavailability. Autoimmune screening (ANA, anti-dsDNA, ANCA) was negative. Tests for antiphospholipid antibodies, including lupus anticoagulant, anti-cardiolipin, and â2-glycoprotein I antibodies, were also negative. CRP and ESR were not elevated. CBC, renal and liver function tests, electrolytes, coagulation profile (other than aPTT), lipid profile, and thyroid function tests were within normal limits.

He was initiated on therapeutic anticoagulation with low molecular weight heparin (enoxaparin 1 mg/kg BID), transitioned to oral warfarin with INR monitoring, and started on dual antiplatelet therapy (aspirin 75 mg and clopidogrel 75 mg daily). He received vitamin supplementation with high-dose vitamin B12, folic acid, and pyridoxine. He was advised to discontinue smoking, maintain hydration, and follow up for vascular surgery consultation and repeat imaging after 6 weeks. The patient was discharged in stable condition after a one-week hospital stay with improvement in symptoms and preserved distal perfusion.

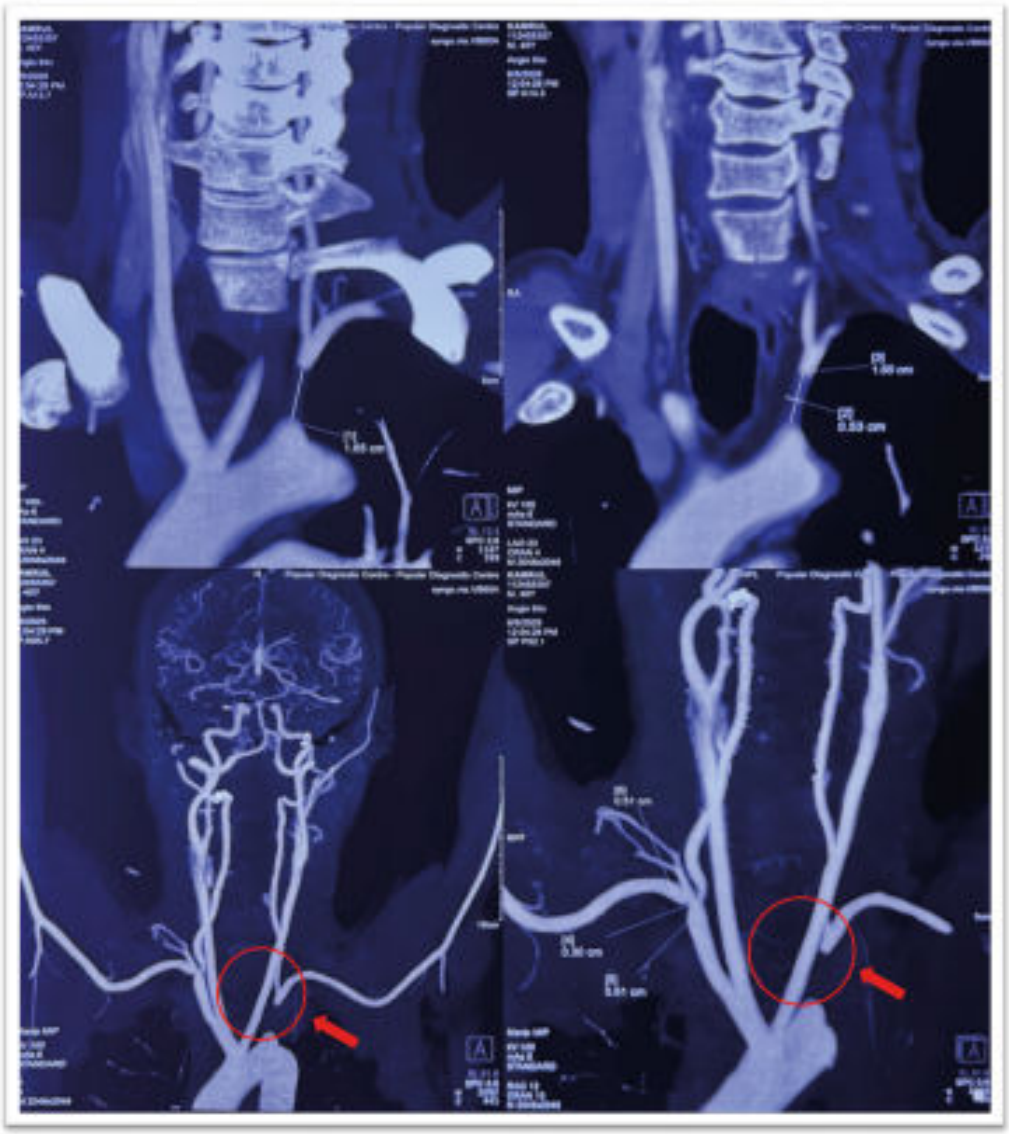

**Figure 1:** *Thrombotic occlusion in S1 segment of proximal left subclavian artery, length of the occluded segment about 16mm. (indicated by circle & arrow)*

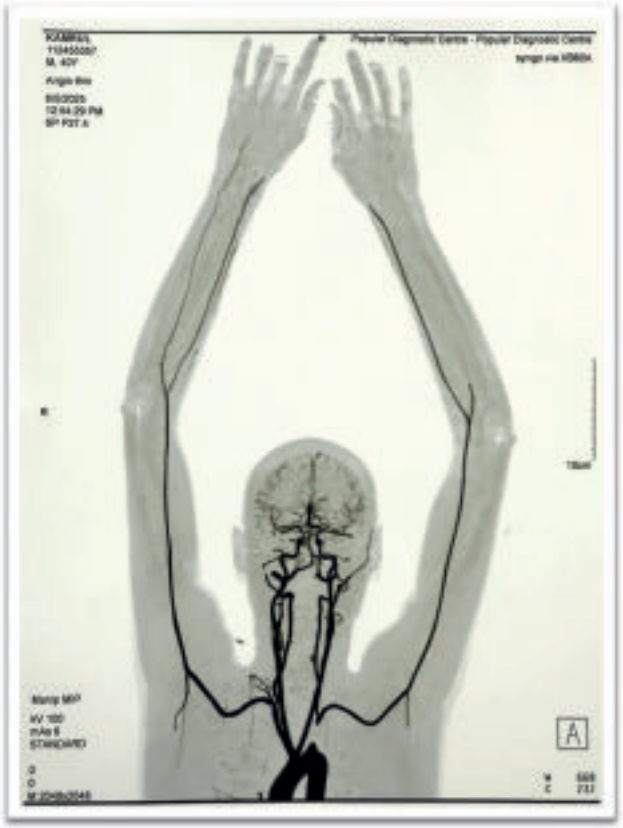

**Figure 2:** *a) Thrombotic occlusion with reconstituted moderate flow in the left distal subclavian, axillary, brachial and radial artery. b) Narrowing within the distal flow in left ulnar and interosseous artery.*

**Discussion:**

This case illustrates a rare yet clinically important presentation of subclavian artery thrombosis in a relatively young individual without conventional cardiovascular risk factors such as hypertension, diabetes, or dyslipidaemia. The presence of multiple thrombophilic abnormalities—notably elevated homocysteine, reduced protein C and S, and heterozygous Factor V Leiden mutation—indicates an underlying hypercoagulable state as the likely primary etiology.

The subclavian artery, being large-calibre and well-collateralized, is relatively resistant to thrombosis unless provoked by significant endothelial injury or systemic prothrombotic conditions. In this patient, the absence of structural arterial anomalies, thoracic outlet syndrome, or embolic sources from the heart or great vessels makes in situ thrombosis secondary to metabolic and genetic prothrombotic factors the most plausible cause.

Hyperhomocysteinemia is well known to promote arterial and venous thrombosis through several mechanisms: it impairs endothelial function, reduces nitric oxide bioavailability, promotes oxidative stress through generation of reactive oxygen species, and induces smooth muscle proliferation and matrix remodelling.[10,11] It also increases platelet activation and enhances expression of tissue factor, thus accelerating thrombogenesis.

Although traditionally associated with venous thromboembolism, homocysteine has a growing body of evidence linking it with arterial thrombosis, including myocardial infarction, ischemic stroke, and peripheral arterial disease.[12,13]. A landmark meta-analysis by the Homocysteine Studies Collaboration confirmed a dose-dependent association between plasma homocysteine and vascular risk, independent of conventional factors.[14] The level in our patient—43 µmol/L—places him in the intermediate category, which confers a markedly increased vascular risk.

Moreover, this patient had reduced protein C and protein S levels (65% and 51%, respectively). While congenital deficiencies could not be confirmed, acquired reductions can occur during acute thrombosis, due to consumption or hepatic downregulation. Importantly, homocysteine itself has been shown to impair natural anticoagulant pathways by reducing thrombomodulin expression and protein C activation, thereby compounding the prothrombotic risk.[18] The ongoing thrombotic process may further consume protein C and S, as noted in acute thrombotic conditions.[19]

Additionally, heterozygous Factor V Leiden mutation was identified. This mutation renders Factor V resistant to degradation by activated protein C, thereby prolonging thrombin generation and promoting clot persistence.[20] While Factor V Leiden is more strongly associated with venous thrombosis, its combination with other risk factors (such as hyperhomocysteinemia) may significantly raise arterial thrombotic potential, especially in unusual vascular territories.

Interestingly, serum vitamin B12 and folate levels were elevated, which might appear contradictory. However, functional deficiencies can persist at the intracellular level, especially in chronic smokers with high oxidative stress. Recent subclinical supplementation, impaired cellular uptake, or defects in remethylation pathways (e.g., MTHFR mutation—not tested here) can result in elevated serum levels while failing to reduce homocysteine.[21,22] Thus, high serum levels do not necessarily negate the diagnosis of functionally significant hyperhomocysteinemia.

Other differential diagnoses such as vasculitis (excluded by negative ANA, ANCA, and anti-dsDNA),

paraneoplastic thrombosis, aortic arch syndrome, and antiphospholipid syndrome (negative triple antibody panel) were reasonably ruled out through thorough clinical and laboratory evaluation. Imaging showed no embolic source, aneurysms, or compressive pathology.

Therapeutically, the patient was managed with anticoagulation, dual antiplatelet therapy, and vitamin supplementation, consistent with current practice in arterial thrombosis secondary to hypercoagulable states. Although randomized controlled trials (e.g., HOPE-2, NORVIT) have questioned the efficacy of homocysteine-lowering therapy in cardiovascular event prevention, these trials largely enrolled high-risk atherosclerotic populations, not patients with overt thrombosis and multiple inherited defects (16,17). In such individuals, targeted correction of metabolic abnormalities remains justified to reduce recurrence risk.

This case emphasizes the clinical utility of comprehensive thrombophilia screening in young patients presenting with arterial occlusion at unusual sites. Recognition of correctable metabolic and genetic factors enables personalized management and supports decisions about long-term anticoagulation, family screening, and lifestyle counselling.

**Conclusion:**

This case points out subclavian artery thrombosis as a rare but significant vascular manifestation of hyperhomocysteinemia, especially when combined with inherited thrombophilic defects such as protein C and S deficiency and Factor V Leiden mutation, in the absence of traditional atherosclerotic or autoimmune risk factors. It emphasizes the need for clinicians to maintain a high index of suspicion for metabolic and thrombophilic causes in patients presenting with arterial thrombosis at atypical sites or at a younger age. Early identification and correction of elevated homocysteine levels and inherited thrombophilic abnormalities, alongside appropriate anticoagulation and antiplatelet therapy, may improve outcomes and reduce recurrence. This case also reinforces the value of including comprehensive thrombophilia screening in the evaluation of arterial thrombotic events.

**Conflict of Interest:**

The authors stated that there is no conflict of interest in this study.

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**Consent for publication:**

Informed written consent was taken from the parents of the patient to publish details relevant to the disease and management.

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**Competing interests:**

None.

**Authors' contributions:**

All authors were involved in the management of the patient and all authors contributed to the conception, writing, and editing of the case report.

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