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Three-Territory Sign on Brain MRI as a Clue to Trousseau Syndrome in an Occult Adenocarcinoma: A Case Report

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ABSTRACT

Cerebrovascular complications are a recognized cause of morbidity in the oncological population. However, an acute ischemic stroke can occasionally serve as the primary clinical manifestation of a previously concealed malignancy. Trousseau syndrome, broadly defined as a cancer-associated hypercoagulable state, frequently precipitates catastrophic thromboembolic events, including ischemic strokes across multiple distinct vascular territories.

We report the case of a 60-year-old patient admitted to the emergency department for diffuse abdominal pain. An abdominal computed tomography CT scan revealed multiple suspicious hepatic lesions without peritoneal carcinomatosis. An ultrasound-guided liver biopsy was subsequently performed. Histopathological examination demonstrated infiltration of the hepatic parenchyma by malignant gland- forming epithelial cells, consistent with a moderately differentiated adenocarcinoma. During the clinical course, the patient developed a deep vein thrombosis and acute altered mental status accompanied by severe agitation. While the agitation precluded a cholangiopancreatography MRI to locate the primary tumor, an urgent brain magnetic resonance imaging was successfully performed. Diffusion-weighted imaging and Apparent Diffusion Coefficient mapping objectified multiple, widely disseminated acute ischemic foci involving both the anterior and posterior compartments. Initial evaluation revealed no major cardioembolic source, atrial fibrillation, or significant extracranial arterial stenosis. Recognition of the "Three-Territory Sign" may serve as an important clue suggesting an underlying cancer-associated hypercoagulable state and may prompt further investigation for occult malignancy. A diagnosis of Trousseau syndrome secondary to an adenocarcinoma of unknown primary was consequently established.

This case highlights the importance of considering cancer-associated hypercoagulability in patients presenting with unprovoked, multi-territorial acute ischemic strokes. Recognition of the "Three-Territory Sign" on diffusion-weighted MRI may provide a valuable clue to an otherwise occult malignancy and should prompt further evaluation for an underlying cancer-associated hypercoagulable state.

KEYWORDS

Brain mri, cancer-associated ischemic stroke, occult adenocarcinoma, three-territory sign, trousseau syndrome

MAIN ARTICLE

INTRODUCTION

The intersection of oncology and neurovascular disease presents a complex diagnostic challenge. Cerebrovascular complications in patients with cancer have been well-documented for decades, often resulting in devastating neurological outcomes [1]. While some strokes in cancer patients are driven by conventional risk factors, a significant proportion may be related to malignancy-associated mechanisms, including cancer-induced hypercoagulability [2]. First described by Armand Trousseau in the 19th century as migratory thrombophlebitis, "Trousseau's syndrome" is now a broader eponym that encompasses a wide spectrum of cancer-associated coagulopathies, ranging from venous thromboembolism to nonbacterial thrombotic endocarditis (NBTE) and acute arterial ischemic stroke [3,4]. Importantly, an acute ischemic stroke can act as the very first clinical manifestation of a systemic, yet concealed, malignancy [5,6].

Mucin-producing carcinomas, particularly adenocarcinomas, are notoriously implicated in this paraneoplastic hypercoagulable state. In cancer patients presenting with stroke, the underlying pathophysiological mechanisms frequently diverge from conventional etiologies such as large-vessel atherosclerosis or atrial fibrillation [7]. Instead, the stroke mechanism is often related to micro-embolic showers originating from NBTE or in situ intravascular coagulation [8]. These unique mechanisms generate highly distinct radiological signatures. Among the radiological patterns described in cancer-associated stroke, the recently described "Three-Territory Sign" has emerged as a valuable imaging marker that may suggest an underlying cancer-associated hypercoagulable state. By presenting a case of an adenocarcinoma of unknown primary presenting with deep vein thrombosis and acute disseminated cerebral infarctions, this report highlights the potential diagnostic value of this MRI pattern in raising suspicion for malignancy-related coagulopathy.

CASE PRESENTATION

A 60-year-old patient was admitted to the emergency department presenting with newly developed diffuse abdominal pain. Initial clinical evaluation sought to rule out a surgical emergency. Consequently, a contrast-enhanced abdominal computed tomography (CT) scan was performed. The imaging revealed multiple, diffuse hypodense hepatic lesions highly suspicious for metastatic disease, notably without any associated lesions or signs of peritoneal carcinomatosis (Figure *1*).

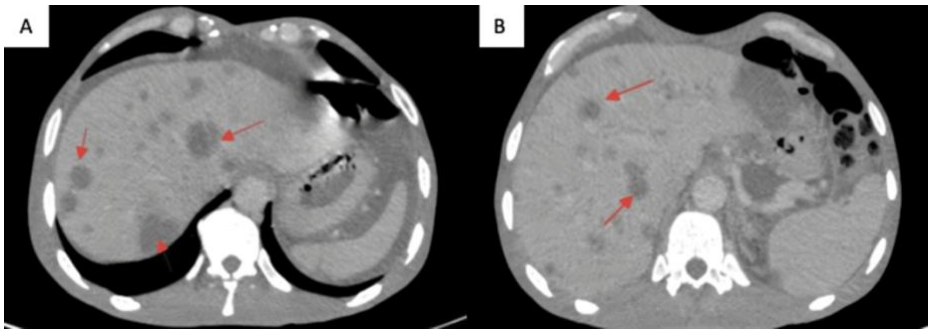


FIGURE 1: Contrast-enhanced axial abdominal CT images demonstrating multiple hypodense hepatic lesions (arrows) consistent with metastatic disease, without evidence of peritoneal carcinomatosis

To determine the etiology of the hepatic lesions, an ultrasound-guided liver biopsy was promptly performed. Histopathological examination revealed infiltration of the hepatic parenchyma by malignant gland-forming epithelial cells. The neoplastic cells exhibited glandular differentiation and cytological atypia, consistent with a moderately differentiated adenocarcinoma (Figure *2*).

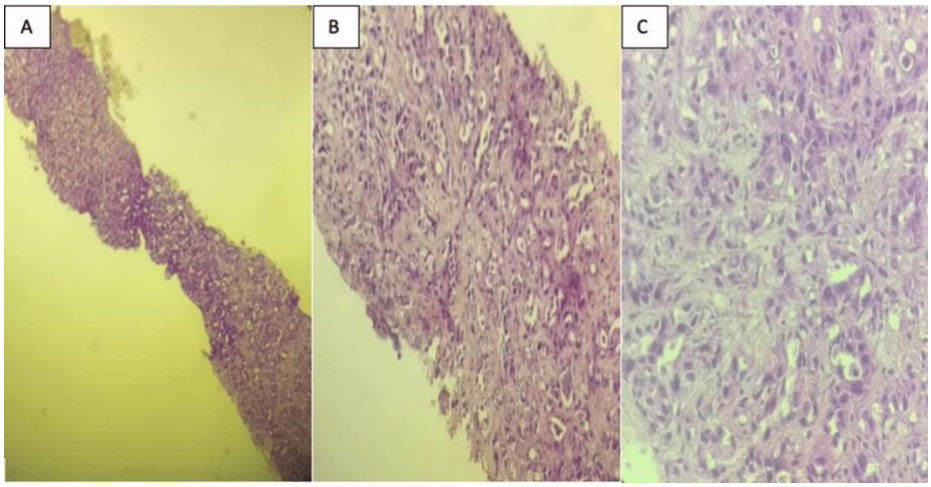


FIGURE 2: Histopathological examination of the liver lesion.
A : Low-power photomicrograph showing infiltration of the hepatic parenchyma by adenocarcinoma (H&E stain, ×100).
B : Intermediate-power view demonstrating the gland-forming architecture of the tumor (H&E stain, ×200).
C : High-power view highlighting the cytological atypia of the malignant glandular epithelial cells, consistent with a moderately differentiated adenocarcinoma (H&E stain, ×400).

Concurrently, the patient was diagnosed with a lower extremity deep vein thrombosis (DVT), providing the first overt clinical evidence of a systemic hypercoagulable state. During the hospitalization, the patient's clinical status deteriorated rapidly, marked by the acute onset of altered mental status and severe psychomotor agitation. This sudden neurological decline necessitated urgent neurovascular exploration. Although a cholangiopancreatography MRI (CP-MRI) was planned to search for the primary neoplastic site, the patient's severe agitation rendered the examination impossible. Consequently, the primary origin of the adenocarcinoma remained unknown. However, an urgent brain magnetic resonance imaging (MRI) was successfully acquired to evaluate the acute neurological deterioration.The neuroimaging revealed a striking and extensive pattern of cerebral ischemia. Diffusion-Weighted Imaging (DWI) visualized multiple, bilateral, and widely disseminated hyperintense lesions scattered across several distinct arterial distributions. The corresponding Apparent Diffusion Coefficient (ADC) maps demonstrated marked signal hypointensity within these lesions, confirming restricted water diffusion compatible with acute cytotoxic edema and true ischemic infarction. Furthermore, Fluid-Attenuated Inversion Recovery (FLAIR) sequences showed distinct hyperintense signal alterations within the corresponding ischemic beds. Crucially, the topographic distribution of these infarcts involved both anterior circulations (bilateral middle cerebral artery territories) and the posterior circulation (right posterior cerebral artery territory)(Figure *3*).

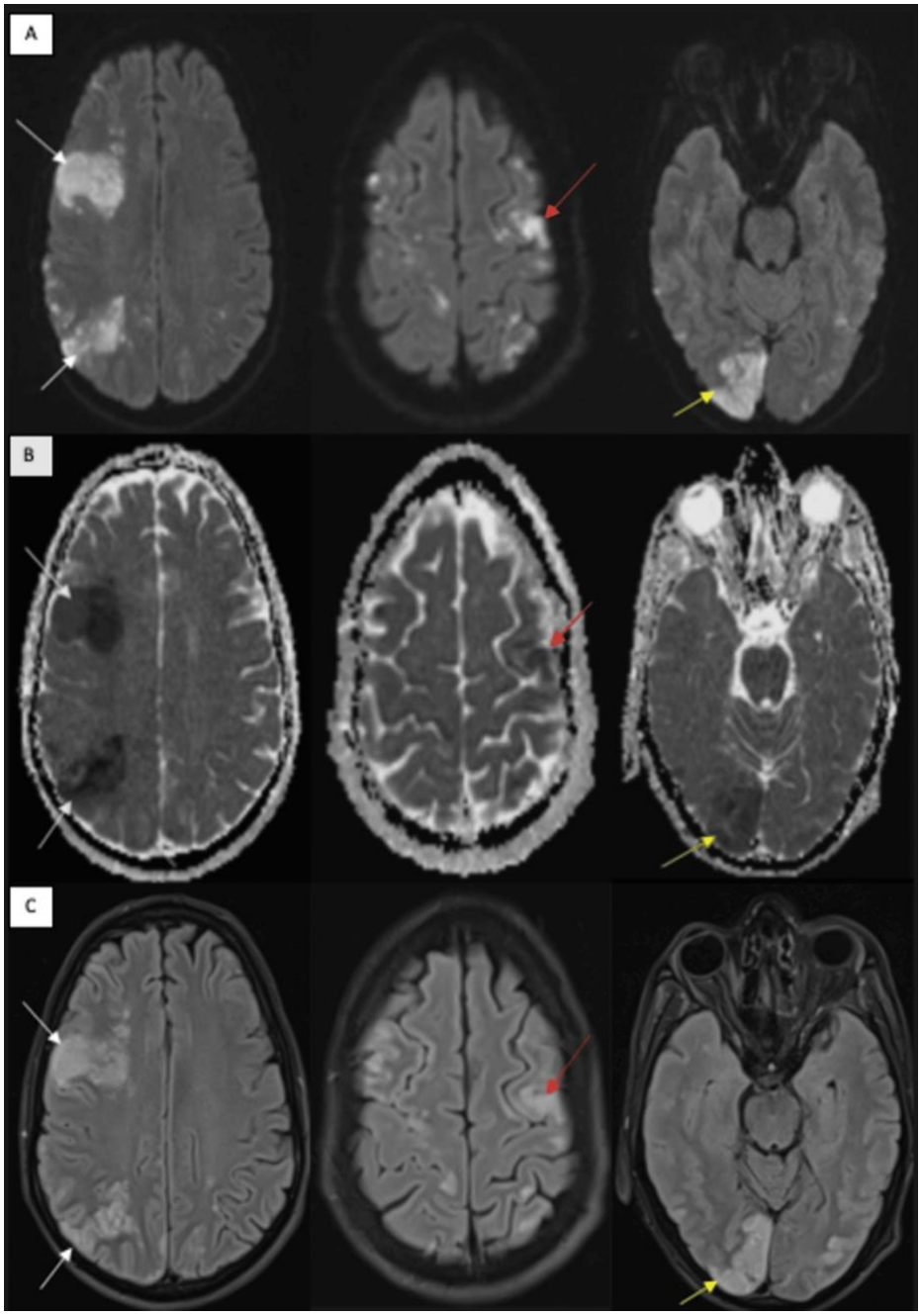


FIGURE 3: MRI demonstration of the "Three-Territory Sign" in Trousseau Syndrome. Axial brain MRI revealing widely disseminated, multi-territorial acute ischemic infarctions.

A : Diffusion-Weighted Imaging (DWI) demonstrates multiple punctate and confluent hyperintense lesions.

B : Corresponding Apparent Diffusion Coefficient (ADC) maps confirm restricted diffusion (hypointensity), consistent with cytotoxic edema.

C : Fluid-Attenuated Inversion Recovery (FLAIR) sequences demonstrate distinct hyperintense signal alteration in the corresponding vascular territories, indicating established acute infarctions.

Solid white arrowshighlight acute infarcts within the right middle cerebral artery (MCA) territory, correlating clinically with the patient's left hemiparesis.

Red arrows indicate concurrent lesions in the left middle cerebral circulation.

Yellow arrows highlight ischemic foci in the right posterior cerebral artery (PCA) territory. The simultaneous involvement of bilateral anterior circulations and the posterior circulation corresponds to the "Three-Territory Sign," a highly specific neuroimaging pattern associated with malignancy-related hypercoagulability in Trousseau syndrome.

No major cardioembolic source, atrial fibrillation, or significant extracranial arterial stenosis was identified during the initial clinical and imaging evaluation. Although the patient's rapid clinical deterioration precluded an exhaustive biological coagulation workup and definitive evaluation for all potential mechanisms of cancer-associated stroke, the simultaneous involvement of multiple vascular territories, combined with the recent diagnosis of DVT and an occult adenocarcinoma, was highly suggestive of a cancer-associated hypercoagulable state consistent with Trousseau syndrome.

DISCUSSION

The management and diagnosis of neurological deficits in the oncological population require a paradigm shift away from standard stroke algorithms. Our case perfectly illustrates the intersection of a concealed malignancy and catastrophic neurovascular events, emphasizing the pivotal role of the radiologist in identifying the underlying etiology based on imaging patterns. The pathogenesis of Trousseau syndrome is complex, multifactorial, and highly dependent on the histological subtype of the tumor. Adenocarcinomas are particularly thrombogenic. The release of tumor-derived products triggers widespread, systemic activation of the coagulation cascade [3]. Furthermore, Varki (2007) elegantly described how mucins secreted by adenocarcinomas enter the bloodstream and interact with selectins on platelets and endothelial cells, forming platelet-rich microthrombi and exacerbating the hypercoagulable state [4]. This biochemical environment directly predisposes the patient to both venous and arterial thrombotic events, which can occasionally be the initiating clinical sign of a concealed cancer, as observed in our patient who developed both a DVT and cerebral infarctions [5,6].

When an ischemic stroke occurs in a cancer patient, it is imperative to distinguish between conventional mechanisms and non-conventional mechanisms directly tied to the malignancy. A multicenter study by Kim et al. demonstrated that cancer patients with stroke frequently lack conventional risk factors, and their strokes are more likely to be driven by tumor-specific prothrombotic pathways [7]. Historically, it has been debated whether these ischemic events are a direct manifestation of hypercoagulability [2]. Current evidence supports a strong association between cancer and ischemic stroke, with nonbacterial thrombotic endocarditis

(NBTE) being recognized as an important potential mechanism. In NBTE, sterile, friable vegetations composed of platelets and fibrin deposit on cardiac valves and may subsequently fragment, resulting in systemic embolization and cerebral infarctions. However, cancer-associated stroke is a multifactorial condition, and other mechanisms should also be considered, including paradoxical embolism through cancer-related venous thrombosis, tumor emboli, disseminated intravascular coagulation, and treatment-related vascular injury such as chemotherapy-induced endothelial dysfunction [5,6,8].

The key diagnostic element in our patient was the characteristic MRI pattern of infarct distribution. Trousseau syndrome-related cerebral infarctions display characteristic MRI features that differ significantly from standard strokes. They typically present as small, multiple, and widely disseminated hyperintense lesions on DWI, frequently accompanied by complex clinical manifestations such as the sudden consciousness disorders and agitation seen in our patient [9]. From a diagnostic perspective, The spatial distribution of these infarcts may provide an important diagnostic clue. Finelli and Nouh (2016) defined the "Three-Territory DWI acute infarcts" sign as a distinct imaging biomarker for cancer-associated hypercoagulation [10]. This sign is characterized by the simultaneous presence of acute ischemic lesions involving at least three independent vascular beds-most commonly both the left and right anterior circulations alongside the posterior (vertebrobasilar) circulation. Subsequent studies further supported the association between the "Three-Territory Sign" and malignancy-related ischemic stroke, suggesting that this imaging pattern may represent a valuable clue in patients with suspected cancer-associated hypercoagulability [11,12]. In our patient, the identification of bilateral anterior circulation and posterior circulation infarcts fulfilled the criteria for this radiological pattern and, in the context of concomitant DVT and occult adenocarcinoma, supported the diagnosis of a cancer-associated prothrombotic state.

CONCLUSIONS

Disseminated cerebral infarctions, particularly when accompanied by venous thromboembolism, can serve as a devastating and abrupt indicator of Trousseau syndrome. This case emphasizes that in patients presenting with acute altered mental status and multi-territorial ischemic strokes, clinicians should maintain a high index of suspicion for an underlying malignancy, even when initial abdominal presentations mimic general emergencies. Recognition of the "Three-Territory Sign" on diffusion-weighted MRI may provide an important clue to an otherwise occult malignancy and should prompt further investigation for an underlying cancer-associated hypercoagulable state. Early identification

of cancer-associated stroke may also have therapeutic implications, including consideration of anticoagulation strategies in selected patients, rather than conventional antiplatelet-based approaches alone.

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REFERENCES

1. Graus F, Rogers LR, Posner JB: Cerebrovascular complications in patients with cancer . Medicine. 1985, 64:16-35. 10.1097/00005792-198501000-00002
https://doi.org/10.1097/00005792-198501000-00002

2. Chaturvedi S, Ansell J, Recht L: Should cerebral ischemic events in cancer patients be considered a manifestation of hypercoagulability?. Stroke. 1994, 25:1215-8. 10.1161/01.str.25.6.1215
https://doi.org/10.1161/01.STR.25.6.1215

3. Ikushima S, Ono R, Fukuda K, Sakayori M, Awano N, Kondo K: Trousseau's syndrome: cancer-associated thrombosis.JpnJClinOncol.2016,46:204-8. 10.1093/jjco/hyv165
https://doi.org/10.1093/jjco/hyv165

4. Varki A: Trousseau's syndrome: multiple definitions and multiple mechanisms . Blood. 2007, 110:1723-9.
https://doi.org/10.1182/blood-2006-10-053736

10.1182/blood-2006-10-053736
https://doi.org/10.1182/blood-2006-10-053736

5. Kwon H-M, Kang BS, Yoon B-W: Stroke as the first manifestation of concealed cancer. J Neurol Sci . 2007, 258:80-3. 10.1016/j.jns.2007.02.035
https://doi.org/10.1016/j.jns.2007.02.035

6. Taccone FS, Jeangette SM, Blecic SA: First-Ever stroke as initial presentation of systemic cancer. J Stroke Cerebrovasc Dis. 2008, 17:169-74. 10.1016/j.jstrokecerebrovasdis.2008.01.007
https://doi.org/10.1016/j.jstrokecerebrovasdis.2008.01.007

7. Kim SG, Hong JM, Kim HY, et al.: Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke. 2010, 41:798-801. 10.1161/STROKEAHA.109.571356
https://doi.org/10.1161/STROKEAHA.109.571356

8. el-Shami K, Griffiths E, Streiff M: Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. Oncologist. 2007, 12:518-23. 10.1634/theoncologist.12-5-518
https://doi.org/10.1634/theoncologist.12-5-518

9. Bao L, Zhang S, Gong X, Cui G: Trousseau syndrome related cerebral infarction: clinical manifestations, laboratory findings and radiological features. J Stroke Cerebrovasc Dis. 2020, 29:104891. 10.1016/j.jstrokecerebrovasdis.2020.104891
https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104891

10. Finelli PF, Nouh A: Three-Territory DWI acute infarcts: diagnostic value in cancer-associated hypercoagulation stroke (Trousseau syndrome). AJNR Am J Neuroradiol. 2016, 37:2033-6. 10.3174/ajnr.A4846
https://doi.org/10.3174/ajnr.A4846

11. Nouh AM, Staff I, Finelli PF: Three Territory sign: an MRI marker of malignancy-related ischemic stroke (Trousseau syndrome). Neurol Clin Pract. 2019, 9:124-8. 10.1212/CPJ.0000000000000603
https://doi.org/10.1212/CPJ.0000000000000603

12. 12. Ryan D, Bou Dargham T, Ikramuddin S, Shekhar S, Sengupta S, Feng W.: "Epidemiology, Pathophysiology, and Management of Cancer-Associated Ischemic Stroke.". Cancers (Basel). 2024, 16:10.3390/cancers16234016
https://doi.org/10.3390/cancers16234016