A case of synchronous ileocecal adenocarcinoma and plasmacytoma initially presenting with multiple cerebral infarctions

Zihan Meng[1,2], Hongbo Gao[3], Kai Zhang[4], Peiyao Li[5,6], Jiaqi Chen[5,6], Lan Ye[5,6] and Chunning Zheng[1,2*]

[1] Shandong First Medical University, Jinan, Shandong 250117, China
[2] Department of Gastrointestinal Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong 250021, China
[3] Department of General Surgery, Zhangqiu People's Hospital, Jinan, Shandong 250200, China
[4] Department of General Surgery, Wenshang People's Hospital, Jining, Shandong 272501, China
[5] Cheeloo College of Medicine, Shandong University, Jinan, Shandong 250012, China
[6] Cancer Center, The Second Hospital of Shandong University, Jinan, Shandong 250033, China
* Correspondence: zhengchunning@sdfmu.edu.cn (Zheng C)

Abstract

Acute multiple cerebral infarctions as the initial manifestation of multiple primary malignant neoplasms are very rare. Studies have shown that it may even be the initial manifestation of occult systemic malignancy in up to 3% of patients. We retrospectively reported a 74-year-old male who initially presented with right hemiparesis. Magnetic resonance imaging and diffusion-weighted imaging of the brain showed acute small infarcts in the left parietal and right temporal lobes, and acute multiple cerebral infarctions were diagnosed. At the same time, computed tomography scans of the chest and abdomen revealed the concurrent ileocecal wall thickening and a left pleural mass with associated adjacent rib destruction. Subsequently, colonoscopy and biopsy of the rib lesion confirmed that the patient was diagnosed with synchronous ileocecal adenocarcinoma and plasmacytoma. Given that cerebral infarction may be the first sign of multiple primary malignant neoplasms, a precise etiological diagnosis is crucial to guiding treatment strategies and optimizing clinical prognosis.

Introduction

Although the majority of cerebral infarctions stem from conventional mechanisms such as atherosclerosis or cardioembolism, malignancy is an important yet often underrecognized or overlooked etiology in clinical practice. Recent research has advocated for the recognition of "cancer-related stroke" as a distinct etiologic subtype within stroke classification systems to enhance clinical vigilance and promote targeted investigations[1]. This entity is typically defined by three criteria: The absence of a definite conventional cause, a diagnosis of malignancy within 6 months of the stroke's onset, and no history of anticancer treatment prior to the stroke event[2]. It is estimated that approximately 5%–10% of stroke patients harbor an occult systemic malignancy (OSM)[3], which refers to a noncentral nervous system malignancy first detected during the stroke work-up, lacking clinically evident warning signs like deep vein thrombosis[2,4]. Although the association between stroke and cancer is established, cases where acute multiple cerebral infarctions (AMCIs) serve as the initial manifestation of multiple primary malignant neoplasms (MPMNs) are exceedingly rare.

Among solid tumors, gastrointestinal adenocarcinoma carries the highest risk of cancer-associated thrombosis, with hypercoagulability being a key pathophysiological mechanism underlying cryptogenic stroke in cancer patients[5]. Furthermore, MPMN itself—defined as the occurrence of two or more distinct histologically confirmed malignancies in a single patient, either synchronously or metachronously—is an uncommon phenomenon. Its reported incidence varies widely[6–8]. MPMNs frequently arise within cognate systems or paired organs, making the co-occurrence of a gastrointestinal adenocarcinoma and a hematologic malignancy, such as plasmacytoma, an even rarer clinical entity.

Here, we present a singular case of synchronous ileocecal adenocarcinoma and solitary bone plasmacytoma, which initially manifested as AMCI. This case embodies three rare features: Cryptogenic stroke, MPMN, and the coexistence of gastrointestinal and hematologic malignancies. We aim to heighten the clinical awareness that stroke can be the inaugural sign of underlying occult malignancies, and to elucidate the complex pathophysiological interplay, diagnostic challenges, and therapeutic dilemmas present in such cases.

Case report

A 74-year-old man was admitted to a local hospital following the acute onset of right-sided limb weakness. Brain magnetic resonance imaging (MRI)–diffusion-weighted imaging (DWI) revealed an AMCI involving bilateral anterior and posterior circulations (Fig. 1). Initial laboratory investigations demonstrated an elevated serum carcinoembryonic antigen (CEA) level of 12.68 ng/mL (normal range: 0–5.2 ng/mL) and a significantly reduced hemoglobin level of 88 g/L (normal range: 130–175 g/L), indicative of anemia and potential malignancy.

To elucidate the underlying etiology, contrast-enhanced computed tomography (CT) of the chest and abdomen was performed. The scans revealed irregular wall thickening in the ileocecal region (Fig. 2b) and a concomitant destructive mass in the left pleural cavity with adjacent rib erosion (Fig. 3a, b), both highly suggestive of malignant processes.

The patient was subsequently transferred to our institution for comprehensive management. Colonoscopy identified an ulcerative mass in the ileocecal area (Fig. 2a), and a histopathological examination via an endoscopic biopsy confirmed a moderately

differentiated ileocecal adenocarcinoma (Fig. 2c, d). Concurrently, a biopsy of the left rib mass was conducted. The histological analysis revealed sheets of monomorphic plasma cells (Fig. 4a, b). Immunohistochemistry (IHC) showed that the neoplastic cells were strongly positive for CD38 and CD138 (Fig. 4c, d) and exhibited lambda light chain restriction (kappa-negative, lambda-positive) (Fig. 4e, f). Although his bone marrow morphology showed only 1% plasma cells, and flow cytometry did not detect a monoclonal population, the presence of clonal lambda-restricted cells supported a diagnosis of plasmacytoma. Whole-body MRI was performed to differentiate between solitary bone plasmacytoma (SBP) and multiple myeloma (MM), revealing no other bony lesions or distant metastases (Fig. 3c, d). A bone marrow biopsy further confirmed minimal involvement (Fig. 3e, f).

Following a discussion among the multidisciplinary team (MDT), the patient was definitively diagnosed with MPMN: Synchronous ileocecal adenocarcinoma and SBP with minimal bone marrow involvement, initially presenting as AMCI.
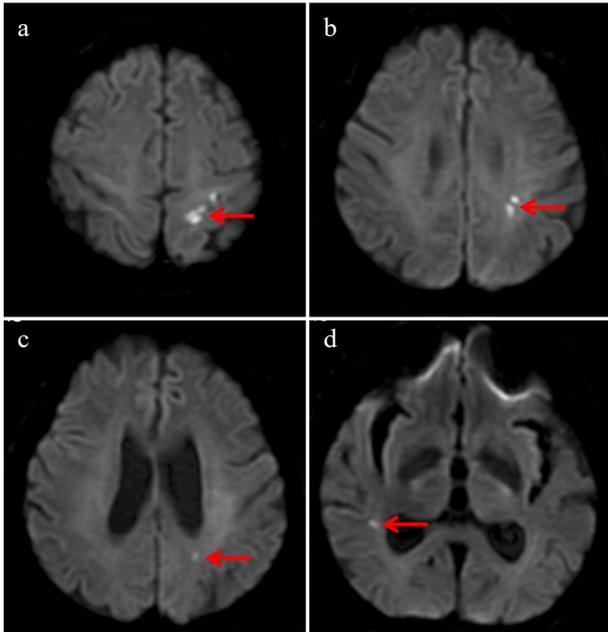

Fig. 1 Brain magnetic resonance imaging–diffusion-weighted imaging (MRI-DWI) demonstrated multiple cerebral infarctions involving both the anterior and posterior circulations. Acute infarction in (a) the left anterior cerebral artery (ACA) region, (b) the left middle cerebral artery (MCA) region, (c) the left posterior cerebral artery (PCA) region, and (d) the right MCA region.
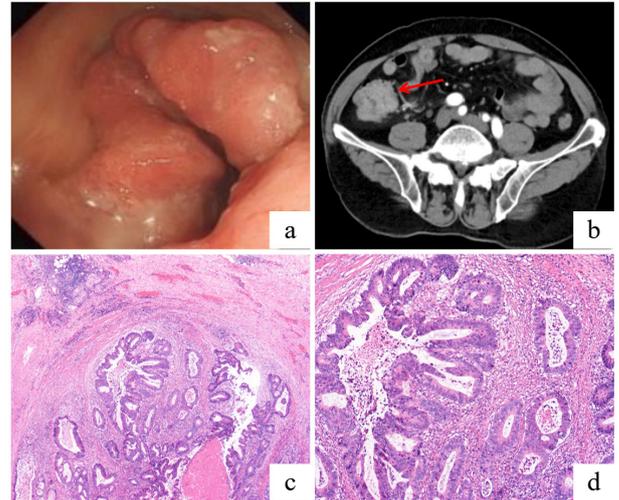

Fig. 2 Diagnostic and histopathological findings of ileocecal adenocarcinoma. (a) Colonoscopic view of a large, irregular mass in the ileocecal region. (b) Contrast-enhanced abdominal CT scan (axial view) showing irregular wall thickening with a marked enhancement in the ascending colon and ileocecal region. (c) Low-power photomicrograph (hematoxylin and eosin [HE] staining) of the resected specimen revealing an ulcerated, moderately differentiated adenocarcinoma with transmural invasion into the muscular layer. (d) High-power photomicrograph (HE staining) demonstrating the neoplastic glands with enlarged, hyperchromatic nuclei and evident mitotic activity. No significant perineural or lymphovascular invasion was identified.
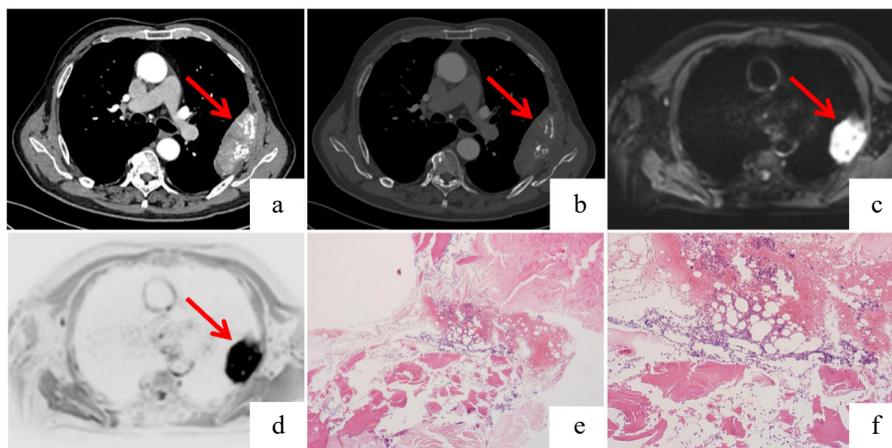

Fig. 3 Imaging and histopathological findings of the plasmacytoma. (a), (b) Axial and coronal contrast-enhanced chest CT scans demonstrating irregular left pleural thickening (measuring approximately 9.8 × 3.1 cm in the maximum cross-section) with associated destruction of the adjacent rib. (c), (d) Fusion positron emission tomography (PET)-MRI images reveal a rounded mass in the left chest wall showing hyperintensity on DWI with corresponding hypointensity on the apparent diffusion coefficient (ADC) map, consistent with restricted diffusion. Increased signal intensity is also noted in the adjacent rib on the MRI sequence. (e), (f) The bone marrow biopsy specimens show scattered plasma cells with lambda light chain restriction indicated by immunohistochemistry: (f) lambda-positive; (e) kappa-negative. This confirmed the presence of monoclonal plasma cells. The overall cellularity and number of plasma cells were not significantly increased.
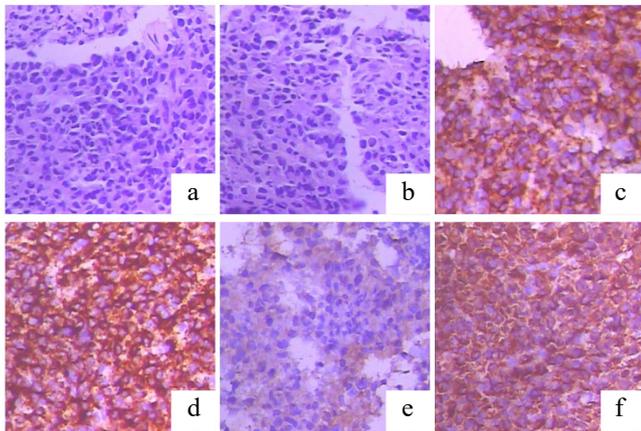
Fig. 4 Histopathological and immunohistochemical (IHC) features of the left rib mass, diagnostic of plasmacytoma. (a), (b) Hematoxylin and eosin (H&E) staining reveals sheets of monomorphic plasma cells. (c), (d) The neoplastic cells show strong and diffuse positivity for the plasma cell markers (c) CD38 and (d) CD138. (e), (f) IHC staining demonstrates lambda light chain restriction, supporting a monoclonal plasma cell proliferation: (f) positive for lambda light chains; (e) negative for kappa light chains.

The MDT's consensus prioritized surgical resection of the ileoce-cal adenocarcinoma because of its more aggressive potential. The patient underwent a radical right hemicolectomy. The final postop-erative pathological confirmed a moderately to well-differentiated tubular adenocarcinoma (pT3N1bM0, Stage IIIB). The patient recov-ered well from surgery. At the 1-month postoperative follow-up, he was in good condition and was transferred to the hematology department for subsequent radiotherapy targeting the SBP. At the 6-month postoperative telephone follow-up, the patient reported no recurrence of cerebral infarction, with good recovery of neuro-logical function and no re-elevation in D-dimer levels. The solitary bone plasmacytoma responded well to local radiotherapy, achiev-ing local control without radiotherapy-related adverse effects, although its long-term efficacy still requires regular monitoring. The patient's intestinal function has also recovered very well, with no signs of recurrence such as anastomotic thickening, and his hemoglobin levels have returned to normal. At the 1-year postoper-ative telephone follow-up, no long-term treatment-related adverse effects were observed, and the patient's condition remained stable.

Discussion

Patients presenting with cryptogenic stroke constitute a popula-tion at an elevated risk for underlying occult malignancy. Epidemio-logical studies suggest that approximately 20% of strokes with an undetermined etiology may be associated with a cancer diagnosis at presentation[9]. Prospective data from cohorts like the Norwegian Stroke Research Registry ($n = 1,646$) confirm that 5.0% of ischemic stroke patients harbor a concurrent active cancer, with a signifi-cantly heightened risk of cancer diagnosis within the ensuing 6–12 months[3]. Compared with stroke patients without cancer, those with an underlying occult malignancy experience poorer clinical outcomes, higher degrees of disability, and greater healthcare expenditures[10]. Across multiple studies, pulmonary and gastro-intestinal adenocarcinomas are the predominant malignancies identi-fied in stroke patients with cancer[10,11]. Although solid tumors are most common, hematologic neoplasms such as non-Hodgkin lymphoma have also been documented in this context[12].

Adenocarcinomas represent the most frequent histological subtype among cancer-related stroke patients[10,12,13], a predilection largely attributed to their mucin-secreting properties[14]. Mucin, a high-molecular-weight molecule, promotes microthrombus formation by interacting with cell adhesion molecules like P- and L-selectins. Nevertheless, the precise mechanisms of cancer-related stroke have not been fully elucidated. The prevailing pathophysiological model centers on cancer-induced perturbations of coagulation and fibri-nolysis[15]. Tumor cells release procoagulant factors and inflamma-tory cytokines that directly or indirectly activate the coagulation cascade, creating a systemic hypercoagulable state. This, in turn, predisposes patients to intracranial microthrombosis and dissemi-nated intravascular coagulation. In patients with plasmacytoma and multiple myeloma, a comprehensive dysregulation of both the coagulation and fibrinolysis, driven by a cytokine network, collec-tively leads to an increased risk of thrombosis[16]. First, patients with plasmacytoma and multiple myeloma commonly exhibit enhanced endogenous thrombogenic potential. Concurrently, impaired fibri-nolytic activity makes the formed thrombi more resistant to lysis. Second, the M-protein secreted by malignant plasma cells, which is the predominant paraprotein, not only increases blood viscosity but also interferes with normal fibrin polymerization, resulting in an abnormal fibrin structure. This abnormal structure impedes the binding of coagulation Factor XIII and plasmin, ultimately leading to the formation of more compact thrombi that are more resistant to fibrinolysis. The aforementioned dysregulation primarily mediated by inflammatory cytokines, particularly interleukin (IL)-6 and vascu-lar endothelial growth factor (VEGF). The cytokine imbalance ulti-mately increases von Willebrand factor (vWF) antigens, Factor VIII coagulant activity, and fibrinogen levels, which collectively promote the formation of thrombosis[16,17]. Therefore, further mechanistic research is crucial to facilitate earlier detection of occult malignan-cies in patients presenting with cryptogenic stroke.

When discussing cancer-related stroke, Trousseau's syndrome is a critical concept. First described by French physician Armand Trousseau in 1865, this syndrome represents a spectrum of clinical manifestations, resulting from a cancer-associated hypercoagulable state. It is recognized as a type of paraneoplastic syndrome and represents the second leading cause of death in cancer patients, surpassed only by the malignancy itself[18]. AMCI is a well-docu-mented manifestation of Trousseau's syndrome and can even be its initial presentation[4,19]. Although no universally accepted diagnos-tic criteria exist, several key features are characteristic. Neuroimag-ing often reveals multiple small infarcts across multiple vascular territories, with the "three territory sign" (TTS) (involving the bilat-eral anterior and posterior circulation) holding significant diagnos-tic value[20]. Furthermore, markedly elevated D-dimer levels are a common laboratory finding[14,21,22]. As a product of fibrin degrada-tion, D-dimer is a sensitive, though nonspecific, biomarker of coagu-lation activation and thrombosis; its elevation indicates a systemic hypercoagulable state and has been identified as an independent risk factor for cancer-related stroke. Crucially, since acute multiple cerebral infarcts in MRI-DWI are not pathognomonic for Trousseau's syndrome and are also observed in cardiogenic embolism (most frequently atrial fibrillation)[23], a comprehensive work-up including electrocardiography (ECG) and echocardiography is mandatory to exclude cardioembolic sources before attributing the stroke to Trousseau's syndrome.

Applying these diagnostic considerations to our patient, a defini-tive diagnosis of Trousseau's syndrome remains challenging, despite suggestive features. Although the patient had confirmed active malignancy and the MRI-DWI demonstrated the TTS, several critical

factors preclude a conclusive diagnosis. First, the absence of universally accepted diagnostic criteria for Trousseau's syndrome introduces inherent ambiguity. Second, the patient's D-dimer level was only mildly elevated (1.3 mg/L; normal range: 0–0.5 mg/L), contrasting with the markedly elevated levels typically reported in classic cases. Third, although routine ECG and transthoracic echocardiography (TTE) revealed no abnormalities, the inherent limitations of TTE in detecting left atrial appendage thrombi and nonbacterial thrombotic endocarditis (NBTE) compared with transesophageal echocardiography (TEE), coupled with the absence of prolonged Holter monitoring to exclude paroxysmal atrial fibrillation, mean that potential cardioembolic sources cannot be fully eliminated. Finally, the contribution of traditional stroke risk factors (advanced age, hypertension, smoking history) cannot be entirely disentangled from a potential paraneoplastic mechanism. Therefore, although Trousseau's syndrome represents a plausible diagnostic consideration, this case is most accurately classified as cryptogenic stroke representing the initial manifestation of occult systemic malignancies.

This diagnostic dilemma underscores that routine cancer screening is not warranted for all cryptogenic stroke patients because of the cost considerations. However, the presence of specific clinical indicators—including bilateral infarctions or TTS on MRI-DWI, particularly when combined with elevated D-dimer levels and relevant tumor markers such as carcinoembryonic antigen (CEA) and CA125—should prompt targeted investigation for occult malignancy. In such selected cases, timely cancer screening and initiation of appropriate antitumor therapy may potentially improve clinical outcomes.

MPMNs represent a rare but clinically significant phenomenon in oncology. Although numerous MPMN cases have been documented worldwide, the synchronous occurrence of ileocecal adenocarcinoma and SBP described in our case appears to be the first reported instance. The diagnosis of MPMN follows the classical Warren and Gates criteria (1932), requiring: (1) a histological confirmation of malignancy in each tumor; (2) distinct pathological features between tumors; and (3) development in separate anatomical sites with definitive exclusion of metastatic spread or recurrence. The reported incidence of MPMN varies substantially across populations, likely reflecting interethnic genomic differences and variations in the duration of clinical follow-up. This epidemiological variability necessitates cautious interpretation of the prevalence data. Equally important is recognizing the diagnostic challenge posed by MPMN. A kack of clinical suspicion frequently leads to misclassification as metastatic disease, particularly in the context of declining autopsy rates—a procedure that historically has been crucial for a definitive diagnosis. Among MPMN cases, double primary malignant neoplasms (DPMNs) represent the most common presentation, with adenocarcinoma being the predominant histological type. The extreme complexity of MPMN is illustrated by a reported case involving 17 distinct primary malignancies in a single patient[24], highlighting the remarkable potential for multiple oncogenic processes to coexist.

The precise etiology and pathogenesis of MPMNs remain incompletely elucidated. Current evidence indicates that their development involves synergistic interactions among multiple determinants, including genetic susceptibility, somatic mutations, iatrogenic exposure, endocrine influences, environmental factors, and the immunosenescence associated with aging. At the cellular level, carcinogenesis represents a multistep process involving cumulative genetic alterations. With advanced age, a progressive decline in immune surveillance and DNA repair capacity coincides with increased proto-oncogene activation, collectively elevating susceptibility to cancer. Epidemiological studies have revealed that approximately one-third of cancer survivors over the age of 60 develop second primary malignancies[25]. Specific risk factors for MPMN include hereditary cancer syndromes such as Lynch syndrome and familial adenomatous polyposis (FAP)[26,27], with epidermal growth factor receptor (EGFR) mutations representing an established molecular risk factor. Iatrogenic contributions are well-documented, as chemoradiotherapy for primary malignancies can induce second neoplasms[28,29]. Endocrine pathways contribute to MPMNs' pathogenesis, evidenced by the bidirectional risk association between breast and thyroid cancers[30]. Environmental and lifestyle factors account for up to 90% of cancer cases[31], with smoking, obesity, and insulin resistance increasing the risk of secondary cancer[32]. Future research should focus on elucidating the molecular pathogenesis of MPMNs to facilitate effective prevention and early detection strategies.

Early detection and accurate diagnosis are critically important in managing MPMNs. Given the high prevalence of metastatic disease, the emergence of new tumor lesions following an initial cancer diagnosis often leads to a presumptive diagnosis of metastasis, potentially overlooking MPMN. Since the treatment principles for MPMNs (typically with curative intent) differ fundamentally from those for metastatic cancer (palliative), maintaining vigilance when multiple lesions are identified is essential, with thorough investigations conducted to confirm the diagnosis. In the present case, after confirming ileocecal adenocarcinoma, the biopsy of the suspicious left chest wall lesion revealed plasmacytoma, establishing the diagnosis of synchronous MPMNs. This accurate diagnosis provided the crucial foundation for the subsequent MDT discussion, leading to the decision to prioritize radical surgery for the ileocecal adenocarcinoma and ensuring an evidence-based therapeutic pathway.

The management of cancer-related stroke is complex, and the current guidelines lack definitive recommendations on the optimal antithrombotic strategies to prevent recurrence. Antiplatelet therapy is often the pragmatic choice because of its favorable safety profile and potential antitumor effects via inhibiting platelet-mediated oncogenesis, but it may be insufficient to counteract the systemic hypercoagulable state[33]. Anticoagulation, particularly with low-molecular-weight heparin (LMWH), is the guideline-endorsed first-line intervention, though its efficacy for arterial stroke prevention remains inconclusive, as evidence primarily derives from venous thromboembolism studies. The significant bleeding risk in cancer patients, with an annual incidence of major hemorrhage reaching 20%[15], must be carefully weighed against the thrombotic risk. For this patient, the MDT implemented a perioperative LMWH protocol, discontinuing subcutaneous administration 24 hours preoperatively and reinstating it as early as feasible postoperatively, with vigilant monitoring.

No established evidence-based guidelines exist for managing MPMNs. Therapeutic decisions require personalized strategies through the MDT's evaluation of factors including age, life expectancy, tumor types, pathological staging, and nutritional status. In this case, the MDT prioritized managing the more aggressive ileocecal adenocarcinoma with radical surgery. Postoperative pathology confirming Stage IIIB disease led to a further MDT review, which concluded that although adjuvant CAPEOX chemotherapy would typically be indicated, priority should be given to treating the coexisting plasmacytoma. This case underscores the pivotal importance of the MDT's approach in managing complex MPMN presentations.

Conclusions

The co-occurrence of ileocecal adenocarcinoma and SBP presenting as cryptogenic stroke is exceptionally rare and carries significant clinical implications. On the basis of existing evidence demonstrating that cryptogenic stroke in cancer patients typically shows elevated D-dimer levels and multi-territorial cerebral infarcts[21], we propose that patients exhibiting these characteristics, along with no evidence of cardiogenic embolism, should raise a strong suspicion of underlying occult systemic malignancy.

The management and prognosis of MPMNs differ fundamentally from those of metastatic cancer. Enhancing clinical research to reduce misdiagnosis is therefore crucial for optimizing patient outcomes. The MDT approach has become essential in oncology care, proving particularly valuable in complex cases such as MPMNs accompanied by cerebral infarction. Through a comprehensive risk–benefit analysis, the MDT model enables the formulation of precise treatment strategies that can improve overall survival and quality of life for these patients.

Ethical statements

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. All identifiable information has been removed to protect the patient's privacy. The article is exempt from Ethical Committee approval, as it is a case report that does not include data collection and analysis.

Author contributions

The authors confirm their contributions to the paper as follows: conceptualization: Zheng C; writing – original draft, investigation: Meng Z; supervision: Zheng C, Ye L; project administration: Gao H, Zhang K; data curation: Gao H, Li P; writing – review and editing: Ye L, Chen J. All authors reviewed the results and approved the final version of the manuscript.

Data availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Acknowledgments

Conflict of interest

The authors declare that they have no conflict of interest.

Dates

References

[1] Bang OY, Chung JW, Lee MJ, Seo WK, Kim GM, et al. 2020. Cancer-related stroke: an emerging subtype of ischemic stroke with unique pathomechanisms. *Journal of stroke* 22:1–10

[2] Kwon HM, Kang BS, Yoon BW. 2007. Stroke as the first manifestation of concealed cancer. *Journal of the Neurological Sciences* 258:80–83

[3] Salazar-Camelo RA, Moreno-Vargas EA, Cardona AF, Bayona-Ortiz HF. 2021. Ischemic stroke: a paradoxical manifestation of cancer. *Critical Reviews in Oncology/Hematology* 157:103181

[4] Taccone FS, Jeangette SM, Blecic SA. 2008. First-ever stroke as initial presentation of systemic cancer. *Journal of Stroke and Cerebrovascular Diseases* 17:169–174

[5] Grazioli S, Paciaroni M, Agnelli G, Acciarresi M, Alberti A, et al. 2018. Cancer-associated ischemic stroke: a retrospective multicentre cohort study. *Thrombosis Research* 165:33–37

[6] Demandante CG, Troyer DA, Miles TP. 2003. Multiple primary malignant neoplasms: case report and a comprehensive review of the literature. *American Journal of Clinical Oncology* 26:79–83

[7] Liu Z, Liu C, Guo W, Li S, Bai O. 2015. Clinical analysis of 152 cases of multiple primary malignant tumors in 15, 398 patients with malignant tumors. *PLoS One* 10:e0125754

[8] Zhai C, Cai Y, Lou F, Liu Z, Xie J, et al. 2018. Multiple primary malignant tumors – a clinical analysis of 15,321 patients with malignancies at a single center in China. *Journal of Cancer* 9:2795–2801

[9] Selvik HA, Bjerkreim AT, Thomassen L, Waje-Andreassen U, Naess H, et al. 2018. When to screen ischaemic stroke patients for cancer. *Cerebrovascular Diseases* 45:42–47

[10] Dearborn JL, Urrutia VC, Zeiler SR. 2014. Stroke and cancer - a complicated relationship. *Journal of Neurology & Translational Neuroscience* 2:1039

[11] Navi BB, Singer S, Merkler AE, Cheng NT, Stone JB, et al. 2014. Cryptogenic subtype predicts reduced survival among cancer patients with ischemic stroke. *Stroke* 45:2292–2297

[12] Quintas S, Rogado J, Gullón P, Pacheco-Barcia V, Dotor García-Soto J, et al. 2018. Predictors of unknown cancer in patients with ischemic stroke. *Journal of Neuro-oncology* 137:551–557

[13] Lee MJ, Chung JW, Ahn MJ, Kim S, Seok JM, et al. 2017. Hypercoagulability and mortality of patients with stroke and active cancer: the OASIS-CANCER study. *Journal of stroke* 19:77–87

[14] Schwarzbach CJ, Schaefer A, Ebert A, Held V, Bolognese M, et al. 2012. Stroke and cancer: the importance of cancer-associated hypercoagulation as a possible stroke etiology. *Stroke* 43:3029–3034

[15] Navi BB, Iadecola C. 2018. Ischemic stroke in cancer patients: a review of an underappreciated pathology. *Annals of Neurology* 83:873–883

[16] Uaprasert N, Voorhees PM, Mackman N, Key NS. 2010. Venous thromboembolism in multiple myeloma: current perspectives in pathogenesis. *European Journal of Cancer* 46:1790–1799

[17] Coppola A, Tufano A, Di Capua M, Franchini M. 2011. Bleeding and thrombosis in multiple myeloma and related plasma cell disorders. *Seminars in Thrombosis and Hemostasis* 37:929–945

[18] Varki A. 2007. Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood* 110:1723–1729

[19] Kim SJ, Park JH, Lee MJ, Park YG, Ahn MJ, et al. 2012. Clues to occult cancer in patients with ischemic stroke. *PLoS One* 7:e44959

[20] Nouh AM, Staff I, Finelli PF. 2019. Three Territory Sign: An MRI marker of malignancy-related ischemic stroke (Trousseau syndrome). *Neurology. Clinical Practice* 9:124–128

[21] Kim SG, Hong JM, Kim HY, Lee J, Chung PW, et al. 2010. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. *Stroke* 41:798–801

[22] Tsushima M, Metoki N, Hagii J, Saito S, Shiroto H, et al. 2020. D-dimer and C-reactive Protein as Potential Biomarkers for Diagnosis of Trousseau's Syndrome in Patients with Cerebral Embolism. *Journal of Stroke and Cerebrovascular Diseases* 29:104534

[23] Ito S, Ueda A, Murate K, Hirota S, Fukui T, et al. 2016. Differentiation of cancer from atrial fibrillation in patients with acute multifocal stroke. *Journal of the Neurological Sciences* 368:344–348

[24] Nutting C, Camplejohn RS, Gilchrist R, Tait D, Blake P, et al. 2000. A patient with 17 primary tumours and a germ line mutation in TP53: tumour induction by adjuvant therapy? *Clinical Oncology* 12:300–304

[25] Soerjomataram I, Coebergh JW. 2009. Epidemiology of multiple primary cancers. In *Cancer Epidemiology. Methods in Molecular Biology*,

ed. Verma M. 471. Totowa, NJ: Humana Press. pp. 85–105 doi: 10.1007/978-1-59745-416-2_5

[26] Lam AK, Chan SS, Leung M. 2014. Synchronous colorectal cancer: clinical, pathological and molecular implications. *World Journal of Gastroenterology* 20:6815–6820

[27] Liu X, Goldblum JR, Zhao Z, Landau M, Heald B, et al. 2012. Distinct clinicohistologic features of inflammatory bowel disease-associated colorectal adenocarcinoma: in comparison with sporadic microsatellite-stable and Lynch syndrome-related colorectal adenocarcinoma. *The American Journal of Surgical Pathology* 36:1228–1233

[28] Chen SC, Liu CJ, Hu YW, Yeh CM, Hu LY, et al. 2016. Second primary malignancy risk among patients with gastric cancer: a nationwide population-based study in Taiwan. *Gastric Cancer* 19:490–497

[29] Tao L, Clarke CA, Rosenberg AS, Advani RH, Jonas BA, et al. 2017. Subsequent primary malignancies after diffuse large B-cell lymphoma in the modern treatment era. *British Journal of Haematology* 178:72–80

[30] Nielsen SM, White MG, Hong S, Aschebrook-Kilfoy B, Kaplan EL, et al. 2016. The breast-thyroid cancer link: a systematic review and meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention* 25:231–238

[31] Wu S, Powers S, Zhu W, Hannun YA. 2016. Substantial contribution of extrinsic risk factors to cancer development. *Nature* 529:43–47

[32] Park SM, Lim MK, Jung KW, Shin SA, Yoo KY, et al. 2007. Prediagnosis smoking, obesity, insulin resistance, and second primary cancer risk in male cancer survivors: National Health Insurance Corporation Study. *Journal of Clinical Oncology* 25:4835–4843

[33] Li N. 2016. Platelets in cancer metastasis: to help the "villain" to do evil. *International Journal of Cancer* 138:2078–2087