Diverse Manifestations and Underlying Mechanisms of Ischemic Infarctions in Individuals Afflicted by Systemic Malignancies - A Case Series

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Abstract

This study delves into the diverse manifestations and underlying mechanisms of ischemic infarctions in individuals suffering from systemic malignancies. Four distinct cases illuminate the intricate interplay between cancer, therapeutic interventions, and the resultant complications. The first case involves a 35-year-old male with chronic eosinophilic leukemia undergoing a grave course marked by variable responses to treatment, ischemic events, and nosocomial infections. The second case involves a 42-year-old woman diagnosed with breast cancer, who suffered from severe headaches, seizures, and neurological decline, ultimately passing away due to suspected carcinomatous meningitis and ischemic strokes.

The third case describes a 38-year-old woman with pancreaticobiliary carcinoma, pulmonary embolism, and an acute/subacute ischemic infarction in the right middle cerebral artery (MCA) territory, likely due to a thrombo-embolic phenomenon.

Lastly, a 45-year-old woman with ovarian carcinoma showcases the intricacies of ischemic stroke involving both anterior and posterior circulation likely due to hypercoagulability.

Keywords: *Embolic stroke, meningeal carcinomatosis, chronic eosinophilic leukemia, ovarian neoplasm, middle-aged, adult.*

INTRODUCTION

Cerebrovascular diseases (CVDs) are common among individuals with cancer, with approximately 15% having a concurrent CVD. Data from the National Inpatient Sample indicates that approximately 10% of patients diagnosed with ischemic stroke, regardless of the cause, have a documented history of malignancy.

Cancer can influence stroke pathophysiology either directly or through coagulation disorders that induce hypercoagulation, as well as through infections. Additionally, cancer treatment modalities such as chemotherapy, radiotherapy, and surgery have been demonstrated to increase the risk of stroke [1, 2].

Malignancies have historically been recognized for causing venous thrombosis but have also emerged as significant risk factors for arterial thromboembolism [3]—consequently, the acknowledgment of cancer as a cause of ischemic stroke is growing. Given the considerable morbidity and mortality linked to both ailments, understanding the interplay between stroke and cancer should remain foremost [4]. Historically, malignancies have been acknowledged for causing venous thrombosis and have also emerged as significant risk factors for arterial thromboembolism [3]. As a result, awareness of cancer as a cause of ischemic stroke is increasing.

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Received: December 28, 2023; Revised: May 14, 2024; Accepted: July 14, 2024
DOI: https://doi.org/10.37184/lnjcc.2789-0112.5.16

However, despite significant research, approximately 30% of stroke cases still have an undetermined origin[5, 6]. About one-quarter to one-third of patients suffering from ischemic stroke have an embolic stroke of undetermined source (ESUS). Among this group, approximately 5% to 10% are diagnosed with active cancer [7]. Tailoring stroke prevention and treatment for patients with cancer is imperative, considering the distinct risk profile of each individual.

Here, we present a case series of four patients who were diagnosed with cancer and experienced stroke. Tragically, two of these patients did not survive. The stroke in each patient was attributed to distinct pathophysiologies influenced by their respective types of cancer.

Case 1

A 35-year-old gentleman who had a known case of chronic eosinophilic leukemia was previously on Tab Imatinib. Recently, he switched to Tab Nilotinib 150 mg, two tablets twice a day for one week. He had a history of ischemic heart disease, which was recently diagnosed. Cardiac angiography revealed normal findings, but there was a depressed ejection fraction of 40% with global hypokinesia.

He presented, with a sudden impairment in speech. The neurological assessment showed that the patient displayed global aphasia, left upper motor neuron facial weakness, bilaterally reactive pupils, absence of limb movements, depressed deep tendon reflexes, and bilateral extensor plantar responses. He had a similar

  ISSN: 2789-0120 (Online) Liaquat National Journal of Cancer Care 2024; 6(1): 23-30

Table 1: Laboratory parameters with treatments given (*H-Hydrea, N- Niolotinib).

Variables	Day 1	Day 3	Day 7	Day 10	Day 12	Day 15	Day 16	Day 17	Day 18
Treatment	*H&N	*H & N	*H & N	*H & N	*H & N	*H & N	*H & N	*H & N	*N Stopped
Anticoagulation	Heparin cont.	Heparin Cont.	Heparin stopped	Heparin stopped	Heparin stopped	Heparin cont.	Heparin cont.	Heparin cont.	Heparin Stopped
		Leukopharesi-s	Bleeding P/R						
Hemoglobin	8.2 gm/dl	8.3	8.4	6.3	7.5	8	8.10	7.8	7.8
Total leucocyte count	187 x 10^3/µL	184	177	158	65	44	56	55	22
Platelets	97 x 10^3/µL	91	84	82	132	129	137	103	60
Eosinophils	57%	-	-	60%	-	-	-	-	-
Neutrophils	2%	-	-	2%	-	-	-	-	-
Lymphocytes	1%	-	-	1%	-	-	-	-	-
INR	1.27	-	-	1.18	-	-	-	-	-
Urea	66	72	77	-	178	185	170	160	212
Creatinine	1.2 mg/dl	1.7	2.0	-	2.9	2.91	2.58	2.6	2.2
Sodium	130 mEq	134	138	-	142	143	143	144	146
Potassium	4.1 mEq	4.2	3.8	-	5.8	5.6	4.9	5.0	4.5
Uric acid	4.30 mg/dl	-	-	-	-	-	-	-	-
Amylase	73 U/L	-	-	-	-	-	-	-	-
SGPT	9 U/L	-	-	-	-	-	-	-	-
Urine D/R	Normal	-	-	-	-	-	-	-	-
Calcium	7.3	-	-	-	-	-	-	-	-
Magnesium	2.19	-	-	-	-	-	-	-	-
C-reactive protein	22.8	-	-	-	-	-	-	-	-
Albumin	2.61	-	-	-	-	-	-	-	-
CSF D/R		-	-	-	-	-	-	-	-
Glucose	73 gm/dl	-	-	-	-	-	-	-	-
Protein	101 mg/dl	-	-	-	-	-	-	-	-
WBC	5 x 10^3/ul	-	-	-	-	-	-	-	-

history of left-sided weakness and difficulty in speaking 6 months back as well.

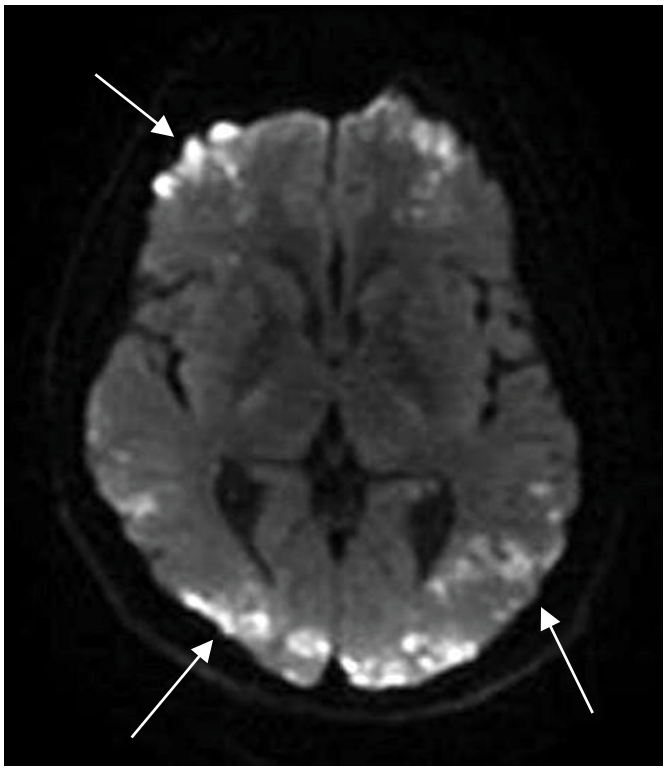

Fig. (1): MRI of the BRAIN (DWI) – showing restricted diffusion in bilateral PCA-MCA-ACA territories (white arrows).

At that time, his MRI brain showed patchy areas of ischemic infarctions in the left middle cerebral artery territory. He received a single antiplatelet and a statin, and his cardiac medications were modified. Over three months, his symptoms improved. Anticoagulation was not considered earlier due to instability in his platelet counts. This time, his repeat MRI brain revealed multiple small ischemic infarctions in the anterior and posterior circulations (**Fig. 1**). MRI of the cervical spine was unremarkable. Due to his unstable condition, an MR angiogram of the brain was not performed, and he was transferred to the ICU. An echocardiogram showed a persistent low ejection fraction (EF) of 45-50% with mild global hypokinesia, and no left ventricular (LV) clot or vegetation was observed. Cerebrospinal fluid (CSF) studies were conducted to eliminate the possibility of an infective etiology, and the results were within normal limits. A detailed lab workup is shown below in Table **1**.

However, the patient's condition deteriorated rapidly, with a drop in oxygen saturation and the onset of fever. Blood cultures were negative, but tracheal cultures indicated the growth of Acinetobacter. The infectious disease team was involved, and the patient received multiple broad-spectrum antibiotics during the ICU stay. Anticoagulation with heparin at a thrice-daily dose of 5000 IU was initiated. After receiving three doses, a notable decrease in platelet count was observed, accompanied by rectal bleeding. As a result, anticoagulation had to be

discontinued. The hematology department considered stopping nilotinib as well as considering it to be the culprit for declining platelet count. The patient was managed conservatively and remained in a vegetative state with no clinical improvement. This case highlights the challenging management of a primary hematological malignancy.

Case 2

A 42-year-old woman with breast carcinoma, diagnosed one year ago, underwent five sessions of chemotherapy in her hometown, details of which were unavailable. The most recent session occurred one month ago. She presented to the emergency department, with complaints of headache for one month, fever for two weeks, difficulty in speaking for one week, and visual disturbance for a few days. Headache was moderate to severe in intensity, associated with photophobia and phonophobia, nausea, and vomiting, followed by a high-grade fever, documented to be 102 F, intermittent with rigors and chills. She received antipyretics and anti-malarial treatment. As her condition further deteriorated she was brought to the hospital setup where she was noticed to have brief episodes of generalized tonic-clonic seizures lasting for 1 minute. Caretakers denied any history of diabetes, hypertension, addictions, or tuberculosis. On examination, her BP was 130/90 mm Hg, pulse was 120 beats/minute, respiratory rate was 18 breaths/minute, and oxygen saturation was 98 percent on room air. She was drowsy, arousable by painful stimuli, and aphasic. Her pupils were 2 mm symmetrical and reactive to light. Cranial nerve examination revealed left upper motor neuron (UMN) facial nerve palsy. On motor examination, the bulk, and tone of all four limbs were reduced, localizing from the left upper extremity, there was no movement on the right side. Deep tendon reflexes (DTRs) were not elicited. Extensor plantar response on the left while the right was normal. Bilateral chest crepitations were heard on auscultation. MRI of the Brain showed areas of diffusion restriction in the right parieto-occipital region and bilateral occipital lobe. MRA- showed compromised anterior and posterior circulation (**Fig. 2a and 2b**). EEG showed diffuse theta-delta slowing, signifying diffuse cerebral dysfunction. Her detailed laboratory workup is shown in Table **2** and Table **3** below.

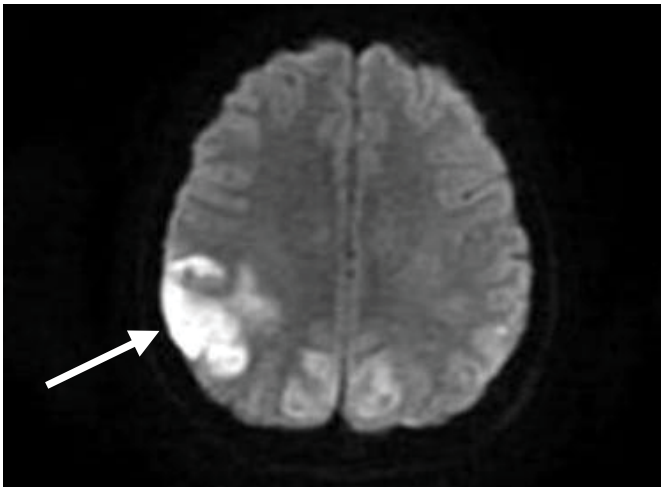

Fig. (2a): MRI of the brain (DWI) restricted diffusion predominantly in the right MCA territory (white arrow).

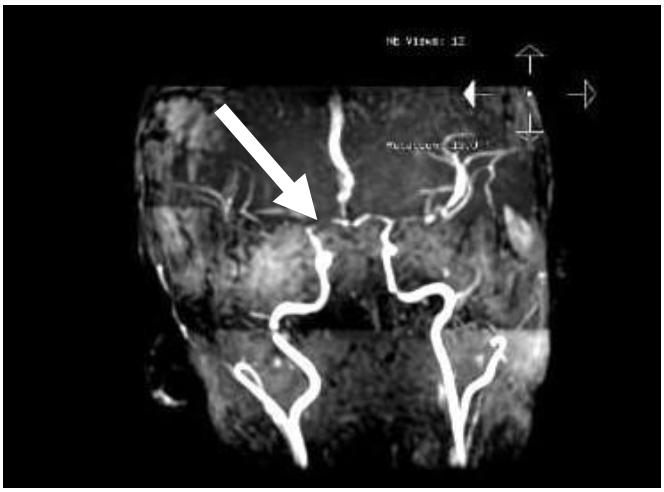

Fig. (2b): MRA of the brain showed significant stenosis of intracranial vasculature (white arrow).

She received antibiotics in meningitic doses, meropenem 2 grams intravenously thrice daily, acyclovir 750 mg thrice daily, vancomycin 750 mg 6 hourly, dexamethasone 10 mg 6 hourly, LMWH, 40 mg subcutaneously twice daily and antiplatelet aspirin 75 mg once daily. After CSF studies, antibiotics were adjusted with the continuation of meropenem and steroids. Anti-tuberculous and antifungal treatments were administered but discontinued because cultures yielded negative results.

She was followed by oncology with the possibility of carcinomatous meningitis but as her condition worsened significantly they were not able to proceed with intrathecal methotrexate. The transthoracic echocardiogram did not show any vegetation. Unfortunately, she expired on the 10th day of hospitalization.

Table 2: Laboratory workup.

Investigation	Result
Hemoglobin	14 gm/dl
Total leucocyte count	14.9 x 10^3/µL
Platelets	170 x 10^3/µL
Urea	18
Creatinine	0.74 mg/dl
Sodium	135 mEq
Calcium	9.55 mEq
Phosphorus	4.08 mEq
Albumin	3.74 mg/dl
Total bilirubin	1.06 mg/dl
SGPT	95 U/L
HbsAg	Negative
Anti-HCV	Negative
Blood culture/urine culture	Negative
Urine D/R	14-16 pus cells
MP-Malarial parasite	Negative
Dengue serologies	Negative

Table 3: CSF detailed reports.

Parameters	Day 1	Day 5	Normative values
Glucose	8 gm/dl	5 gm/dl	2/3rd of serum
Protein	81 gm/dl	108 gm/dl	45 gm/dl
WBC	5 /cumm	5 /cumm	0-5/cumm
RBC	Zero /cumm	60 /cumm	-
Gram stain	Negative	-	-
Culture	Negative	-	-
MTB PCR	Negative	Negative	-
Fungal smear	Negative	-	-
Fungal culture	Negative	-	-
Cytology	-	Atypical cells were seen.	-

Case 3

A 38-year-old female came to ED, with a constellation of alarming symptoms, including sudden-onset left-sided weakness, headache, vomiting, yellow discoloration of the face, and abdominal distension. Immediate admission was deemed necessary, and the National Institutes of Health Stroke Scale Score at presentation was 12. The patient's medical history included a laparoscopic cholecystectomy in 2022 for cholelithiasis, recurrent ERCP, and stenting for choledocholithiasis. A recent ultrasound-guided biopsy confirmed an invasive cholangiocarcinoma with mucinous differentiation in the pancreaticobiliary tract. Upon examination, the patient displayed a Glasgow Coma Scale score of 15/15, with bilaterally equal and reactive pupils. Clinically, a prominent yellowish discoloration of the face and sclera was noted. Neurological evaluation revealed profound global left-sided weakness, marked by a power of 1/5 in both the upper and lower limbs, accompanied by left-sided UMN facial weakness, particularly noticeable in the drooping of the angle of the mouth. Babinski's sign was positive on the left. A comprehensive blood analysis was conducted, summarized in Table **4**. The results showed an elevated total leukocyte count and C-reactive protein (CRP) levels. Furthermore, elevated D-dimer levels were detected, indicating hypercoagulability. Liver function tests revealed abnormalities, likely attributed to an underlying oncological condition, and the lipid profile was mildly deranged. Cultures were sent for further investigation, but no growth was observed. Imaging studies, including a brain MRI, indicated the presence of acute/subacute ischemic infarcts in the right middle cerebral artery. Magnetic resonance angiography (MRA) showed an ICA occlusion (**Fig. 3a and 3b**). The absence of significant findings in these major vessels

Table 4: Laboratory workup.

Investigation	Result
Hematology:	
Hemoglobin	10.2 g/dL
TLC (Total Leukocyte Count)	18.2 x 10^3/µL
Platelets	150 x 10^3/µL
Coagulation Profile:	
PT (Prothrombin Time)	13.4 seconds
APTT (Activated Partial Thromboplastin Time)	27.4 seconds
INR (International Normalized Ratio)	1.36
D-dimer	10.38 µg/mL
Inflammatory Markers:	
CRP (C-Reactive Protein)	22.9 mg/L
Liver Function Tests:	
Total Bilirubin	4.69 mg/dL
Direct Bilirubin	3.84 mg/dL
Indirect Bilirubin	0.85 mg/dL
ALT (GPT)	34 U/L
Alkaline Phosphatase	2056 U/L
GGT (Gamma GT)	701.00 U/L
AST (GOT)	94.00 U/L
Lipid Profile:	
Cholesterol	206.00 mg/dL
Triglycerides	131.00 mg/dL
HDL (High-Density Lipoprotein)	24.00 mg/dL
LDL (Low-Density Lipoprotein)	116.00 mg/dL
VLDL (Very Low-Density Lipoprotein)	26.00 mg/dL
Urine Analysis:	
Color	Orange
Quantity	50 mL
Specific Gravity	1.025
pH	5.0
Nitrite	Positive
Protein	75 mg/dL
Glucose	Negative
Ketones	50 mg/dL
Urobilinogen	4.0 mg/dL
Bilirubin	Negative
Microscopic Examination of Urine:	
RBC (Red Blood Cells)	Numerous/HPF
Pus Cells	18-20/HPF
Epithelial Cells	2-4/HPF
Casts	Granular (1-2)/LPF
Crystals	NIL

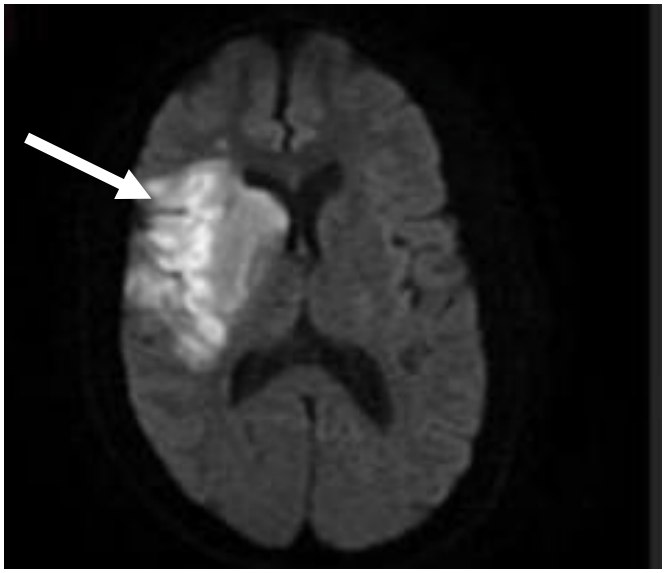

Fig. (3a): MRI of the brain (DWI) -Restricted diffusion in right MCA territory (white arrow).

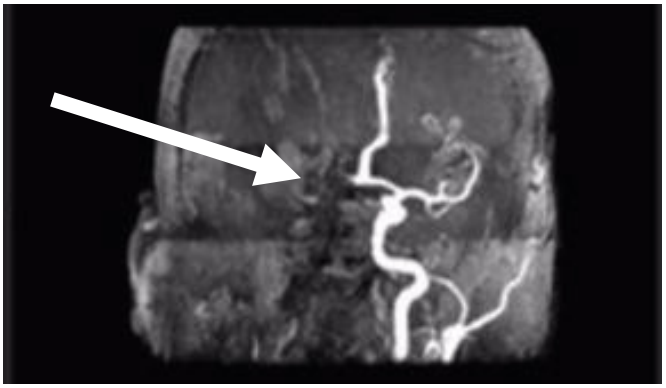

Fig. (3b): MRA of the brain showing right ICA cut off (complete thrombo-embolic occlusion) (white arrow).

contributed valuable information to rule out potential sources of emboli or stenosis. An ultrasound abdomen was done which showed mild to moderate ascites, minimal to mild left-sided pleural effusion, and a bulky pancreas with maximum width in the region of the body measuring 2.1cm. She became hypoxic and tachypneic during the hospital stay. CTPA was performed which showed extensive pulmonary embolism. Given the patient's delayed presentation, anticoagulant therapy, including aspirin (75mg once daily) and Clexane injection 40mg s/c twice daily), was started. Empiric antibiotics were initiated for a suspected urinary tract infection. Physiotherapy of limbs was implemented to aid rehabilitation. Conservative management was adopted for the ongoing oncological condition, with plans for chemotherapy once stability was achieved. Upon improvement and achieving vital stability, the patient was discharged on injection of Clexane, tablet Merol (25mg twice daily), and tablet Norvasc (5mg once daily) as she was mildly tachycardiac on presentation. Follow-up on an outpatient basis was advised for ongoing care and consideration of future chemotherapy. She was re-admitted after 1 week with severe respiratory distress and expired after a day of hospitalization.

Table 5: Laboratory workup with results.

Investigations	Results
Hemoglobin	11.5 gm/dl
Total leukocyte count	21 x 10^3/µL
Platelets	189 x 10^3/µL
PT	10.9 seconds
INR	1.10
CREATININE	0.63 mEq
SODIUM	130 mEq
POTASSIUM	3.4 mEq
BICARBONATE	21 mEq
CALCIUM	9.25 mg/dl
PHOSPHORUS	1.9 mg/dl
SGPT	35 U/L
AMYLASE	107 U/L
LIPASE	12 U/L
C-REACTIVE PROTEIN	35.2
BETA-HCG	NEGATIVE
D-DIMER	18.24 (NORMAL < 0.50)
CA-125	651.8 (NORMAL < 35)

Case 4

A 45-year-old woman presented to the ED department, with complaints of abdominal pain, inability to speak, and difficulty in walking for the last 3 days. On examination, her BP was 135/70 mmHg, her pulse was 74 beats/minute and she was afebrile. On abdominal examination, the abdomen was soft and non-tender, and a mass was palpable in the right iliac fossa with a firm consistency. On neurological assessment, the patient was awake and lethargic. She had right upper motor neuron facial paralysis. She had normal extraocular movements and no tongue deviation. She had a right arm pronator drift with a power of 4/5, reflexes were intact and the Babiniski sign was positive on the right side.

Detailed investigations are shown in Table **5**. Diffusion-weighted MRI (**Fig. 4a**) of the brain visualized non-hemorrhagic infarcts in the right and left middle cerebral arteries (MCAs), suggestive of embolic stroke. Tests were performed to evaluate factors that could contribute to blood vessel-related risks and other potential reasons for the stroke, but the results came back as normal. These included magnetic resonance angiography (MRA) of neck vessels and the circle of Willis, which showed no occlusion (**Fig. 4b**). Furthermore, transthoracic echocardiography showed the presence of mild mitral regurgitation with no vegetation. Other specific imaging modalities included ultrasound and CT of the abdomen, which revealed multiple large wedge-shaped and irregular non-enhancing areas in the spleen suggestive

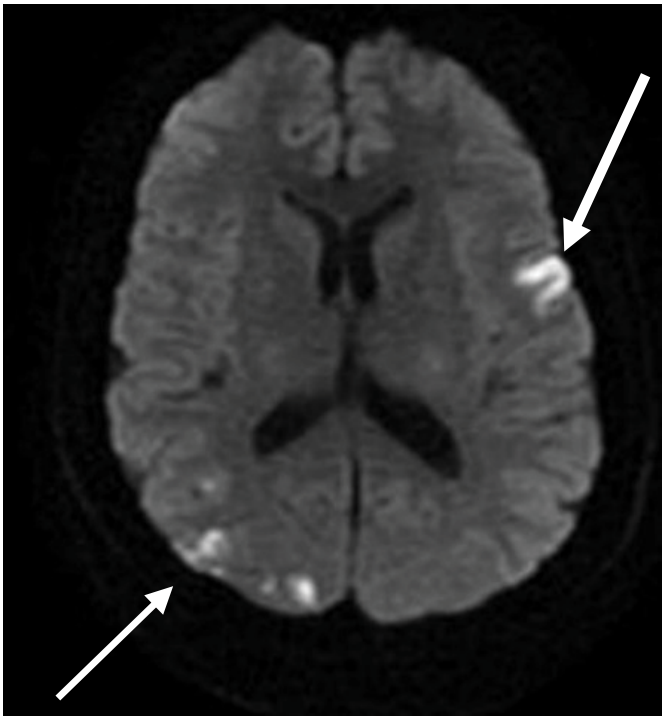

Fig. (4a): MRI of the brain (DWI) showing small areas of restricted diffusions in right posterior parietal & left anterior parietal regions (white arrows).

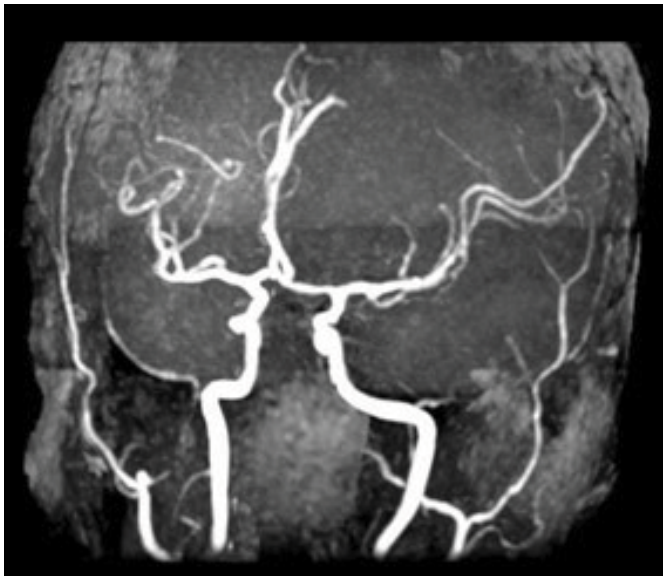

Fig. (4b): MRA of the brain –normal.

of acute splenic infarction, multiple small wedge-shaped non enhancing areas in the cortex of both kidneys representing cortical infarction, and a left ovarian mass raising the possibility of malignancy. Her serum cancer antigen 125 (CA-125) was greater than 600 (normal <35). A diagnosis of ovarian carcinoma was established. The patient was denied further hospital management due to financial constraints.

DISCUSSION

The emergence of stroke in cancer patients stems from distinct factors compared to non-cancer patients, with connections to both the cancer itself and the specific treatments employed. Typically, hypercoagulability is closely linked to the occurrence of ischemic strokes in this population. The other predominant causes of ischemic strokes encompass cardio-embolism, large-vessel occlusion, and small-vessel lipo hyalinosis, with non-bacterial thrombotic endocarditis being a less frequent occurrence. Active cancer, marked by the recurrence of malignancy, spread to other organs, or continuing chemo and radiotherapy, significantly influences both the development and prognosis of acute ischemic strokes [8-13]. The likelihood of experiencing a stroke also appears to correlate with cancer severity. Cancers known for their higher stroke risks, such as lung, pancreatic, and colorectal cancers, tend to be diagnosed at more advanced stages than prostate and breast cancers [14].

Determining whether a cerebrovascular event is the result of the malignancy itself or its consequences can be challenging. It may arise from treatment-related complications, and there is often a complex interplay of factors involved, leading to the simultaneous occurrence of both hemorrhagic and ischemic strokes. Consequently, strokes in individuals with an active disease process are more commonly categorized as 'of undetermined etiology' or 'other determined etiology' according to the TOAST classification [15, 16].

In the first described case of chronic eosinophilic leukemia, a rare entity among hematological malignancies, the patient's clinical course worsened due to the onset of ischemic infarctions in both cerebral hemispheres. The potential cause of these infarctions was either cardio-embolism or leukostasis. However, due to the patient's critical condition, we opted not to proceed with transesophageal echocardiogram (TE) and computed tomography angiography (CTA) of the aorta. Initially, we initiated therapeutic doses of heparin for two days, but it had to be discontinued as the patient developed thrombocytopenia and rectal bleeding. Consequently, we continued him on a single antiplatelet agent for secondary stroke prevention, although this proved to be insufficient. Upon attempting to resume heparin therapy, the patient experienced further platelet drops. A review of the literature revealed that hyperleukocytosis, characterized by a white blood cell (WBC) count exceeding 100,000 per mm3, is frequently observed in leukemia patients and can lead to central nervous system (CNS) leukostasis. The accumulation of leukemic blast cells within the capillary vascular lumen represents a potential cause of ischemia, predominantly affecting medium-sized vessels [17].

The second case presented with a clinical picture consistent with meningoencephalitis, likely stemming from carcinomatous meningitis. Leptomeningeal metastasis, also known as meningeal carcinomatosis or neoplastic meningitis, is primarily associated with breast cancer, lung cancer, and malignant melanoma. This condition occurs when cancer cells enter the cerebrospinal fluid within the subarachnoid space. Leptomeningeal metastasis affects about 5% of all cancer patients, ranking as the third most common metastatic complication of the central nervous system (CNS). In individuals with neuroblastoma, lymphoma, and lung cancer, multiple lesions and venous sinus occlusion are more frequently observed in the context of leptomeningeal carcinomatosis. This can lead to cerebral infarctions due to tumor growth within the Virchow-Robin perivascular spaces, resulting in vessel thrombosis or spasm and the infiltration of vessel walls [18, 19].

In the third case of a young lady with hepatobiliary malignancy and acute right middle cerebral artery infarction, MRA showed complete occlusion of the right ICA. Upon receiving therapeutic heparin for a few days, her symptoms started to improve. However, her clinical course was further complicated by the development of pulmonary embolism. The underlying cause in this case was likely hypercoagulability contributing towards the systemic embolism. Among cancer patients, a commonly observed cause of cerebrovascular thrombosis, as noted in various clinical series, is the presence of a hypercoagulable state linked to cancer. This leads to thrombosis occurring in both systemic and cerebral arterial or venous pathways, as evidenced in the third case. Intravascular coagulation

appears to have a multifactorial origin, involving tumor procoagulant activity, host inflammatory responses, and extrinsic factors. It is well-known that tumor cells release inflammatory cytokines and vascular endothelial growth factors, which act as mediators intensifying procoagulant activity and angiogenesis. Moreover, tumor cells tend to overexpress cytokines that attract leukocytes, potentially initiating an inflammatory response with prothrombotic effects. Notably, lung and pancreatic cancers are the predominant cancer types associated with this coagulopathy [20, 21].

In the fourth case, a middle-aged woman presented with multiple areas of ischemic infarctions, alongside suspicion of ovarian malignancy. Neuroimaging revealed multiple areas of diffusion restriction in both anterior and posterior circulation, with a completely normal MR angiogram. This raised the possibility of cardioembolism although the source remained undetermined due to lack of finances [22].

Recombinant tissue plasminogen activator (rTPA) has shown efficacy in treating acute strokes even in patients with active cancer, challenging the notion that active cancer is an absolute contraindication to its use. Clinical evidence, including small-scale trials such as that conducted by Cappellari *et al.* (2013), suggests that intravenous thrombolysis does not carry a higher risk of hemorrhage in cancer patients. On the contrary, it has been observed to improve the neurological status of these patients.

Similar conclusions were drawn from an analysis by Sobolewski *et al.* on the use of intravenous thrombolysis, showing no adverse impact of neoplastic disease on unfavorable outcomes. When addressing leptomeningeal metastases, treatment strategies may involve a combination of irradiation, surgical intervention, and chemotherapy, tailored to individual patient needs. Radiotherapy typically targets the affected disease sites, while chemotherapy can be administered intrathecally and systemically into the cerebrospinal fluid. Anticoagulation therapy plays a pivotal role in preventing recurrent embolization, with the American College of Chest Physician Guidelines advocating for long-term anticoagulation regardless of evidence of emboli. Unfractionated heparin has demonstrated effectiveness in reducing thromboembolic events, especially in patients with malignancies, whereas warfarin is not recommended for this purpose [23-25].

CONCLUSION

Stroke occurring in conjunction with cancer requires careful attention. Patients in this scenario often experience poorer clinical outcomes, which makes the management of stroke particularly challenging due to the potential for adverse and unexpected outcomes.

CONSENT FOR PUBLICATION

Informed consent was obtained from the patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Dr. Rashna Ramani, Neurology Resident for her contribution towards the laboratory data collection.

AUTHORS' CONTRIBUTION

All authors contributed equally to this work.

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