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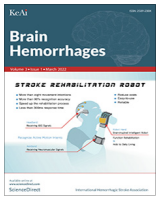

Review article

Cerebrovascular disorders in patients with malignant tumors

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ABSTRACT

Patients with malignant tumors face an elevated risk of cerebrovascular complications, such as intratumoral hemorrhage, tumor invasion into arterial and venous sinuses, leptomeningeal infiltration, and tumor embolism. This review examines the significant role and implications of cisplatin and radiation therapy in the development of these cerebrovascular complications, which can occur at various stages: before, during, or long after the completion of cancer treatment. Detailed clinical case studies of CNS involvement during oncological therapy are presented to illustrate these complications. The mechanisms by which cisplatin and radiation therapy contribute to cerebrovascular disorders are multifaceted. Cisplatin, a widely used chemotherapeutic agent, is associated with endothelial damage and thromboembolic events, while radiation therapy can cause vascular injury, leading to long-term changes in cerebral vasculature. These treatments, though effective in managing malignancies, pose significant risks to cerebrovascular health. The review underscores the diverse types and mechanisms of stroke encountered in cancer patients, influenced by tumor stage and pathological characteristics. These include ischemic stroke, hemorrhagic stroke, and transient ischemic attacks, each requiring specific diagnostic and therapeutic strategies. The interaction between cancer pathology and cerebrovascular health necessitates a multidisciplinary approach, integrating oncology, neurology, radiology, and vascular surgery. Such an approach is crucial for effective management and prognosis evaluation in this patient population. Early recognition and intervention are paramount to mitigating risks and improving outcomes. By understanding these complex interactions, healthcare providers can better anticipate and manage cerebrovascular risks in patients undergoing cancer treatment. This comprehensive understanding helps in formulating personalized treatment plans, optimizing both oncological and neurological care, and ultimately enhancing patient quality of life and survival rates.

1. Introduction

Currently, there is a widespread increase in the number of individuals with malignant neoplasms (MN). The presence of oncological diseases increases the risk of developing cerebrovascular complications, which in turn significantly worsens the overall prognosis.[1–2] Approximately 15 % of MN patients have concomitant cardiovascular diseases.[1] This co-occurrence further complicates their medical condition and treatment outcomes. In 1985, F. Graus and colleagues[3] demonstrated that the most common CNS manifestations in patients with MN are metastasis and cerebral infarction. Metastatic brain lesions represent a severe complication during MN, occurring in approximately 50 % of cancer patients. These metastases can significantly impact neurological function and overall patient survival. CNS metastases are most observed in patients with lung, breast, kidney, and colorectal cancers, as well as melanoma.[4] These cancers tend to metastasize to the brain more frequently than other types. The peak incidence of metastasis occurs in the age group of 55–65 years.

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Approximately 80 % of intracranial metastases are in the brain hemispheres, 15–17 % in the cerebellum, and 3–5 % in the basal ganglia and brainstem.[4] This distribution reflects the pathways of metastatic spread and the affinity of certain cancer types for specific brain regions. Previous studies have documented the occurrence of both ischemic (IS) and hemorrhagic strokes in patients with MN.[5–6] These cerebrovascular events further complicate the clinical management of cancer patients, often leading to worse outcomes. In a study by T. Kitano and colleagues, the impact of chemotherapy on the risk of stroke in MN patients was analyzed.[7] The authors screened 27,932 patients from the Osaka University Hospital Cancer Registry between 2007 and 2015.[7] Medical records of 19,006 patients were reviewed to identify the incidence of stroke and its association with chemotherapy. The association between chemotherapy and stroke was analyzed using the Kaplan-Meier method and the Cox regression model.[7] Out of 19,006 patients, 5,887 (31 %) received chemotherapy. Stroke occurred in 44 (0.75 %) patients in the chemotherapy group, whereas the incidence was 51 (0.39 %) in the MN patients without chemotherapy. Kaplan-Meier analysis revealed that patients who received chemotherapy had a higher risk of stroke than those who did not receive chemotherapy, with a hazard ratio of 1.84 (95 % confidence interval (CI), 1.23–2.75). This finding indicates a statistically significant increase in stroke risk associated with chemotherapy. According to the researchers, the increased risk of stroke in cancer patients receiving chemotherapy was presumably due to the late stage of MN, rather than the chemotherapy itself being a direct cause of increased stroke risk.[7] It is suggested that the risk of stroke correlates with the aggressiveness of the tumors and their advanced stage at diagnosis. The highest risk of stroke is registered among patients with lung, pancreatic, and colorectal cancers, which are often diagnosed at advanced stages and tend to be more aggressive. These cancers are associated with a higher burden of systemic disease, including factors that contribute to cerebrovascular complications. Understanding the interplay between malignant neoplasms, their treatment, and cerebrovascular risks is crucial for improving patient outcomes. This knowledge enables healthcare providers to implement more effective monitoring and preventive strategies, thereby enhancing the overall management of patients with MN.

2. Chemotherapy-induced cerebrovascular disorder and potential mechanisms

Stroke is recognized as a disease with multiple etiologies.[8–10] Research indicates that approximately 1 in 7–8 patients with ischemic stroke (IS) has either diagnosed or undiagnosed MN, with nearly 40 % of these cases associated with cancer-induced coagulopathy.[11] In the United States, around 1 in 10 hospitalized patients with IS also suffers from comorbid cancer.[12] Population-based studies have revealed that MN is newly diagnosed in 2.8 % of patients presenting with stroke.[13] Similar findings have been reported in Spain, where 2.1 % of stroke patients were newly diagnosed with MN.[14] In Norway, researchers found that hidden MN might be the cause of IS in 4.3 % of cases,[15] while in Japan, this figure stands at 3.0 %.[16] There is also evidence suggesting that prostate cancer is linked to the development of hemorrhagic stroke.[17] Current scientific understanding identifies the direct toxic effects of chemotherapy and radiation therapy on the vascular endothelium as a primary pathogenetic mechanism behind cerebrovascular complications in MN patients (Fig. 1). International guidelines express significant concerns that the vasotoxic effects of these treatments could lead to premature disability and mortality among cancer survivors.[18] Peripheral vascular disease and stroke are now considered among the nine cardiovascular complications associated with cancer therapy.[18] Some of the drugs used in cancer treatment have adverse effects that can lead to cerebrovascular complications with regular use.[18]

A notable example is the platinum-based chemotherapy agent, cisplatin. Following intravenous administration, cisplatin is rapidly distributed across various tissues, achieving peak concentrations in the liver, kidneys, bladder, muscle tissue, skin, testes, prostate, pancreas, and spleen.[19] However, cisplatin has limited penetration through the blood–brain barrier (BBB). The drug has a detrimental impact on vascular endothelium, often exhibiting a procoagulant effect, and can induce Raynaud's phenomenon.[20–21] Cisplatin is also known to cause hypomagnesemia, which can lead to increased contraction of vascular smooth muscles.[22–23] The molecular mechanisms underlying cisplatin-induced vascular toxicity include reduced activity of protein C[24] and elevated levels of von Willebrand factor,[25] both of which are known to promote hypercoagulable states. Additionally, changes in platelet aggregation properties during cisplatin therapy have been reported.[23]

Managing cancer patients who develop cerebrovascular complications is further complicated by these adverse effects (Fig. 2).

The combined impact of cancer pathology and its treatment demands meticulous monitoring and a multidisciplinary approach to mitigate these risks effectively. Understanding the underlying mechanisms and potential complications related to chemotherapy and radiation therapy is crucial for optimizing treatment strategies and improving patient outcomes. A comprehensive approach enables healthcare providers to address both oncological and cerebrovascular health concerns, ultimately improving the quality of life and survival rates for patients with malignant neoplasms. Platinum-based chemotherapy drugs, such as cisplatin, are associated with the development of arterial thrombosis and ischemic stroke in approximately 2 % of patients.[18] In a detailed study by A. Khosla and colleagues,[26] a case of cisplatin-induced intestinal ischemia (characterized by mesenteric thrombosis with necrotic changes) was documented in a 56-year-old male patient. This patient arrived at the Al-Hada emergency department complaining of severe diffuse abdominal pain and nausea. His medical history revealed that he had been undergoing chemotherapy with cisplatin and had received 12 doses of radiotherapy for his malignant neoplasm. Recent population-based research has shown that the risk of arterial thromboembolic complications begins to rise about five months prior to the diagnosis of malignant neoplasms, peaking approximately one month before diagnosis.[27] Cisplatin has also been implicated in causing vasculitis. For instance, K. Webb and colleagues[28] reported a case of aortitis in a 51-year-old woman who was receiving adjuvant chemotherapy with cisplatin and topotecan for cervical cancer. Ten days after her third course of chemotherapy, she developed back pain, a dry cough, fever, neutropenia, and elevated levels of C-reactive protein. Following a diagnosis of aortitis, her cisplatin therapy was discontinued, and she was treated with glucocorticoids, which resulted in normalization of her body temperature, resolution of the dry cough, and a decrease in C-reactive protein levels.[28] Another study by Gunaratne and colleagues[29] described cerebral vasculitis in a 50-year-old woman with bladder cancer who was being treated with a combination of gemcitabine and cisplatin. Additionally, another study found antinuclear and anti-endothelial antibodies in the serum of a patient with lung adenocarcinoma, suggesting an autoimmune component induced by cancer treatment.[30]

The clinical presentation of cerebrovascular complications often mimics other conditions such as encephalitis or metastatic lesions of the CNS (Fig. 3).

Typically, the endothelium serves as a barrier that separates platelets and plasma coagulation factors from the subendothelial layers, which include collagen.[31] When the integrity of the endothelium is compromised, the profile of bioactive substances

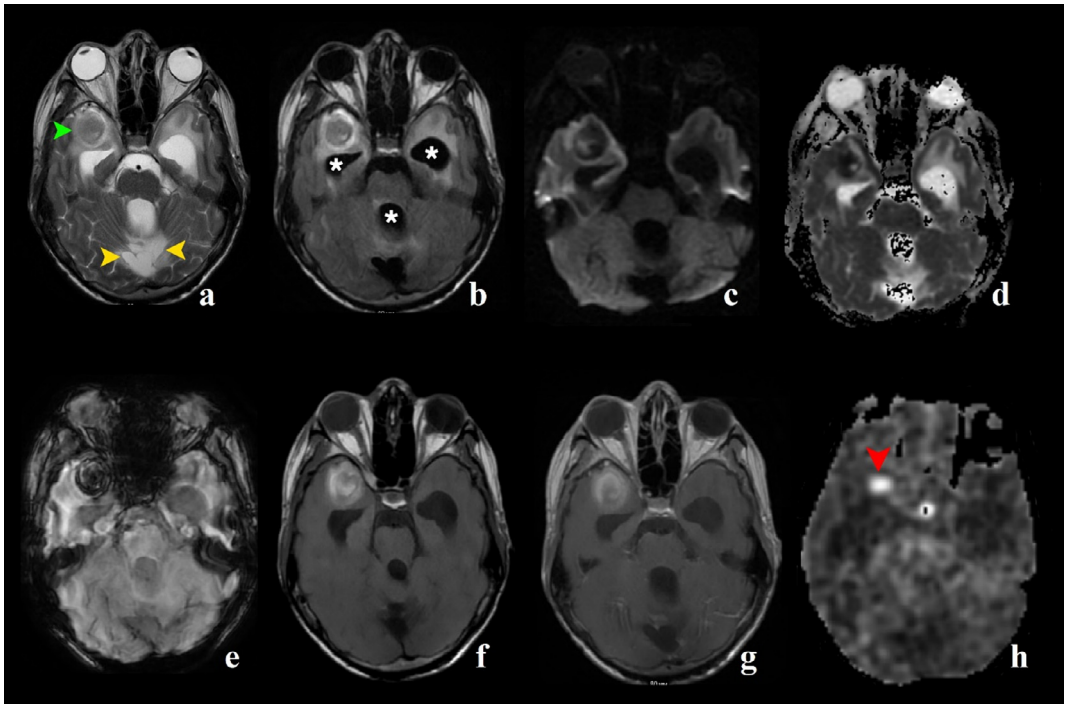

Fig. 1. Patient B., 12 y.o., with central nervous system germinoma after chemotherapy and radiotherapy. T2 and T2 FLAIR axial weighted images (a and b) show the black zone of postoperative encephalomalacia along the pine region approach (yellow arrows). IV-th ventricle and the temporal horns of the lateral ventricles are dilated with transependymal swelling of the periventricular substance (stars in b). In the real pole of the right temporal lobe, an "intra-axial" mass is detected, isointense to the gray matter in T2 and T2 FLAIR (a, green pointer). The signal characteristics correspond to blood (low signal in SWI, e) in the early subacute phase (irregularly high signal in T1, f). Diffusion are limited according to the ADC map (d). The lesion does not demonstrate contrast enhancement against the background of hemorrhage: the pole of the right temporal lobe on pre- and post-contrast T1 images (f and g) does not differ in signal intensity. Raw ASL perfusion data (h) indicate the presence of an area of hyperperfusion (increased cerebral blood flow velocity) in the lesion as a high signal focus at the pole of the right temporal lobe (red pointer).

it releases changes dramatically. The endothelium starts to produce aggregants, coagulants, and vasoconstrictors, facilitating the generalization of the pathological process.[32] These observations underscore the complexities and significant risks associated with platinum-based chemotherapy, especially cisplatin, in treating malignant neoplasms. The adverse vascular effects, including thrombosis and vasculitis, necessitate vigilant patient monitoring and a multidisciplinary approach to management. This approach should incorporate expertise from oncology, cardiology, and neurology to effectively mitigate risks and improve patient outcomes. A thorough understanding of the mechanisms underlying cisplatin-induced vascular damage is essential for developing preventive and therapeutic strategies, ultimately enhancing the quality of life and survival rates for cancer patients. Review studies have demonstrated that endothelial cells exhibit phenotypic variability not only among the blood vessels of different organs but also within the same organ.[33] Substances that induce platelet adhesion and aggregation include von Willebrand factor, platelet-activating factor, adenosine diphosphate, and thromboxane A2. When endothelial damage occurs, the secretion of von Willebrand factor from storage pools mediates the adhesion of circulating platelets to the exposed collagen surface and promotes the interaction between platelets themselves.[31]

In addition, chemotherapy and radiation therapy, especially in elderly patients, activate blood cells and endothelial cells, stimulating the production of microparticles with strong pro-inflammatory effects that further damage the vascular wall. Microparticles are phospholipid vesicles less than 1 μm in diameter, shed from platelets, leukocytes, and endothelial cells, and capable of localizing on the endothelium.[34] During activation, endothelial cells express P-selectin on their surface, a cell adhesion molecule that plays a key role in mediating leukocyte interactions during inflammation.[34] These pathophysiological changes create a predisposition for cerebrovascular complications in patients with malignant neoplasms. Multicenter studies in Korea and Italy have shown that hypercoagulability (indicated by elevated D-dimer levels or the presence of venous thromboembolism) was associated with MN in patients with stroke.[2] In patients with cerebrovascular complications related to MN, hypercoagulability, as measured by D-dimer levels, was a predictor of severe neurological deficits, stroke recurrence, and poorer survival outcomes following cerebrovascular events.[2,35] However, it is important to use D-dimer levels with caution for identifying and monitoring hypercoagulability, as they are nonspecific and can be influenced by treatment or the presence of comorbidities or infection.[2] These findings underscore the complex interplay between cancer pathology, its treatment, and the risk of cerebrovascular complications. Endothelial cells' variability and the impact of chemotherapy and radiation therapy on these cells contribute to an increased risk of thrombosis and inflammation. The activation of endothelial cells and the production of microparticles lead to further endothelial damage and hypercoagulability, creating a cycle that exacerbates the risk of stroke and other cerebrovascular events in cancer patients.

Effective management of these risks requires a comprehensive and multidisciplinary approach, incorporating insights from oncology, hematology, and neurology. By understanding the mechanisms underlying endothelial damage and hypercoagulability, healthcare providers can better anticipate and mitigate cerebrovascular complications, ultimately improving the prognosis and quality of life for patients with malignant neoplasms. Research has revealed that a substantial proportion of patients with embolic stroke of unknown origin also have malignancies (71 out of 348

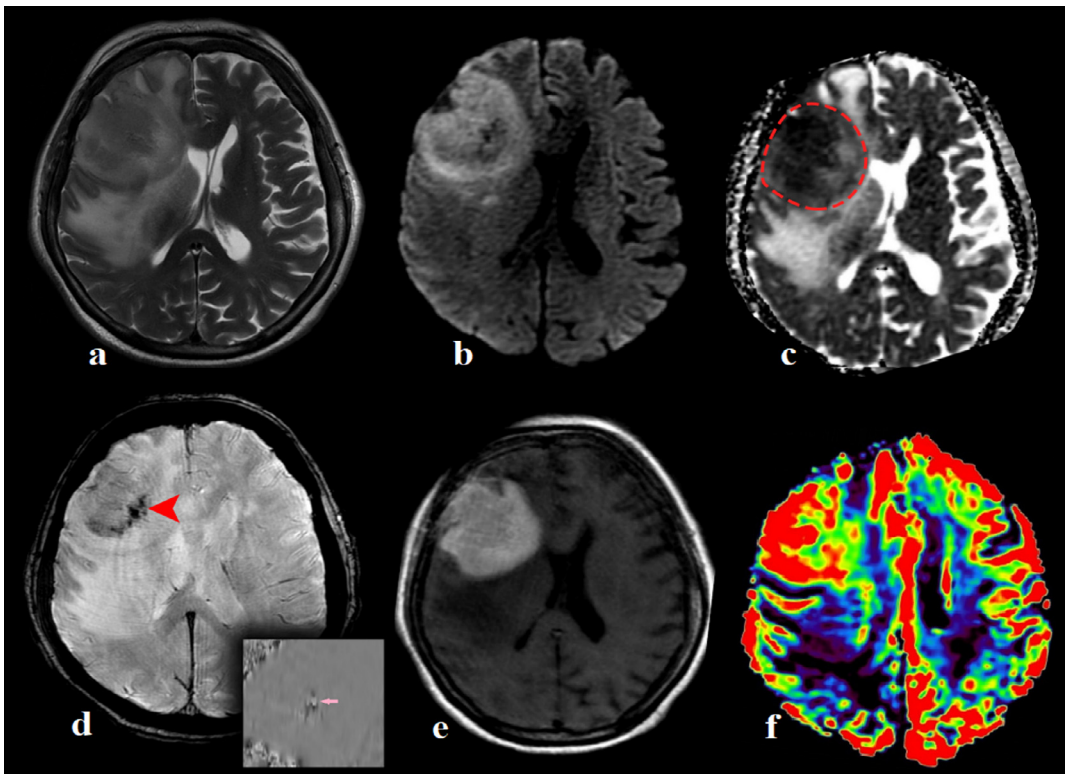

Fig. 2. Patient B., 47 y.o., with primary central nervous lymphoma, after chemotherapy (4 cycles (21-day) – combination Rituximab 375 mg\m2 and Methotrexate 3.5 g/m2). In the right frontal lobe, there is a superficial intracerebral formation without cortical involvement with extensive vasogenic edema on T2 (a). The diffusion restriction is uneven, most pronounced in the central regions as a high signal in DWI b = 1000 (b) and a low, almost black signal on the ADC map (c, inside the dotted red circle). On SWI the mass has hemorrhages (d, red arrow), the presence of hemosiderin is confirmed by reconstruction of phase images as black poles (pink arrow). The lesion shows intense and homogeneous contrast enhancement typical of lymphomas on post-contrast T1 image (e), increased tumor blood volume values with perfusion (f).

patients; 20 %) and elevated D-dimer levels.[13] Lung adenocarcinoma is known to have a procoagulant effect, which contributes to the higher risk of IS observed in these patients.[2] Multiple studies have indicated that patients with MN can develop IS and sensory neuropathy following chemoradiotherapy.[36] Cisplatin, a common chemotherapeutic agent, is frequently associated with peripheral neuropathy.[37] There is evidence suggesting that cisplatin can lead to cerebrovascular complications in MN patients even in the absence of traditional cardiovascular risk factors. For example, I. Meattini et al. documented a case where a young cancer patient developed srtoke during cisplatin therapy despite lacking conventional cardiovascular risk factors.[38] Similarly, Zafar et al.[39] reported the occurrence of IS in a 46-year-old man with seminoma during his second cycle of cisplatin-based chemotherapy. This patient had no cardiovascular risk factors, and investigations revealed acute occlusion of the left internal carotid artery, resulting in an infarction within the middle cerebral artery territory.[39] Neuroimaging studies have identified the middle cerebral artery territory as the most common site of srtoke in patients with malignant neoplasms.[40] Cisplatin-induced peripheral neuropathies are generally sensory in nature but can also include motor deficits such as reduced reflexes and lower limb weakness. Additionally, autonomic neuropathy, seizures, and loss of taste have been reported. There is also an increased risk of epilepsy in the post-stroke period following cisplatin therapy.[39] A cohort retrospective study by S. Li et al.[40] examined the incidence of stroke following chemotherapy and assessed the potential causal relationship between stroke and chemotherapy regimens. The study found that 75 % of IS cases occurred within 10 days after the last chemotherapy session, and 62.5 % occurred after the first cycle of cisplatin-based chemotherapy. The analysis included clinical, anamnesis, and neuroimaging data from MN patients between 1993 and 2004, totaling 10,963 individuals.[40] The overall incidence of IS was 0.137 %.[40] Adenocarcinoma was the most prevalent histological type of MN in IS patients (40 %) and among cancer patients in general (36.7 %). Moreover, Cerrud-Rodriguez et al.[41] reported a case of stroke in a 20-year-old man with testicular cancer undergoing cisplatin-based chemotherapy. These cases underscore the significant risks and complex interactions between cancer therapies, especially cisplatin, and cerebrovascular complications. Understanding these risks is vital for developing preventive strategies and enhancing patient outcomes. Clinicians should maintain a high level of vigilance for cerebrovascular complications in MN patients, particularly during and after chemotherapy. A multidisciplinary approach that involves oncologists, neurologists, and cardiologists is essential for the effective management of these patients, ensuring a better prognosis and improved quality of life.

The use of cisplatin in chemotherapy has been linked to a variety of cerebrovascular and neurological complications. Studies have shown that cisplatin can induce ischemic stroke even in the absence of traditional cardiovascular risk factors. For instance, a young cancer patient developed stroke during cisplatin therapy without any conventional cardiovascular risk factors, highlighting the direct impact of the drug on vascular health.[38] Another case reported by T. Etgen et al. involved a 46-year-old man with seminoma who experienced IS during his second cycle of cisplatin-based chemotherapy. This patient, who also had no cardiovascular risk factors, was found to have an acute occlusion of the left internal carotid artery, resulting in an infarction within the middle cerebral artery territory.[39] Moreover, chemotherapy-induced

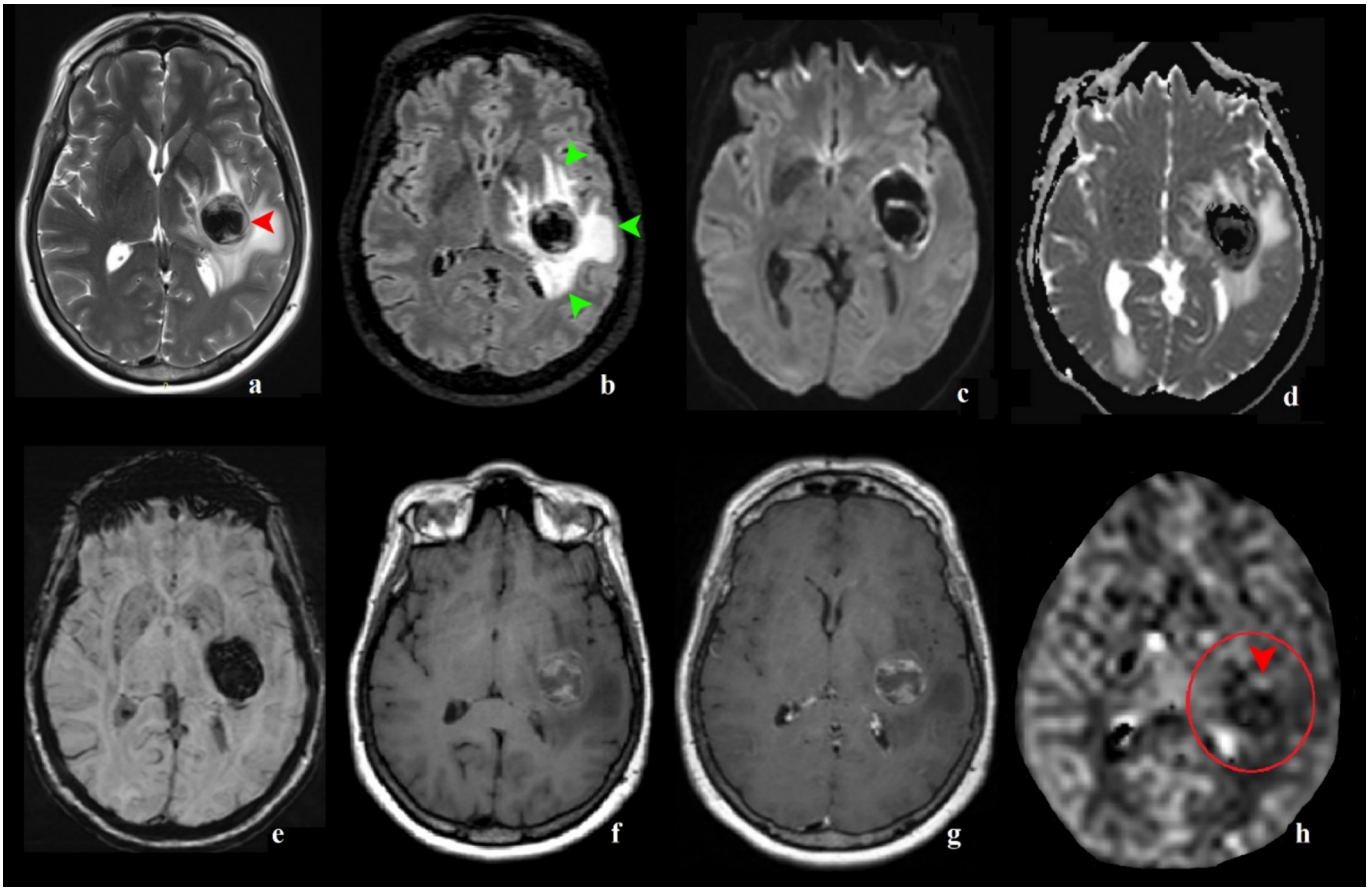

Fig. 3. Patient A., 32 y.o., with hemorrhagic metastases of melanoma. A globular intracerebral mass with low signal in T2 (a, red pointer), T2 FLAIR and SWI (b, e) due to biological products that detect hemoglobin in the acute and early subacute phase after hemorrhage. Low T2 signal from the blood creates signal dropout (or "blackout") signals on the b = 1000 DWI and ADC map (c and d), visually increasing the size of the lesion. A tumor with pronounced perifocal vasogenic edema in T2 and T2 FLAIR (a and b, green arrows), a mass effect in the form of compression of the left lateral ventricle, small structural dislocations of the midline structures and smoothness of the subarachnoid space. Pre- and post-contrast T1 images (e and g) without obvious enhancement, however, on the raw ASL perfusion data (h) against the background of the dropped signal, a single focus of CBF measurement can be detected in the anterior outer parts of the metastasis (red pointer inside the red circle).

peripheral neuropathy, particularly from cisplatin, is a significant concern. These neuropathies are typically sensory but can also include motor deficits such as reduced reflexes and weakness in the lower limbs. Autonomic neuropathy, seizures, and loss of taste are other potential complications. Furthermore, there is an increased risk of epilepsy in the post-stroke period following cisplatin therapy.[39] In a cohort retrospective study, S. Li et al. investigated the incidence of stroke following chemotherapy and assessed the potential causal relationship between stroke and chemotherapy regimens. The study found that 75 % of IS cases occurred within 10 days after the last chemotherapy session, with 62.5 % occurring after the first cycle of cisplatin-based chemotherapy. The study analyzed clinical, anamnesis, and neuroimaging data from MN patients between 1993 and 2004, involving a total of 10,963 individuals.[40] The incidence of IS was 0.137 %, with adenocarcinoma being the most common histological type of MN in IS patients (40 %) and among cancer patients overall (36.7 %).[40] Additionally, A. Santos et al. described a case of stroke in a 20-year-old man with testicular cancer undergoing cisplatin-based chemotherapy. These findings underscore the significant risks and complex interactions between cancer therapies, particularly cisplatin, and cerebrovascular complications.[41]

The findings from a study by K. Khadjooi et al.[42] are noteworthy, as they reported cerebrovascular complications in a 37-year-old man with MN. During a session of cisplatin chemotherapy, the patient experienced sudden weakness in his right arm and episodes of speech disturbances. Brain CT and MRI scans revealed multiple infarcts in the territory of the left middle cerebral artery.[42] Angiography of the precerebral arteries on the left side showed dissection of the vascular wall.[42] The researchers emphasized that decisions regarding the continuation or discontinuation of cisplatin-based chemotherapy should be individualized.[42] The role of cisplatin in the development of cerebrovascular complications was also described in a publication by Brouha et al.,[43] where a 72-year-old woman with MN developed focal neurological deficits during cisplatin treatment, and a brain CT scan revealed an infarct. The patient's cardiovascular risk factors included her age and carotid atherosclerosis.[43] Given the neurological deficits and the presence of an atherosclerotic plaque, cisplatin was replaced with paclitaxel, and the patient was also administered clopidogrel, which resulted in regression of the neurological deficit.[43] For the treatment of neuropathy induced by cisplatin therapy, experimental studies have demonstrated the effectiveness of methoxyflavone (6-MeOF).[37] A promising approach to protecting damaged neurons in stroke is antioxidant therapy. For instance, xanthohumol, a natural flavonoid extracted from hops, has shown potential antioxidant properties, and may be used for neuroprotection in experimental models of stroke.[44] Researchers have noted that xanthohumol treatment limits brain damage, reduces infarct size, and inhibits cell apoptosis, thereby reducing neurological deficits.[44] However, further randomized controlled clinical trials are needed to establish the safety and efficacy of xanthohumol for neuropro-

tection in cerebrovascular complications among MN patients. Additionally, the neuroprotective properties of Cordyceps sinensis extract have been demonstrated in cerebral ischemia.[45] These findings highlight the importance of exploring new therapeutic strategies to mitigate the adverse effects of cancer treatments and improve patient outcomes. Understanding these risks and potential treatments is crucial for developing preventive strategies and enhancing patient care. Clinicians should maintain a high level of vigilance for cerebrovascular complications in MN patients, particularly during and after chemotherapy. A multidisciplinary approach involving oncologists, neurologists, and cardiologists is essential for the effective management of these patients, ensuring a better prognosis and improved quality of life.

3. Radiation-induced cerebrovascular disorders and potential mechanisms

The risk of stroke increases significantly following radiation therapy to the mediastinum, neck, or head regions,[46] as emphasized in international guidelines.[18] This heightened risk is primarily due to endothelial damage and thrombus formation that can occur after the irradiation of small cerebral vessels.[18] In larger brain vessels, radiation can lead to medial necrosis, fibrosis, and occlusion of the vasa vasorum. Chemotherapy and radiation therapy can induce structural changes in the vessel walls, causing adventitial fibrosis and accelerating the progression of atherosclerosis (Fig. 4).[47] These changes, combined with other risk factors, can increase the stiffness of both pre-cerebral and cerebral arteries.[47] Consequently, chronic brain ischemia may develop, often manifesting more than a decade after radiation therapy, and is characterized by cognitive dysfunction.[18,47] Whole-brain irradiation is utilized in cases of miliary dissemination of metastases, multiple or limited lesions, particularly when the prognosis is poor.[4] This treatment is specifically indicated for metastases from lymphosarcoma, small cell lung cancer, and germinogenic tumors, where surgical intervention is not feasible. It is always supplemented with chemotherapy due to the high radiosensitivity of these tumors.[4,48] Neurological symptoms in such cases typically develop gradually over days or weeks, though acute onset can also occur. Common clinical manifestations of metastatic brain involvement include headaches and psychiatric and behavioral

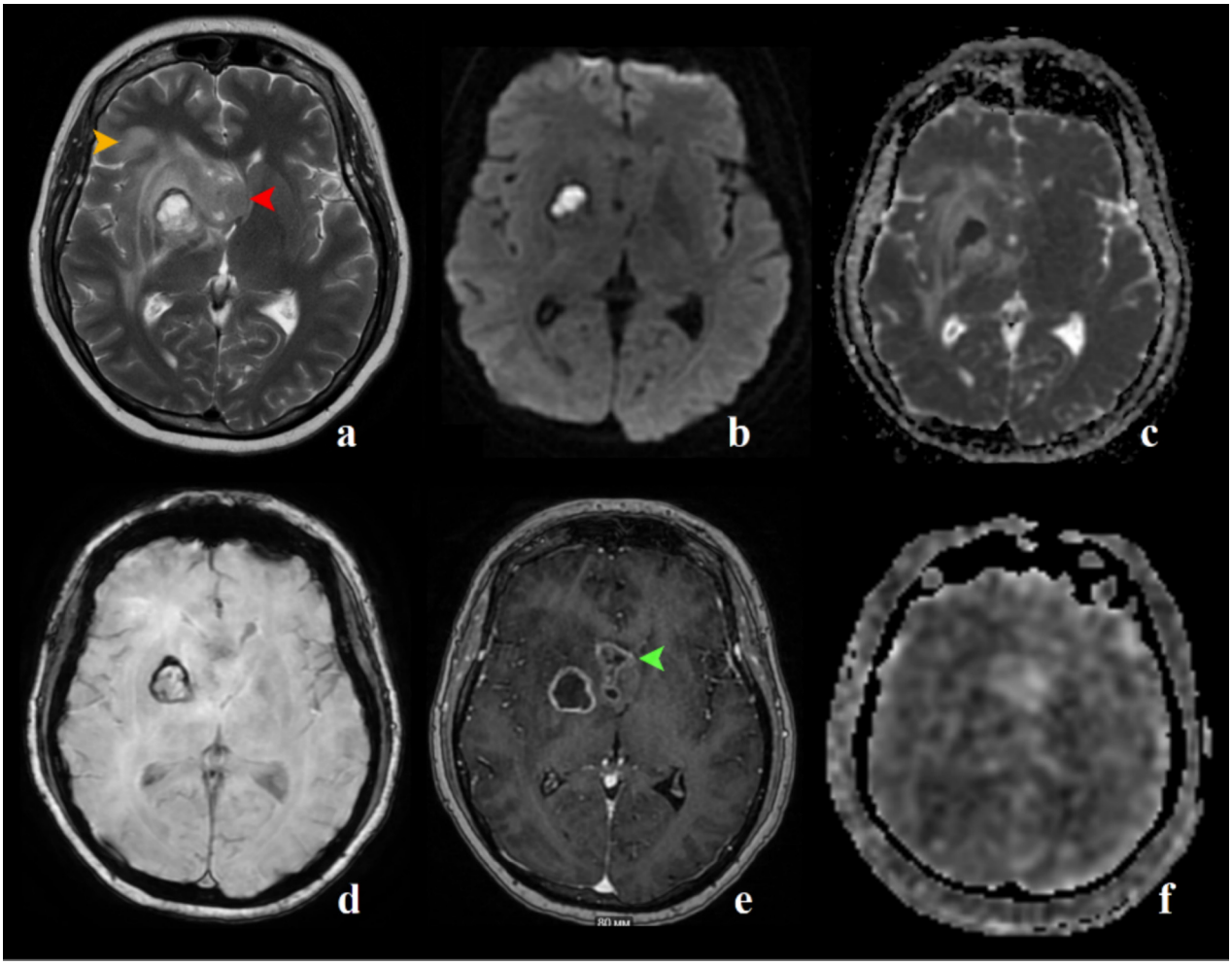

Fig. 4. Patient B., 45 y.o., with multifocal glioblastoma, after «Stupp-protocol» (radiotherapy – total 60 Gy, 2 Gy per daily fraction over 6 weeks; temozolomide – during radiotherapy: 75 mg per square meter of body-surface area per day, 7 days per week; post-radiotherapy (adjuvant): 6 cycles consisting of 150–200 mg for 5 days during each 28-day cycle). On axial T2 images at the level of the basal ganglia (a), the tumor involves the putamen, globus pallidus, and predominantly infiltrates the head of the caudate body and the thickened right fornix (red arrow). In addition, the glioma invades the gray matter of the cortical plate of the frontal operculum (yellow pointer). In the area of the globus pallidus there is a small hematoma in the early subacute phase after hemorrhage, which has a high signal on T2 (a) and T1 (e) images and limits diffusion due to the viscosity of the blood clot, which is manifested by a high signal in DWI b = 1000 (b) and low signal on the ADC (c). The hematoma shows low signal in the periphery on SWI (d) due to hemosiderin, accumulating contrast agent in a closed ring pattern with walls of uniform thickness on post-contrast T1 image (e), due to a disrupted blood–brain barrier. The tumor-affected fornix on the right accumulates contrast in a similar manner but has a "corona effect" in the structure (green pointer), which is found in the necrotic cavities of gliomas, and shows an increase in signal on raw ASL perfusion data (f), characteristic of the most malignant component heterogeneous diffuse glioma.

disturbances. Seizures are especially common with melanoma and choriocarcinoma metastases.[4,48] Less common symptoms include paresthesias, sensory deficits, unstable gait, unilateral twitching, diplopia, ptosis, ataxia, orthostatic hypotension, and hiccups.[4,48]

The primary mechanisms linking cerebrovascular complications and malignant neoplasms include elevated catecholamine levels, electrolyte imbalances, and hypoxia, which are common in both conditions. The functioning of the CNS is largely dependent on catecholaminergic neurotransmitters. These neurotransmitters control the transmission of nerve impulses in synaptic pathways, coordinate many components of central nervous system mechanisms, and are involved in organizing both adaptive and destructive processes.[49] Under the influence of catecholamines, potassium exits the cell into the extracellular space, and the levels of sodium and magnesium in the blood plasma are altered.[50] These intricate interactions highlight the necessity of a multidisciplinary approach in managing patients with malignant neoplasms, especially those undergoing chemotherapy and radiation therapy. By comprehending the underlying mechanisms and potential complications, healthcare providers can better anticipate and mitigate the risks, thus improving patient outcomes and quality of life.

To mitigate these risks, healthcare providers should maintain a high index of suspicion for cerebrovascular complications in MN patients, especially during and after chemotherapy. A multidisciplinary approach involving oncologists, neurologists, and cardiologists is essential for optimizing patient care, improving prognosis, and enhancing quality of life. Catecholamines significantly increase the oxygen demand of the CNS by stimulating oxidative processes in the brain, thereby exerting a stimulatory effect. Studies have indicated that in patients with MN, prolonged chemotherapy and radiation therapy can cause damage and thrombosis in small brain vessels.[20] The pathophysiological mechanisms that elevate the risk of stroke in medium and large vessels include occlusion of the vasa vasorum, leading to medial necrosis and fibrosis, adventitial fibrosis, and the progression of atherosclerosis, which is often observed more than ten years after radiation therapy.[18] Similar damage mechanisms have been described for the aorta and other peripheral vessels, such as the subclavian and iliac-femoral arteries, resulting in limb ischemia. For patients who have undergone radiation therapy to the neck or head region, or those treated for lymphoma, it is recommended that ultrasound examinations of the pre-cerebral vessels be conducted, particularly starting five years after the initiation of radiation therapy.[18] These examinations should be repeated every five years, or more frequently if abnormalities are detected in the initial study. Physical examinations or the presence of relevant symptoms can reveal signs of radiation-induced damage to other arteries. Notably, head and neck irradiation is a well-established risk factor for carotid artery stenosis.

In a study by P. Texakalidis et al.,[51] which aimed to determine the prevalence, frequency, and degree of carotid artery stenosis in patients with a history of head and neck irradiation, it was found that the incidence of carotid artery stenosis increased by more than 50 % annually during the first three years following radiation therapy. A *meta*-analysis of 12 studies[51] involving 1,479 patients revealed that the prevalence of carotid artery stenosis > 50 % was 25 % (95 % CI 19–32 %), >70 % was 12 % (95 % CI 7–17 %), and carotid artery occlusion was 4 % (95 % CI 2–8 %). Additionally, the cumulative 12-month incidence of carotid artery stenosis > 50 % was 4 % (95 % CI 2–5 %), rising to 12 % (95 % CI 9–15 %) at 24 months.[51] Notably, the cumulative 36-month incidence of carotid artery stenosis > 50 % was 21 % (95 % CI 9–36 %).[51] The impact of stroke on mortality and psychosomatic status in MN patients was investigated by Bottinor et al..[52] The authors conducted a retrospective cohort study with longitudinal follow-up of childhood cancer survivors whose tumors were diagnosed between 1970 and 1986. Mortality rates per 100 person-years were calculated across three periods: 1) before the first stroke; 2) after the first stroke and before a recurrent stroke; and 3) after a recurrent stroke.[52] Among 14,358 participants (mean age 39.7 years), 224 experienced a stroke following their cancer diagnosis (161 had a primary stroke, and 63 had a recurrent stroke). The study found that late mortality rates from all causes were 0.70 (95 % CI 0.68–0.73) before the first IS and 1.03 (95 % CI 0.73–1.46) after the primary stroke. This rate

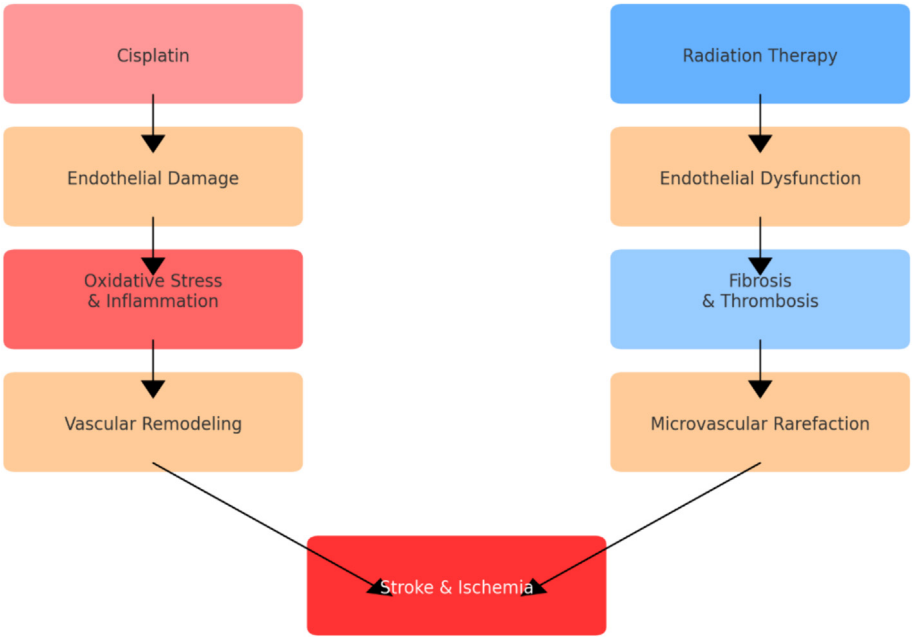

Fig. 5. This diagram representing the mechanisms underlying cisplatin and radiation therapy-induced cerebrovascular disorders. The diagram illustrates how both treatments can lead to conditions like endothelial damage, oxidative stress, inflammation, fibrosis, thrombosis, and ultimately increase the risk of cerebrovascular disorders, including ischemia and stroke.

increased significantly for individuals with recurrent stroke, reaching 2.42 (95 % CI 1.48–3.94).

These findings underscore the critical need for continuous monitoring and a comprehensive approach to managing the long-term vascular health of cancer survivors. By understanding the potential complications and implementing regular follow-ups, healthcare providers can significantly improve outcomes and enhance the quality of life for these patients. This approach is essential to address the multifaceted risks associated with cancer treatment and its long-term effects on vascular health (Fig. 5).

4. Conclusion

The increasing number of oncology patients and the cerebrovascular complications associated with chemotherapy and radiation therapy underscore the urgent need for identifying a distinct high-risk group. These complications, which include ischemic stroke, hemorrhagic stroke, and other vascular disorders, can significantly impact the prognosis and quality of life of cancer patients. Effective prevention and management of these cerebrovascular disorders necessitate a multidisciplinary approach. Oncologists, neurologists, cardiologists, radiologists, and primary care physicians must collaborate to provide comprehensive care. By recognizing the specific risks posed by various cancer treatments and the pathophysiological mechanisms involved, healthcare providers can implement targeted monitoring and intervention strategies. This includes regular screening for vascular abnormalities, managing cardiovascular risk factors, and optimizing cancer treatment protocols to minimize vascular damage. Coordinated care is essential for early detection and prompt management of cerebrovascular complications, potentially reducing morbidity and mortality rates. Future research should focus on understanding the molecular and cellular mechanisms underlying these complications to develop tailored interventions. Additionally, large-scale, longitudinal studies are needed to establish evidence-based guidelines for the prevention, monitoring, and treatment of cerebrovascular disorders in cancer patients. Comprehensive monitoring protocols that include advanced imaging techniques and biomarker analysis will be crucial in identifying at-risk patients early and managing their conditions effectively. Ultimately, by integrating multidisciplinary expertise and advancing research efforts, we can improve the overall outcomes and quality of life for patients with malignant tumors, ensuring they receive the best possible care throughout their treatment journey.

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CRediT authorship contribution statement

Ozal Beylerli: Writing – review & editing, Writing – original draft, Conceptualization. **Rustam Talybov:** Visualization, Resources, Data curation. **Elmar Musaev:** Formal analysis, Data curation. **Tatyana Trofimova:** Supervision. **Huaizhang Shi:** Supervision. **Tatiana Ilyasova:** Data curation, Methodology. **Valentin Pavlov:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical statement

This review article does not contain any studies with human participants or animals performed by any of the authors.

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