



Challenges in the Clinical and Radiological Differential Diagnosis of Cerebrovascular Events and Malignant Primary Brain Tumors: Reports from a Retrospective Case Series

Erdinc CIVELEK¹, Yener AKYUVA², Necati KAPLAN³, Furkan DIREN¹, Osman BOYALI¹, Serdar KABATAS¹

¹University of Health Sciences, Gaziosmanpasa Training and Resarch Hospital, Department of Neurosurgery, Istanbul, Turkey

²Mustafa Kemal University, Department of Neurosurgery, Hatay, Turkey

³Istanbul Rumeli University, Corlu Reyap Hospital, Department of Neurosurgery, Istanbul, Turkey

Corresponding author: Necati KAPLAN ✉ drnecatikaplan@hotmail.com

ABSTRACT

AIM: To reveal difficulties in differential diagnosis of some cases of cerebrovascular events (CVEs) and malignant primary brain tumors (MBTs) even a multidisciplinary evaluation in grand rounds.

MATERIAL and METHODS: This study retrospectively analyzed the patient archives from January 2017–December 2019. The records of 572 patients discussed in these meetings were examined. A total of 8 patients having a challenge in differential diagnosis were detected.

RESULTS: This study has included 8 cases in which neurology–neurosurgery–neuroradiology clinicians have difficulty in differentiating CVE and MBT. In the present study, three patients were evaluated with a preliminary diagnosis of hemorrhagic CVE in the emergency room. Since degradation products of hemoglobin have prevented advanced imaging methods to diagnose in two patients, these patients have been followed closely. The correct diagnosis could be made through the scan performed during control follow-ups. The preliminary diagnosis of seven patients was CVE, but they received the MBT diagnosis during the follow-up. One patient was thought to have MBT initially; however, he/she was diagnosed with CVE after an advanced examination and close follow-up.

CONCLUSION: Despite developing medical imaging methods and diagnostic studies, there are still some difficulties in making differential diagnosis of CVEs and MBTs. In some patients, further examination and imaging methods may be needed such as magnetic resonance imaging-spectroscopy (MRI-S), perfusion magnetic resonance imaging (Per-MRI), digital substratioangiography (DSA). Despite all these neuroradiological examinations and multidisciplinary evaluation, distinction between CVE and MBT may be difficult, and medicolegal problems may be encountered.

KEYWORDS: Brain neoplasms, Cerebrovascular diseases, Differential diagnosis, Malignant

INTRODUCTION

Cerebrovascular event (CVE) is defined as a neurological disease caused by ischemic or hemorrhagic reasons. It often causes acute neuromotor deficits. A rupture in neurovascular structures can cause hemorrhagic CVE. Ischemic CVE may be encountered in cases such as

coagulopathy or cardiovascular embolism. Malignant brain tumors (MBTs) may originate from the primary central nervous system (CNS) or may develop due to brain metastases of organs other than the CNS. Patients often describe a chronic complaint, such as headaches, since MBTs progress more slowly than CVE (8). In general, radiological differences may

Erdinc CIVELEK : 0000-0002-3988-4064
Yener AKYUVA : 0000-0002-2424-3117
Necati KAPLAN : 0000-0001-5672-0566

Furkan DIREN : 0000-0001-6169-9722
Osman BOYALI : 0000-0002-2500-1718
Serdar KABATAS : 0000-0003-2691-6861

also be encountered between MBTs and CVE, as well as clinical differences. Differential diagnoses are facilitated by the presence of intraparenchymal hemorrhage (IPH) in cranial computed tomography (CT) in hemorrhagic CVE and the presence of restricted diffusion in diffusion-weighted imaging (DWI) in ischemic CVE. In MBTs, there are more specific CT and/or magnetic resonance imaging (MRI) findings, such as cystic necrotic image, contrast enhancing pattern, calcification, and digital edema. Therefore, these two pathologies are often easily distinguished from each other. However, further investigation and imaging methods such as MRI-spectroscopy (MRI-S), perfusion MRI (Per-MRI), and digital subtraction angiography (DSA) may be needed, as clinical or radiological findings are not helpful enough to a clinician in some cases. In this study, cases admitted to the neurology and neurosurgery clinics of a training and research hospital, in which the distinction of CVE and MBT was difficult, were discussed with the importance of neuroradiological evaluation and medicolegal problems in the management of these patients.

■ MATERIAL and METHODS

A grand round of neuroradiology consisting of neurologists, neurosurgeons, and neuroradiologists was performed regularly every week in our hospital which is one of the reference and Educating and Training center in Istanbul. This study retrospectively analyzed the patient archives from January 2017–December 2019, which were discussed in the neuroradiology grand round. The records of 572 patients discussed in these meetings were examined.

Procedure Details

In patients presenting with a neurological symptom or finding such a sudden development of motor deficit, epileptic seizure, or chronic headache, a cranial CT was performed to make a standard rapid evaluation. In a cranial CT, the presence of hemorrhagic CVE was investigated, particularly in the deep parts of the brain, such as the thalamus, basal ganglia, and internal capsule. It was further investigated whether there was a space-occupying lesion in another location in the brain's parenchyma. In cases where ischemic CVE was suspected,

a DWI was performed to evaluate the restricted diffusion. If cranial CT and DWI were considered insufficient for diagnoses, a contrast-enhanced cranial MRI examination was performed. As a standard procedure, T1W, T2W, DWI, fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted angiography (SWAN), and contrast T1W sequence were taken in a cranial MRI. The neuroradiology grand round discussed cases where a definitive diagnosis could not be made despite these examinations or when there were doubts about the diagnosis. If the diagnosis could not be made despite a cranial MRI in the council, the patient underwent further imaging techniques, such as DSA, MR angiography (MRA), MRI-S, and Per-MRI. A definitive diagnosis could not be made in some cases, despite all these assessments. The patients and their relatives were informed that a definitive diagnosis could not be made and their examination should be repeated one month later. The diagnosis of eight patients who were followed up in this way was changed during their follow-ups (Table I). Since it was a retrospective study, no ethics committee approval was obtained. This study was planned according to the Declaration of Helsinki. No statistical analysis was performed in this study.

■ RESULTS

Patient 1: A 60-year-old female patient was admitted to the emergency room with a sudden loss of consciousness. Blood pressure was measured to be 180/120 mmHg in the emergency department. The Glasgow Coma Scale (GCS) score of the patient at the time of admission was 6 (E1M4V1). A cranial CT examination showed a parenchymal hematoma of about 5.5 x 4 cm in the right parietal lobe and hypodense area surrounding the hemorrhage. The right lateral ventricle and third ventricle were compressed, and there was a midline shifting of about 13 mm. It was written on the examination note of the patient, who was first evaluated by the neurologist in the emergency room, that hemorrhagic CVE due to hypertension was considered, and neurosurgical consultation was urgently recommended for decompression. The patient was taken for an urgent operation. A right parietooccipital craniotomy, intracerebral hematoma discharge, decompression, and duraplasty operation were planned for the patient. A parietooccipital gyrus resection was

Table I: Summary of the Patients Characteristics and the Results of Preliminary and Definite Diagnosis

Patient #	Gender	Age (years)	Preliminary Diagnosis	Definite Diagnosis	Special Test
1	Female	60	Hemorrhagic cerebrovascular event (CVE)	Glioblastoma	MRI-S
2	Female	40	Hemorrhagic CVE	Glioblastoma	1 Month Follow-up
3	Male	57	Thrombosis	Anaplastic Astrocytoma	1 Month Follow-up
4	Female	67	Thrombosis	Glioblastoma	C+ MRI
5	Female	70	Glioblastoma	Subacute Cerebral Infarction	Per-MRI
6	Male	80	Hemorrhagic CVE	Glioblastoma	1 Month Follow-up
7	Female	61	Acute Cerebral Infarction	Lymphoma	MRI-S
8	Male	66	Acute Cerebral Infarction	Glioblastoma	Per-MRI

performed, and tissue was sent for pathological examination. After surgical treatment, a rapid recovery was observed, and no significant neuromotor sequelae was observed except for a partial loss of vision. The pathology after discharge was reported to be glioblastoma multiforme (GBM). In the contrast-enhanced cranial MRI taken at the postoperative first month, a central cystic necrotic lesion measuring 36x20x30 mm with a peripheral nodular enhancement was observed in the right parietal lobe. In the per-MRI examination, a significant increase in perfusion was observed in this area. The patient was referred to the oncology clinic (Figure 1A-D).

Patient 2: A 40-year-old female patient was admitted to the emergency room after an epileptic seizure. There was no condition in the patient's history other than oral contraceptive use. The GCS score of the patient, who was also found to have status epilepticus, was evaluated as 7 (E1M4V2), and the patient was intubated and sedated. Upon cranial CT, it was observed that a subcortical hyperdense nodular appearance with indefinite boundaries at the level of the right centrum semiovale. A hemorrhagic stroke induced by oral contraceptive use was considered, and clinical neurology follow-up was recommended in the emergency neurosurgery consultation. The MRI could not be performed in the early period since the patient who was followed up as intubated under sedation had recurrent seizures at the stage where the sedation would be stopped. In the cranial MRI report of the

patient, whose MRI can be taken on the 15th day following admission to the emergency room, the lesion measured about 55x48x48mm in the right frontal lobe. This area demonstrated spontaneous hyperintense portions locally in T1 and was hypointense in central and heterogeneous hyperintense in peripheral in T2 and FLAIR weighted images; hence, it was thought to be compatible with hematoma in the early subacute period. No significant contrast enhancement was detected. In the second-month follow-up examination by the neurology clinic, a cranial CT showed a decrease in the size of the hematoma, whereas there was an increase in edema surrounding the hematoma. The patient then underwent cranial MRI. The MRI results showed a hemorrhagic lesion in the cortical-subcortical location on the right frontal lobe, which measured about 50x44 mm at its widest point, including degradation products of hemoglobin and cystic components, and had mild hyperintense components in T1. In the post-contrast series, apart from cystic components, heterogeneous contrast enhancement was observed, particularly in peripheral sections. The pathology of the patient undergoing an operation was reported to be Grade 4 GBM. The patient was referred to the oncology clinic following discharge (Figure 2A-F).

Patient 3: A 57-year-old male patient was admitted to the emergency room with a complaint of sudden headache. The patient, who had a hypertension history and a suspicious lesion in the left parietal region on cranial CT, underwent DWI.

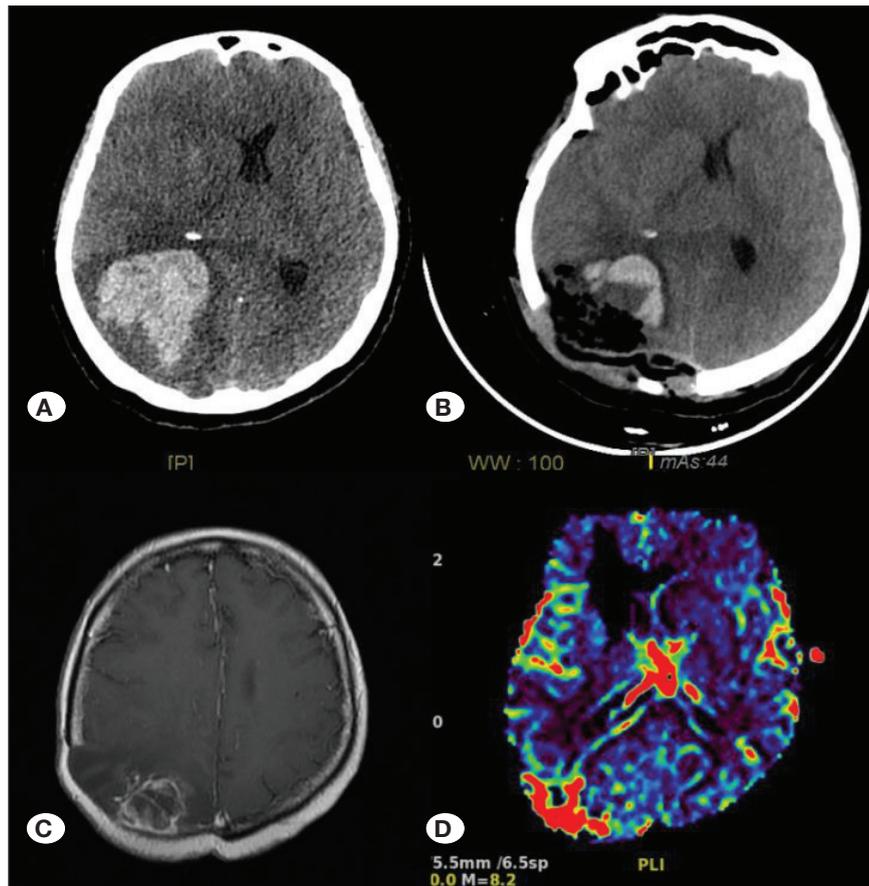


Figure 1: A) Preoperative axial cranial computed tomography (CCT) image, B) postoperative axial CCT image, C) T1-weighted contrast enhanced axial magnetic resonance imaging (MRI) one-month after surgery, and D) perfusion weighted axial MRIs at postoperative second month.

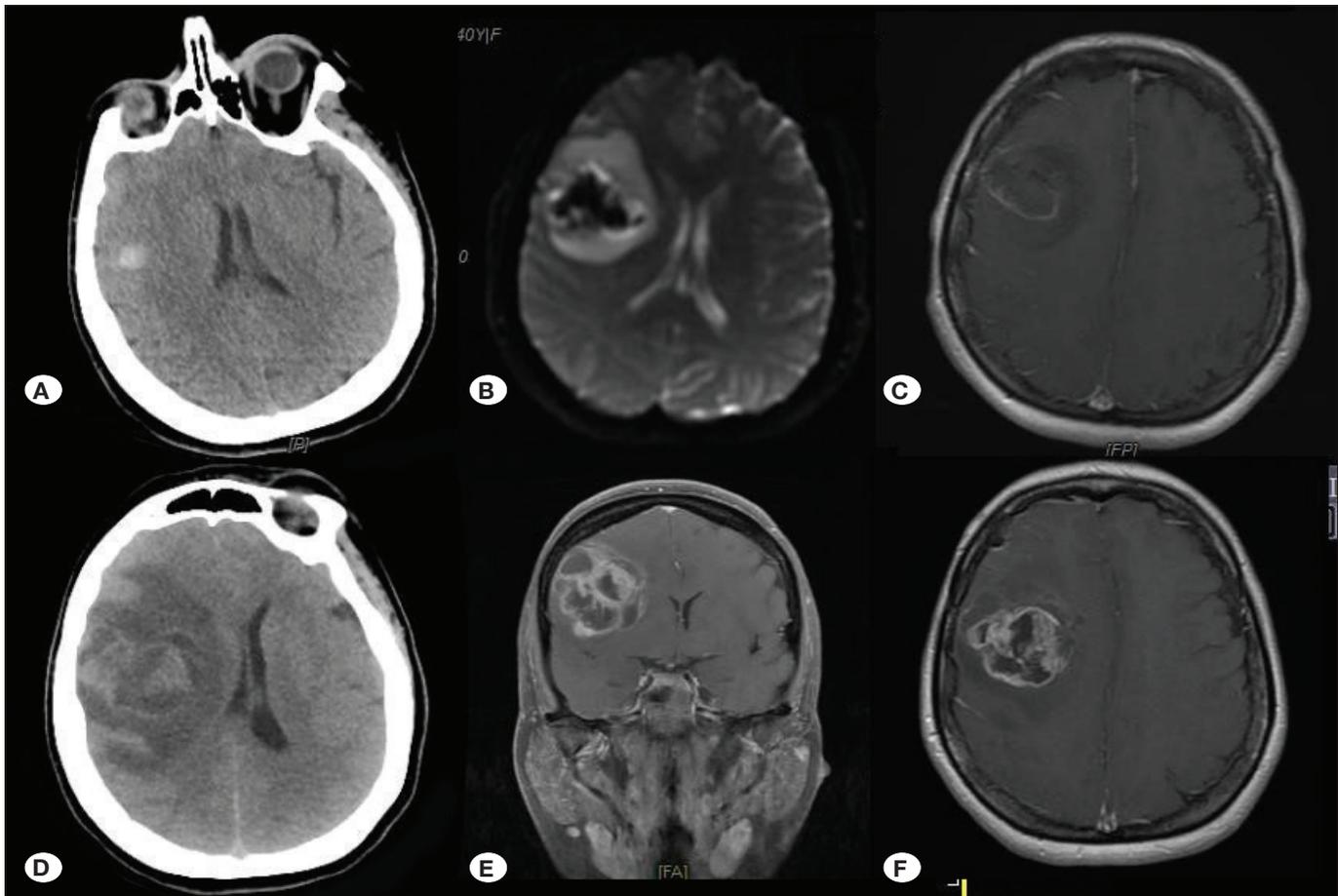


Figure 2: A) Axial section CCT, B) axial section diffusion MRI, C) axial section contrast enhanced T1W brain MRI D) 1st month axial section BBT, E) 1st month coronal section contrast enhanced T1W brain MRI, F) 1st month axial T1W contrast enhanced brain MRI section.

There were hyperintense signals on the ADC map, which could be compatible with subacute infarction in the cortical area of the left superior parietal lobe at the supratentorial level. The patient underwent cranial MRI and MRA; however, no significant finding was observed. MRI-S and per-MRI demonstrated no findings supporting another pathology. Venous infarction was considered primarily, and the treatment was planned by the neurology clinic. The patient presented to the outpatient clinic two months later with an increase in headache. In his brain CT, an axial mass lesion measuring about 3x2 cm, which was surrounded by a vasogenic edema ring, was identified in the left parietal lobe. At the superior territorial level, a T1 hypointense and T2 hyperintense mass lesion measuring 31x30 mm, which showed intense contrast enhancement in post-contrast examinations, was detected in the left parietal lobe cortico-subcortical area. There was prominent vasogenic edema in the peripheral zones of the lesion. The patient was operated upon the detection of increased cerebral blood volume (CBV) and cerebral blood flow (CBF), values of the lesion identified in the perfusion-MRI examination. The pathology result of the patient were reported to be anaplastic astrocytoma. The patient was referred to the oncology clinic following discharge (Figure 3A-F).

Patient 4: A 67-year-old female patient presented to the outpatient neurology clinic with complaints of headache. The cranial MRI of the patient with a history of endovascular cardiac stenting due to myocardial infarction (MI), which was taken upon the recommendation of a neurologist, showed an area with partially restricted diffusion at the central sulcus level in the left parietal region and prominent edema in the same area. Venous infarction was considered primarily in the patient who had a history of MI and stated that she neglected antiaggregant therapy. The patient, whose complaints did not regress despite the medical treatment, underwent contrast-enhanced cranial MRI, and the MRI results revealed a space-occupying peripheral lesion with an axial size of about 47 mm in the left frontoparietal region. The lesion was found to show heterogeneity in all sequences, and an intense heterogeneous contrast involvement pattern compatible with a high-grade glial tumor was detected in IV contrast. The pathology of the operated patient was reported as GBM. The patient was referred to the oncology clinic following discharge (Figure 4A-F).

Patient 5: A 70-year-old female patient was admitted to the emergency department with a complaint of new and increasing headache and imbalance. The cranial CT (CCT) of the patient

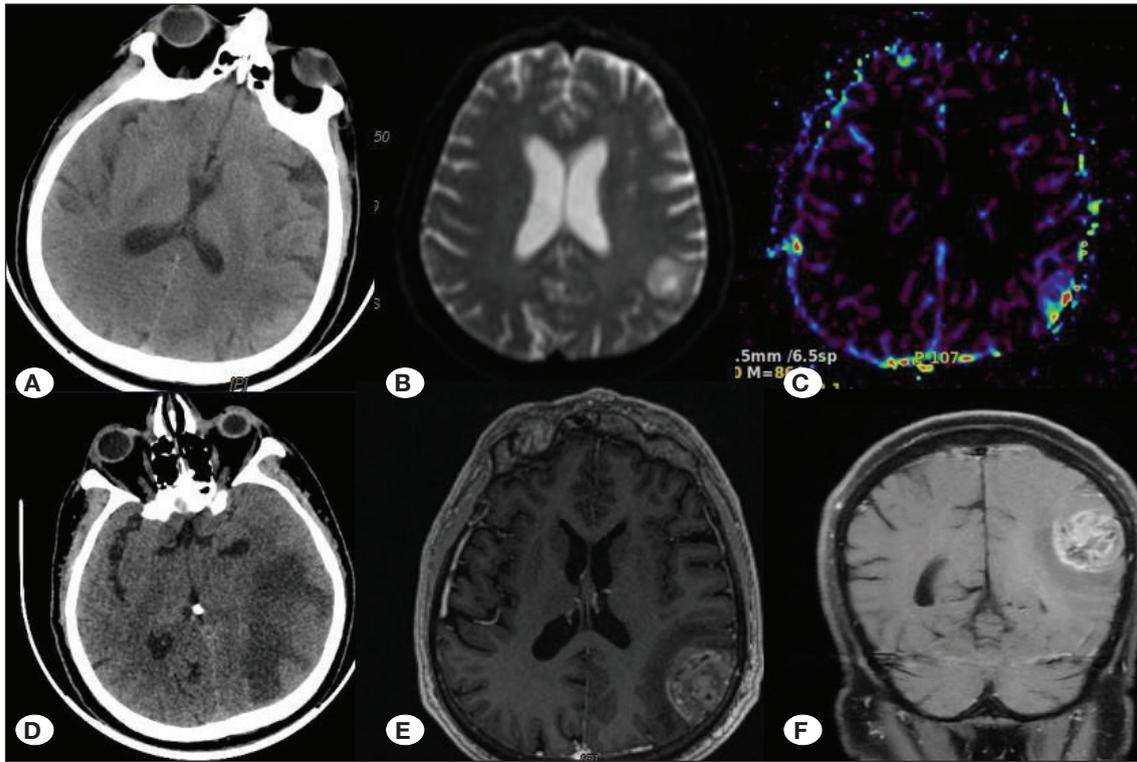


Figure 3: A) Axial section CCT, B) axial section diffusion MRI, C) axial section perfusion weighted brain MRI. D) 1st month axial section CCT, E) 1st contrast enhanced T1W axial brain MRI, F) 1st month contrast enhanced T1W coronal brain MRI.

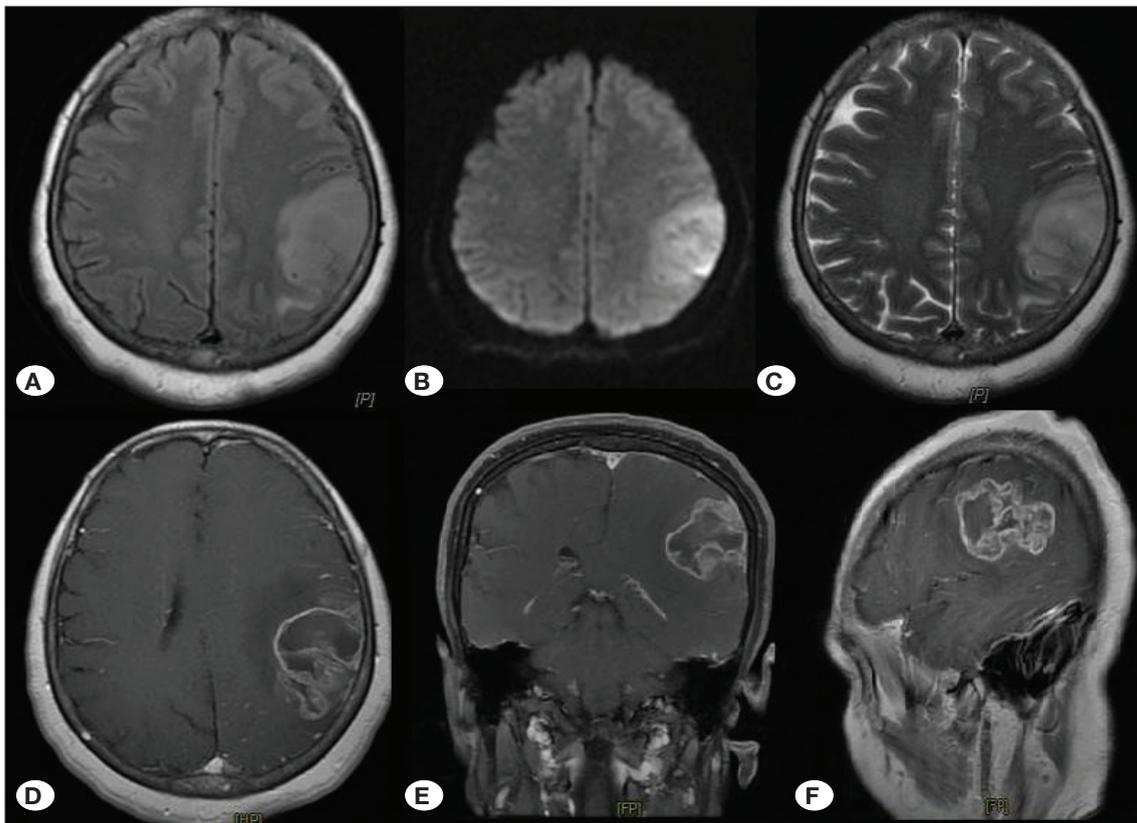


Figure 4: A) Axial section FLAIR section, B) axial section diffusion MRI, C) axial section T2W MRI of the brain. D) 1st month contrast enhanced T1W axial brain MRI, E) 1st month contrast enhanced T1W coronal brain MRI, F) contrast enhanced T1W sagittal brain MRI.

showed a hypodense area extending to the deep white matter in the right occipital cortico-subcortical area and a lesion that was thought to be cortical-sulcal pattern at this level. Her cranial MRI showed a high-grade glial tumor-compatible lesion measuring about 3.5x2.7 cm, which was near the midline in the right occipital lobe at the lateral ventricle level, hypointense in T1A sequences, showed mild heterogeneous signal in T2A sequences, had a surrounding prominent edema area, and showed restricted diffusion in DWI and contrast enhancement in a contrast series. Since the Per-MRI and MRI-S examination was not compatible with MBTs. In a cranial MRI repeated one month later, a contrast enhancement similar to previous examinations was detected in the subcortical area following the administration of an IV contrast medium in the existing lesion involving a spiral-like spontaneous hyperintense pathological signal in T1-weighted sequences without contrast. The lesion, which was initially diagnosed as an MBT upon the spontaneous regression of the lesion and disappearance of edema, was seen to be compatible with the infarction that occurred during the subacute period. Surgical treatment was abandoned, and the patient was recommended to be checked by the neurology outpatient clinic (Figure 5A-F).

Patient 6: An 80-year-old hypertensive male patient was brought to the emergency room with a sudden loss of consciousness and left hemiparesis. The CCT of the patient with a history of MI and coronary bypass surgery revealed a 19-mm-diameter hyperdens appearance suggesting a possible hemorrhage. A third ventricular compression occurred at the basal ganglion level on the right lobe. The patient, who was also evaluated by the neurosurgeon in the emergency room, was recommended to be followed up by the neurology clinic, considering the basal ganglia hemorrhage. No different pathology was considered in a cranial MRI. After a month, the patient was readmitted to the emergency room due to epileptic seizures. The cranial MRI showed a mass lesion measuring 27x17 mm involving the right thalamus anteromedial and extending to the posterior limb of the internal capsule and to the globus pallidus, which was heterogeneous on T2- and hypointense on T1-weighted images, and showed intense heterogeneous contrast enhancement. In the periphery of the identified lesion, vasogenic edema extended to the right cerebral peduncle, and infiltration was observed to increase. The pathology of the patient, who underwent an operation upon the detection of a high choline peak in the MRI-S, was

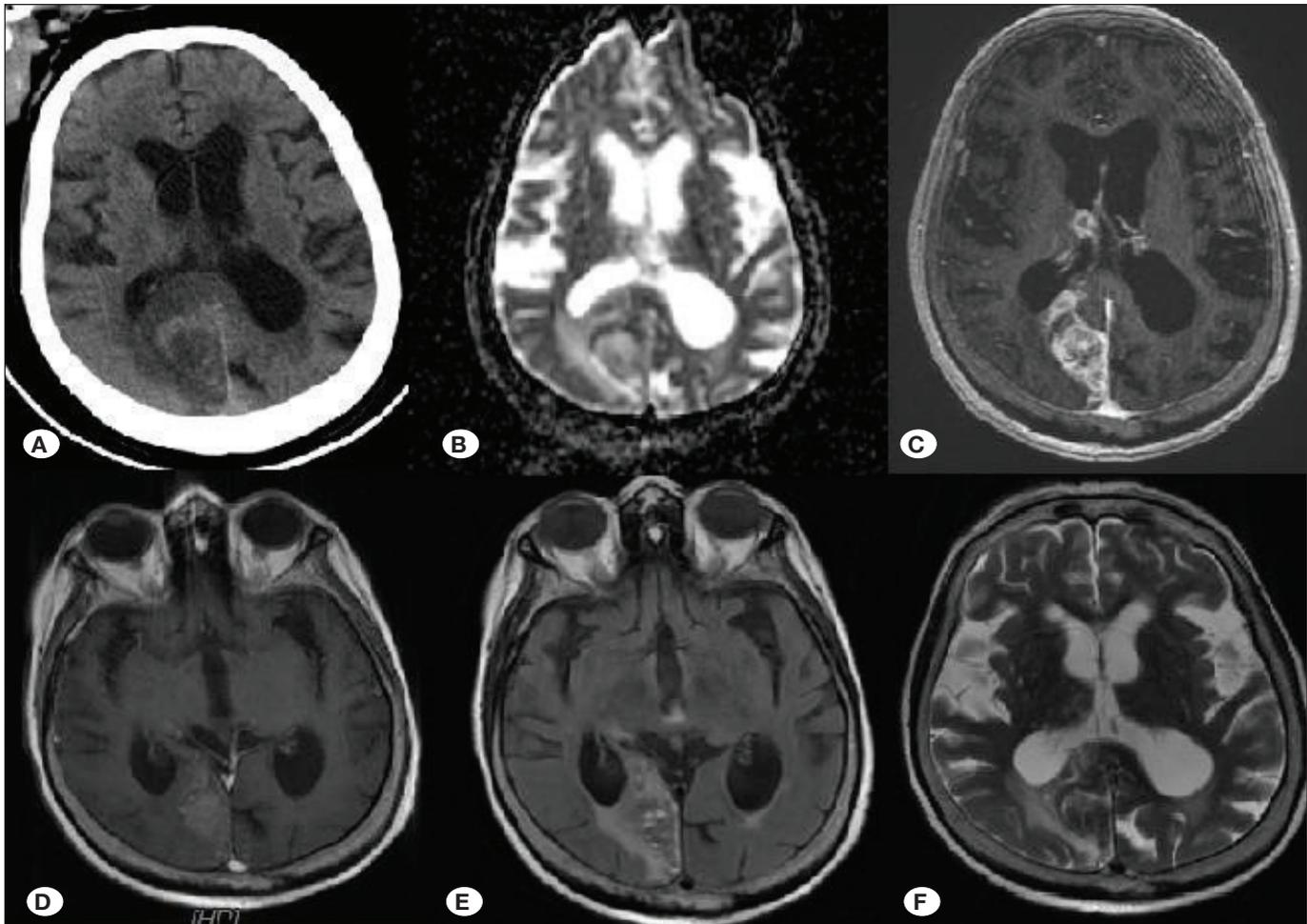


Figure 5: A) Axial section CCT, B) axial section diffusion MRI, C) contrast enhanced T1W axial brain MRI. D) 1st month acontrast enhanced T1W axial brain MRI, E) 1st month axial section FLAIR brain MRI, F) 1st month T2W axial MRI for the brain.

reported to be GBM. After discharge, the patient was referred to the oncology clinic (Figure 6A-H).

Patient 7: A 61-year-old female patient was admitted to the emergency room with a complaint of increasing weakness in the left upper extremity. In the examination, the strengths of the distal muscles and the proximal extensor muscles on the left side were seen to be 2/5 and 4/5, respectively. While CCT did not show any findings at first, a DWI revealed that a restricted diffusion compatible with ischemia was detected at the right frontal cortical level. When the cranial CT results were carefully re-evaluated, hypodensity was observed in this area. There were no findings other than the increase in the T2-FLAIR signal in the subcortical white matter in the right precentral gyrus at the supratentorial level. In the neurosurgery emergency department consultation, it was thought that the existing lesion may be compatible primarily with the cerebral infarction. The patient was followed up in the neurology clinic. A cranial MRI was repeated one month later, and the results revealed an expansile lesion extending from subcortical white matter to cortical structures, which was hyperintense on T2 and FLAIR sequences and showed intense enhancement in post-contrast examinations, accompanied by diffuse localized

contrast enhancement towards the inferior throughout the perivascular areas in the right precentral gyrus at the supratentorial level. A spectroscopic examination performed for this lesion showed suppression in the N-acetylaspartic acid (NAA) peak, increase in the choline peak, and the presence of lactate peak. There was an increase in the CPV and CBF values of this area in the per-MRI results. The lesion compatible with MBT was excised through neuronavigation. The patient whose pathology result was reported to be compatible with the primary CNS lymphoma was referred to the hematology clinic after discharge (Figure 7A-F).

Patient 8: A 66-year-old male patient presented to the outpatient clinic with a complaint of blurred vision. A cranial CT showed a decrease in white-matter density and peripheral edema in the left temporo-parieto-occipital region. The radiologist reported that the current lesion was initially considered as subacute ischemia in the field of left posterior cerebral artery. It was determined that cranial MRI was more hyperintense in this localization compared to parenchyma, and there was no significant enhancement in all sequences. It was thought to be compatible with late subacute hematoma in a cranial MRI. The contrast enhancing and edema of the existing

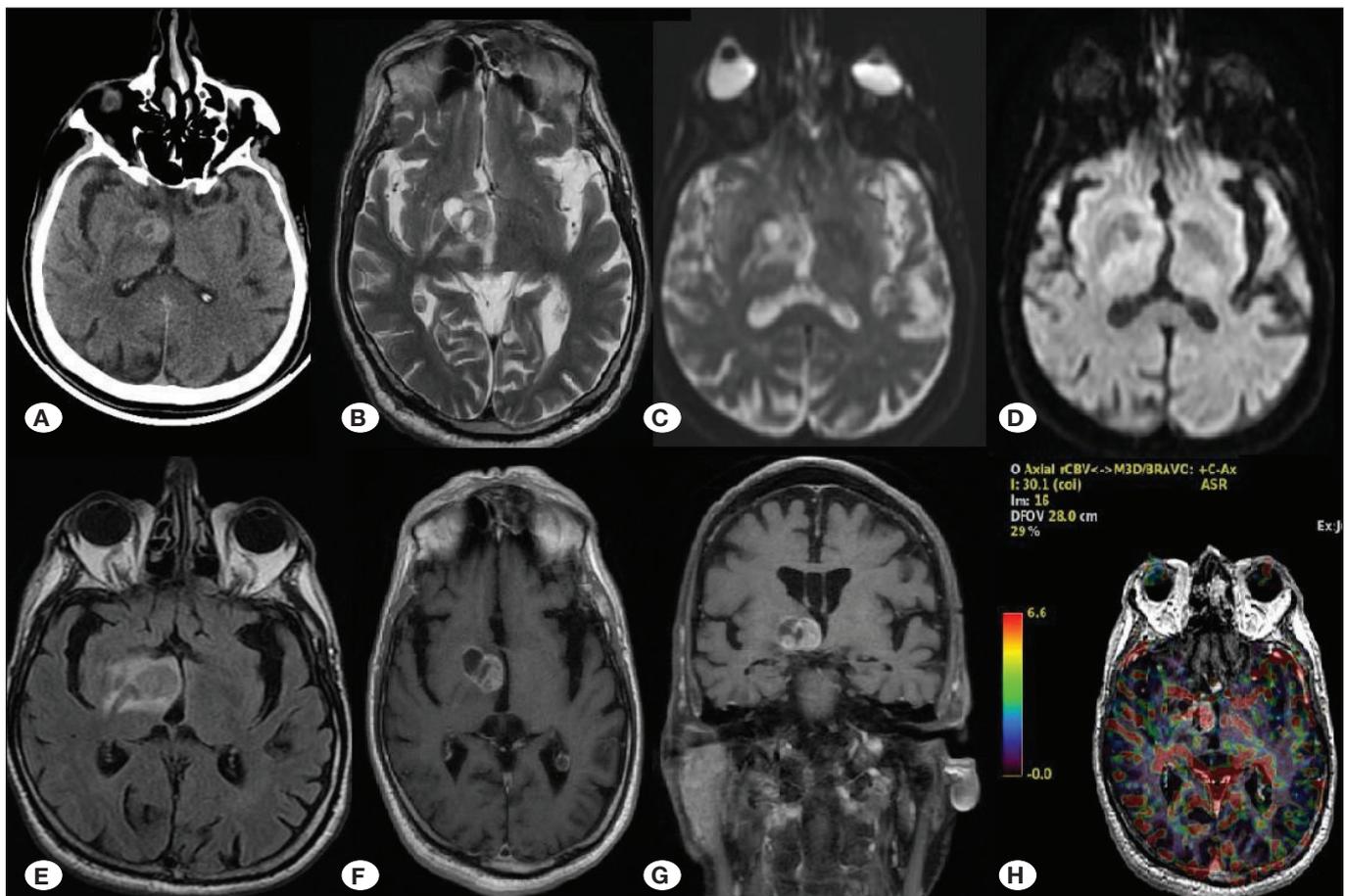


Figure 6: A) Axial section CT, B) axial T2W MRI of the brain, C) axial diffusion MRI, D) axial section FLAIR MRI of the brain. E) 1st month axial section T1W MRI of the brain, F) 1st month contrast enhanced T1W axial brain MRI, G) 1st month contrast enhanced T1W coronal brain MRI, H) 1st month perfusion weighted MRI of the brain.

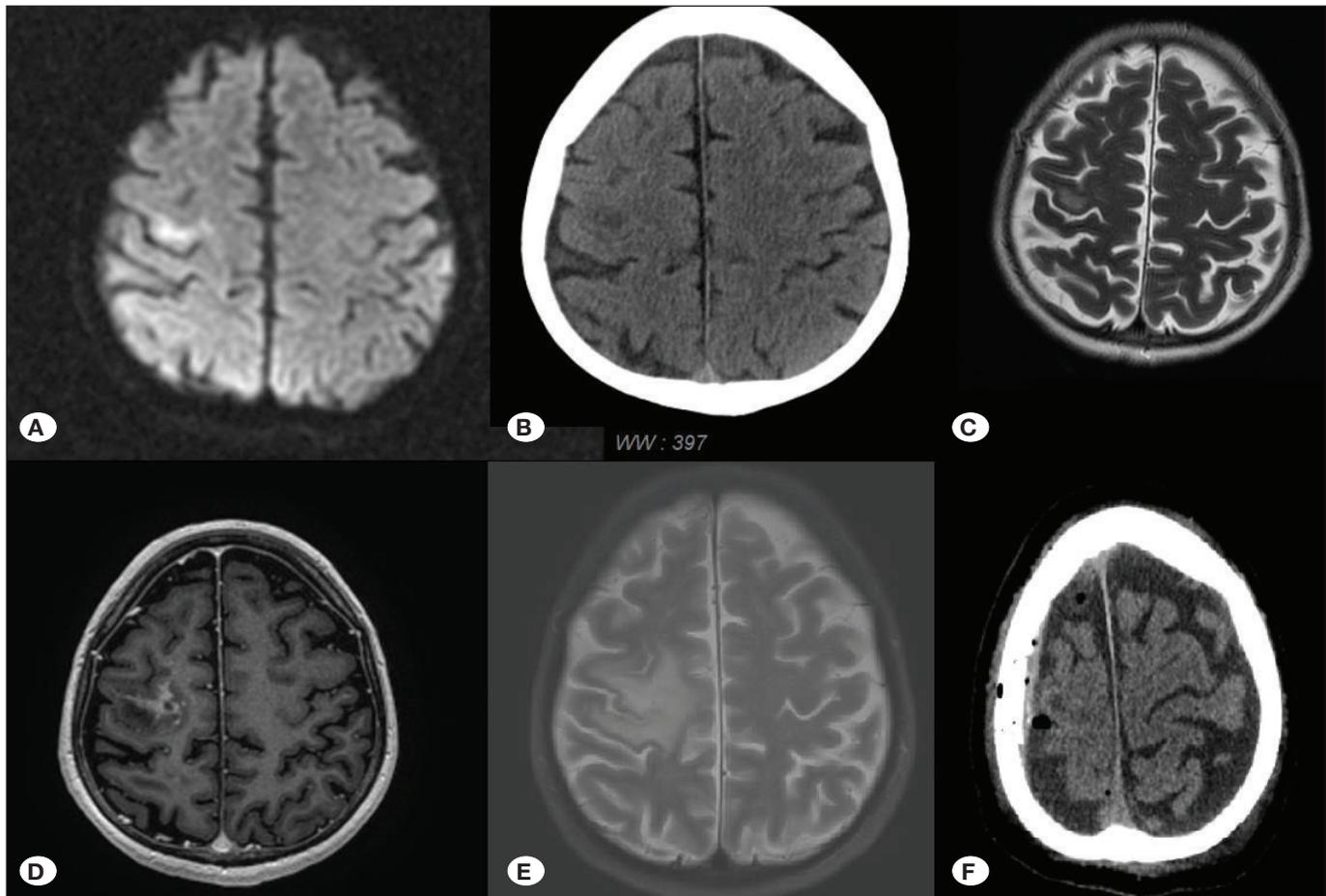


Figure 7: **A)** Axial section Diffusion MRI, **B)** axial section CCT, **C)** axial section T2W brain MRI **D)** 1st month axial section contrast enhanced T1W axial brain MRI, **E)** 1st month axial section T2 brain MRI, **F)** postop axial sectional brain CT.

lesion were seen not to support the preliminary diagnosis. In the patient whose examinations were repeated after 15 days, the existing lesion was found to be compatible with the peripherally contrasting MBT with a cystic necrotic component with a nodule inside. A per-MRI showed a significant increase in perfusion in the nodule and its surroundings. The patient was operated and the pathology, was reported as Grade 4 GBM, and was referred to the oncology department after discharge (Figure 8A-F).

■ DISCUSSION

MBTs can result in a hematoma, embolism, or infarction-like radiological findings within the brain parenchyma. In such cases, the clinician should learn the patients' clinical history and examine them well (13). However, misdiagnosis may occur despite all these evaluations. This study has included cases in which neurology–neurosurgery–neuroradiology clinicians have difficulty differentiating CVE and MBT.

Iwama et al. have emphasized that tumors with high vascularity or high angiogenic properties may be presented with intracranial hemorrhage and cause acute symptoms (5). Prasad et al. have reported that CVE is the most common

reason for applying to the emergency room with acute neurological syndromes (11). Therefore, CVE should be the first diagnosis when a patient presents to the emergency room with intraparenchymal hemorrhage. In the present study, the first, second, and sixth patients were evaluated with a preliminary diagnosis of hemorrhagic CVE in the emergency room. Since degradation products of hemoglobin have prevented advanced imaging methods to diagnose in the second and sixth patients, these patients have been followed closely. The correct diagnosis could be made through the scan performed during control follow-ups. Since the first patient applied with a herniation, the operation was performed without making an advanced evaluation.

Morgenstern and Frankowski have reported that 4.9% of 224 patients with MBT, on whom they operated, have a preliminary diagnosis of CVE and emphasized that distinguishing CVE and MBT can sometimes be quite difficult (9). The authors have further reported that 3% of patients who were operated on with the preliminary diagnosis of CVE during the first examination with CT actually had MBT. These patients have been reported to be mostly elderly, and their pathological diagnoses are GBM. Not taking a biopsy for a pathological examination in a patient operated on with the preliminary di-

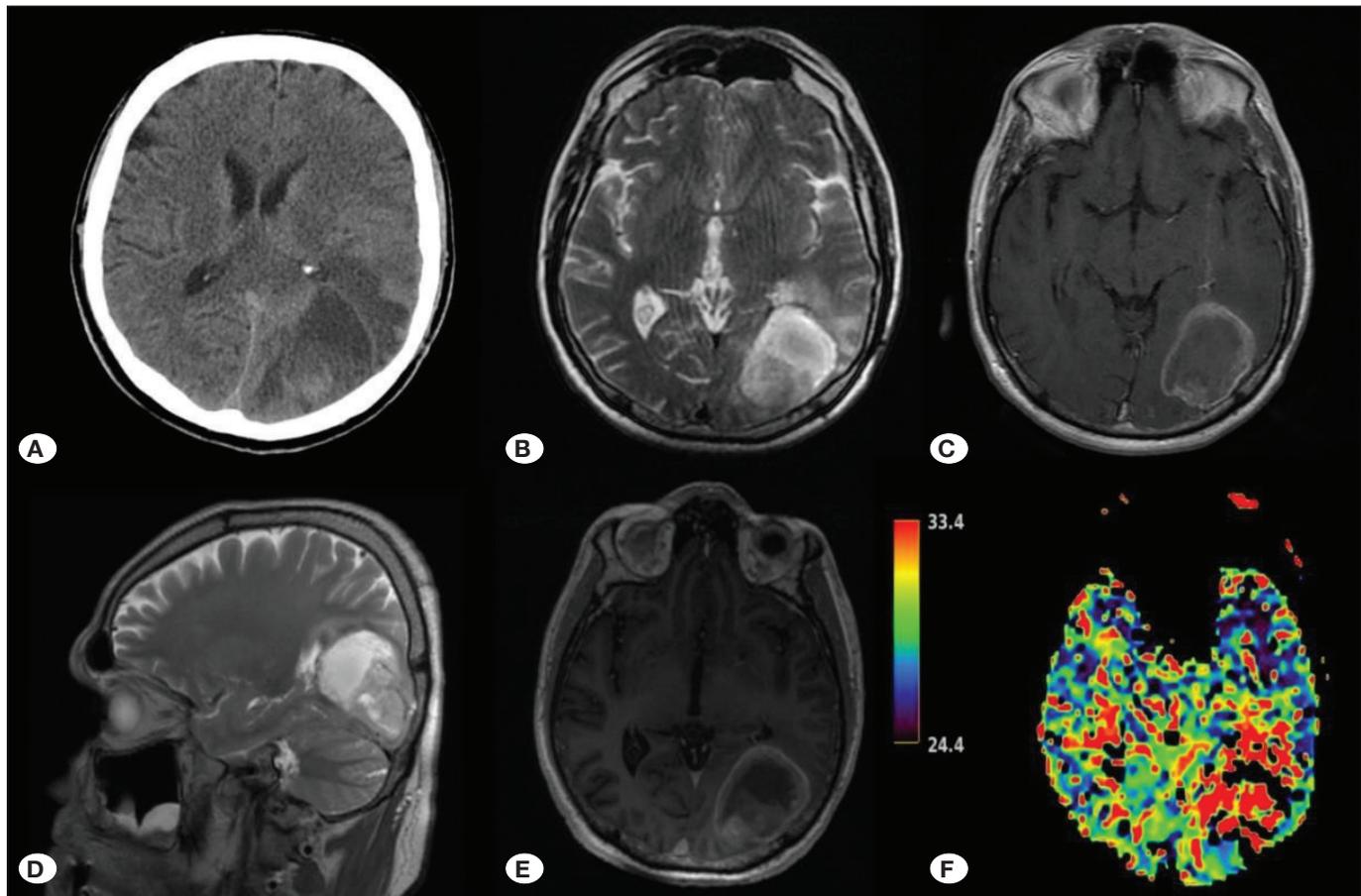


Figure 8: **A)** Axial CCT, **B)** axial T2W MRI of the brain, **C)** contrast enhanced T1W axial brain MRI, **D)** T1W sagittal MRI of the brain on 15th day, **E)** contrast enhanced T1W axial MRI of the brain on 15th day, **F)** perfusion weighted MRI on 15th day.

agnosis of CVE may cause medicolegal problems. Indeed, the first patient in the present study exemplifies this situation. A perioperative biopsy has provided the patient with oncological treatment in the early period and has prevented clinicians from possible malpractice.

Li et al. have reported that CT is not sufficient in the differentiation of CVE and MBT (7), but it should be one of the examinations that should be applied primarily, as it is easy access and ensures a rapid evaluation. In this study, CT applied alone has been misleading in patients whose clinical and radiological data have been presented. Accurate diagnoses of cases could only be made following advanced imaging methods. The first patient in the present study was initially evaluated only with CT, and an accurate diagnosis was made following the completion of pathological diagnosis.

Cha has reported that MBT ranks third among cancer-related deaths in all age groups and that an MRI is, therefore, important and necessary for the accurate diagnosis and grading of brain tumors (2,3). Recent advances in MRI such as DWI, per-MRI, and MRI-S all can provide information about quantitative cellular, hemodynamic, and metabolic characteristics of tumors, which may enhance our knowledge of MBT biology and help us to better assess treatment responses. In our

clinic, advanced MRI techniques (per-MRMRI and I-S) have been used with the help of the neuroradiology department, and possible malpractice has been prevented. Nonetheless, sufficient information could not be obtained through advanced techniques in the second, third, and sixth patients, and an accurate diagnosis could be achieved in control scans performed during a close follow-up.

Morgenstern and Frankowski have shown that thromboembolism is an important problem for MBT, like other cancer types, and there is a significant correlation between GBM and post-operative thromboembolism (9). In a study by Chen et al., it has been shown that MBTs can be presented by an ischemic stroke (4). The authors have reported that MBT probably leads to infarction by damaging neurovascular structures, and the progression of the malignancy becomes evident. They have further reported that radiological findings could not ensure an accurate diagnosis during this period. In the present study, the radiological findings of the third, fourth, and seventh patients at the time of admission have been compatible with ischemic infarction. Particularly in the DWI, the presence of restriction diffusion in this region has misled clinicians in the first evaluation. These patients received accurate diagnoses through the control scans performed during follow-up.

In a meta-analysis study by Tarnutzer et al., it has been reported that misdiagnoses in CVE cannot be prevented despite modern neuroimaging techniques that can be used in the emergency room (12). Norden et al. have explained how the current concept should be for MBT and stated that neuroradiology cannot always be successful despite these evaluations (10). Cervera et al. have conducted an experimental study on dogs regarding MBT and CVE (1). When they evaluated the MRI findings of the subjects, they showed that the finding of the two pathologies can be present in the brain at different times. With the guidance of these studies, an important task falls on the neuroradiology department. It will be understood that the first diagnosis of the fourth and eighth patients is not correct when their MRI findings are examined more carefully. Nevertheless, an unnecessary surgical operation has been prevented because of MRI-S recommendations by the neuroradiologist and careful evaluation in the fifth patient.

Unlike other patients, the fifth patient was initially thought to have MBT, but later, the real diagnosis was understood to be a subacute intracranial hematoma. Clinicians have been misled because the patient stated that the complaints developed slowly. Janssen and Hoff reported that a hematoma may show peripheral contrast enhancement in the subacute period, and edema may develop around it (6). The increase in edema probably caused the patient's double vision problem to become evident. In such cases, MRI-S and per-MRI should be performed.

■ CONCLUSION

Nearly all individuals have been exposed to a misdiagnosis at least once in their lives. It has become a major public health problem today. The widespread use of medical tests and imaging methods usually cannot prevent this problem. These methods, which are expected to help to diagnose, sometimes mislead the clinician. The development stages of CVE and MBT are similar, but their radiological findings are different. Clinicians should evaluate these findings together with the patient's medical history. Moreover, a multidisciplinary approach, in which neurology, neurosurgery, and neuroradiology clinics are involved, should be adopted for these patients. However, despite all these measures and examinations, wrong or inadequate diagnoses can be inevitable.

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