Cerebral Radiation Necrosis Masquerading as Recurrent, High-Grade Meningioma: A Case Report

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Case report

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Abstract

Background: Cerebral radiation necrosis (CRN) is a complication caused by radiation therapy (RT) used for treating high-grade intracranial neoplasms. It is essential to be aware of this condition as it can be frequently mistaken for tumor recurrence. Herein, we report a case of misdiagnosis of CRN in a young male, which has heavily influenced his clinical history.

Case Presentation: We report a 25-year-old male diagnosed with right frontal convexity meningioma based on computerized tomography (CT)/magnetic resonance imaging (MRI). The operation achieved a macroscopically complete tumor resection. The histopathology was an atypical meningioma. Accordingly, the patient received RT. The patient reported new-onset of generalized seizures and worsening of left hemiparesis three months after completion of RT. MRI showed abnormal peripheral enhancement in the right frontal region involving the genu of the corpus callosum and extensive brain edema. Magnetic resonance spectrometry (MRS) changes were suggestive of tumor recurrence. The patient underwent surgery with total resection of the lesion. The histopathology was CRN without evidence of tumor recurrence. Due to refractory progressive brain edema, the patient's clinical status deteriorated until he expired.

Conclusion: CRN carries morbidity and mortality as a complication from brain irradiation. There is no single modality that can reliably distinguish CRN from recurrent tumor. Therefore, a multimodality approach highly recommended.

Background

Meningiomas are non-glial, and extra-axial neoplasms, arising from arachnoid caps cells(1-3). The World Health Organization (WHO) classification of central nervous system tumors stratifies meningiomas in three major groups, reflected by the WHO grades I (benign), II (atypical), and III (malignant) (1-3). The majority of meningiomas are low-grade (benign) with only 10% classified as high-grade neoplasms, atypical and malignant meningiomas, accounting for 5-7%, and 1-3%, respectively, of all meningiomas (2). The five-year overall survival rate is 85.5% for benign lesions, 75.9% for atypical lesions, and 55.4% for malignant lesions (3). Surgery is the mainstay curative treatment for low-grade meningiomas (1-3). However, high-grade meningiomas are aggressive and highy prone to recurrence. Thus, surgery alone is insufficient (1, 2). Recent studies have suggested that immediate, adjuvant RT appears to be strongly associated with improved survival rate of high-grade meningiomas (2, 3). CRN is the most relevant side effect after RT and can masquerade as tumor recurrence (4-16). Thus, both establishing an accurate diagnosis and reaching a prompt treatment decisions are challenging.

This clinical report aims to describe a case of misdiagnosis of CRN as a recurrent, high-grade meningioma, highlighting the diagnostic challenges and the worse clinical outcome.

Case Presentation

A 25-year-old male presented with a nine-month history of intermittent headache, described as ‘ generalized pressure’ and dizziness. The symptoms had become more severe, and weakness on the left side extremities started to progress over the last week. The vital signs were stable, and the patient was fully conscious. Neurological examination showed no abnormality aside from mild left hemiparesis (Grade 4/5 Medical Research Council).

Cranial CT scan showed an extra-axial, slightly hyper-dense mass and extensive vasogenic edema in the right frontal region, containing multiple foci of calcification. The lesion showed homogenous contrast enhancement. Cranial MRI showed an iso-intense mass, with an area of low-intensity corresponding to the calcification observed on the CT scan (Fig. 1). Magnetic resonance arteriogram and magnetic resonance venogram showed multiple feeding arteries mainly from the anterior cerebral arteries and, to a lesser extent, from the distal right middle cerebral arteries with multiple, prominent draining veins. Based on the radiographic appearance of this lesion, a diagnosis of high-grade meningioma was highly suspected.

Intraoperatively, the tumor was infiltrating the brain parenchyma, cerebral falx, and the dura. The tumor was completely resected. The patient had an uneventful postoperative stay. A postoperative cranial CT scan showed no evidence of residual tumor with regression of brain edema (Fig. 2). The histopathology was Atypical meningioma (WHO grade II) (Fig. 3). This case discussed in the multidisciplinary tumor board. Accordingly, the patient was referred for RT for a total dose of 60-Gy (30 fractions of 2-Gy) over six weeks duration, all delivered with intensity-modulated technique.

The patient reported new-onset of generalized seizures and worsening of left hemiparesis (Grade 3/5 Medical Research Council) three months after completion of RT. Contemporaneous electroencephalography recording showed epileptic discharges over the right frontal derivations. Cranial MRI showed a large, irregular, ill-defined, lobulated, and peripheral cut green-pepper enhancing lesion involving the right frontal region and measuring 3.6×4.8×4.8 centimeters. An extensive, peri-lesional edema was extending to involve the contralateral lobe. The lesion was iso-intense in T1-weighted and T2-weighted sequences with extensive central necrosis (Fig. 4) and mild diffusion restriction. Hyper-intense signal on T2-weighted imaging with peripheral enhancement seen involving the genu of the corpus callosum suggestive of tumor recurrence. However, CRN was also considered part of the differential diagnosis given there was an enhancement in a region corresponding to the original radiation plan. MRS was performed during conventional MRI acquisition. The metabolites studied were choline (Cho), which appeared at 1.4ppm, N-acetyl aspartate (NAA) at 0.65ppm, creatine (Cr) at 0.6ppm, and lipid at 1.3ppm (Fig. 5). Using multi-voxel MRS, the Cho/NAA ratio > 2.15 and Cho/lipid>1 was favoring a recurrent tumor rather than radiation necrosis.

The patient underwent right frontal craniotomy. The lesion was completely resected. Intraoperatively, the lesion was non-vascular and intra-axial involving the right frontal lobe parenchyma and deep, abutting the frontal horn of the lateral ventricle. The histopathology was CRN without evidence of tumor recurrence (Fig. 6). The patient was able to ambulate independently after surgery, and he was seizure-free

on a minimal dose of Levetiracetam, but that was temporary. Subsequently, the patient was frequently admitted due to breakthrough seizures and worsening of left hemiparesis. The patient was treated with a high dose of intravenous dexamethasone with concomitant hyperbaric oxygen therapy (HBO2). The HBO2 regimen included 30 treatments in a multi-place chamber with pressurization to 2.5-atmosphere absolute pressure, with 90 total min of 100% oxygen given via oxygen hood, delivered as four 20-min and one 10-min periods each, separated by 5 minutes of breathing air. Hood oxygen flow was 30 L/min. The patient remained symptomatic. Thus, he was elected to receive four cycles of 5mg/kg Bevacizumab intravenously every two weeks. However, due to refractory, progressive brain edema, the patient's clinical status progressively deteriorated until he expired.

Discussion

CRN is a complication caused by RT used for treating high-grade intracranial neoplasms (4–16). The actual incidence of CRN is uncertain but ranges from 2.5–24% (4, 5). It typically occurs two years after radiation (5). In most patients, it tends to regress once diagnosed radiographically with a probability of regression 40% at six months to 76% at 18 months (6), though it can progress as in our case. Although CRN influenced by various risk factors such as total radiation dose, dose per fraction, treatment duration, irradiated volume, and concurrent use of chemotherapy, the rapidly progressive course of CRN raises the susceptibility of underlying genetic mechanisms (4–7). A prospective cohort study by Wang TM et al. in 2019, implicated a radiation injury susceptibility gene (Cep128) as an underlying mechanism of radiation-induced brain injury, as it tightly interacts with multiple radiation-resistant genes (7).

The pathophysiology of CRN is not well understood. However, two main hypotheses suggested. The first hypothesis postulates that radiation causes damage to endothelial cells by upregulating ceramide, resulting in vascular insufficiency and infarction, followed by brain necrosis (4, 6, 8, 9). Hypoxia caused by endothelial cell damage leads to the liberation of hypoxia-inducible factor 1α and vascular endothelial growth factor (VEGF) (4, 6, 8, 9).VEGF induce new vessel formation, but these tend to be leaky capillaries, resulting in perilesional edema (6, 8, 9). The second hypothesis postulates that radiation damages the glial cells, especially oligodendrocytes, aggravating capillary permeability defects and causing demyelination of the white matter (4, 6).

The clinical features of CRN vary depending upon the location and size, including features of increased intracranial pressure. The characteristic findings are seizures, hemiparesis, headache, vomiting, poor concentration, and altered level of consciousness (4–6, 10). The literature also reported Neurocognitive impairment (hippocampus), especially in children, which includes poor academic performance, distorted self-image, and psychological distress (6, 11).

MRI of the brain will demonstrate some degree of contrast enhancement surrounded by edema (4–6, 9, 10). Although, the patterns of enhancement described in the literature as swiss cheese, cut green-paper or soup bubble, are believed to favor CRN, these patterns posse a 88% negative predictive value (12). MRS is used to assess the metabolite composition of the lesion (13, 14). On MRS, the peak of Cho and the

depression of NAA and Cr correlated with recurrent neoplasm than CRN (13). Anbarloui et al. demonstrated that Cho/NAA > 1.8 or Cho/lipid ratio > 1 had increased odds of being pure neoplastic lesions rather than pure necrosis, with sensitivity and specificity of 73% and 75%, respectively, for Cho/NAA ratio, and 87% for Cho/lipid ratio (13).

However, a recent study by Hellstrom J et al. detected false-positive MRS findings in 51/208 cases, altering the clinical management (14). We also reported similar findings, in which the histopathology did not support the MRS diagnosis. It may reflect the difficulty of MRS in differentiating radiation-induced cytolytic changes from reactive gliosis from a recurrent tumor (14). Positron emission tomography (PET) scan uses 18F-fluorodeoxyglucose (FDG) to assess the tissue activity (4, 6, 10). Necrotic tissue will demonstrate low FDG uptake (4, 6, 10). However, a PET scan can provide false-positive findings when epileptic activity coexist (hypermetabolism) (10). As the viable tumor has an intact vasculature, perfusion MRI can be used to distinguish CRN from recurrent tumor (4, 6, 12, 14). Sugahara et al. suggested a relative cerebral blood volume (rCBV) >2.1 favor tumor recurrence, while an rCBV value < 0.6 favor radiation necrosis (15). However, as the clinic of our patient had a progressive deterioration, we could not be able to spare time for this advanced imaging method. We applied emergency surgical intervention to relieve the mass effects.

CRN treatment aims to minimize further loss of neurological functions, preventing progression and, if possible, reversing the pathological process (4, 6, 9, 12). A corticosteroid as the first measure is frequently administered (6, 9, 12). Other supportive treatments include antiplatelet, anticoagulant, and a high dose of vitamins (6, 9). HBOT believed to improve tissue oxygenation and neovascularization (4, 6). However, the efficacy of HBOT is difficult to assess in patients already treated with steroids (4). Only a few studies have discussed the role of HBOT, with no randomized clinical trials (RCTs) published (4, 6). The efficacy of Bevacizumab proven as an anti-vascular endothelial growth factor monoclonal antibody in treating radiation-induced brain edema (4, 6, 8, 9). However, the safety of Bevacizumab warrants further validation as the only RCT published by Zhuang H et al. in 2011 involved a limited number of 14 patients (9). Debulking surgery is the least favorable option and mainly preserved to relieve the mass effect (4, 6, 9, 12). Recently, laser interstitial thermal therapy (LITT) has become a treatment option for lesions that are difficult to access or for patients who are not candidates for surgery (16). A review study by Katherine G et al. documented a favorable clinical response after LITT for CRN (16). Unfortunately, none of the mentioned treatment approaches utilized halted the progression of CRN in this patient.

Conclusion

There is no shadow of uncertainty that a diagnosis of CRN is a matter of high importance in all settings since misdiagnosis can result in delays in treatment and thus noticeable morbidity and mortality. There is no single modality that can reliably distinguish CRN from recurrent tumor. Therefore, a multimodality approach highly recommended.

Abbreviations

CRN: Cerebral radiation necrosis

MRS: Magnetic resonance spectrometry

RT: Radiation therapy

WHO: World Health Organization

MRI: Magnetic resonance imaging

CT: Computed tomography

PET: Positron emission tomography

FDG: 18F-fluorodeoxyglucose

rCBV: relative cerebral blood volume

HBO2: Hyperbaric oxygen therapy

VEGF: Vascular endothelial growth factor

NAA: N-acetyl aspartate

Cho: Choline

Cr: Creatine

RCT: Randomized control trial

LITT: laser interstitial thermal therapy

Declarations

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Competing interests: The authors declare that they have no competing interests.

Consent for publication: The patient's father provided verbal and written consent for this case report

Ethics approval and consent to participate: Approved by the Department of Surgery, Salmaniya Medical Complex, Bahrain.

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Figures

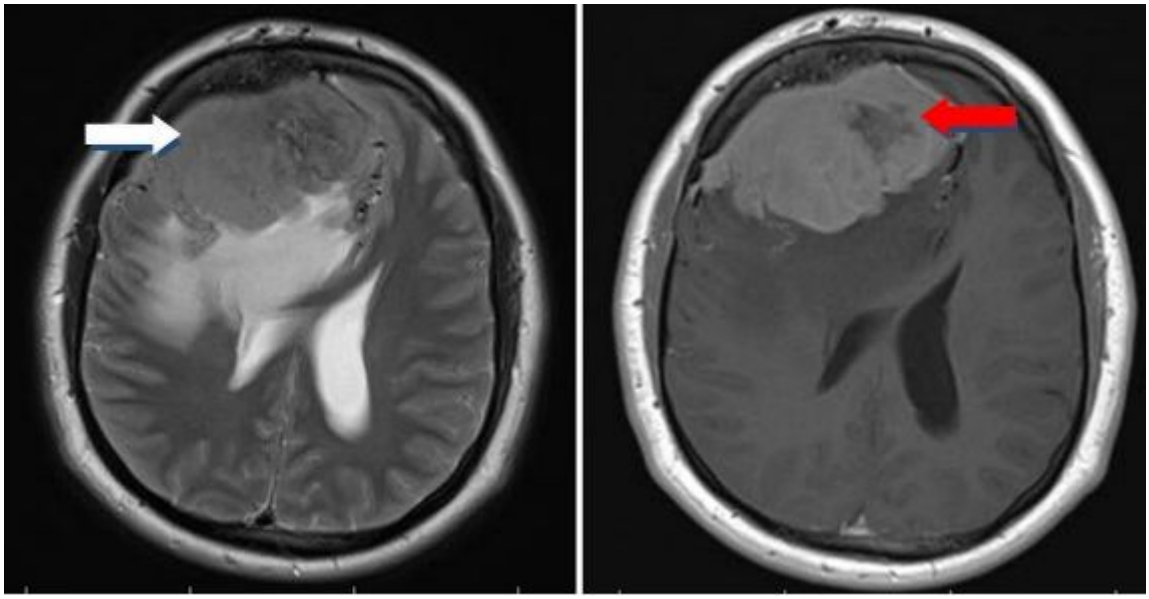

Figure 1

Preoperative, MRI brain of the lesion showing iso-intense signal (White arrow) in the T2-weighted sequence. The tumor homogeneously enhanced with areas of central hypo-intensity (Red arrow) in post-contrast, T1-weighted images.

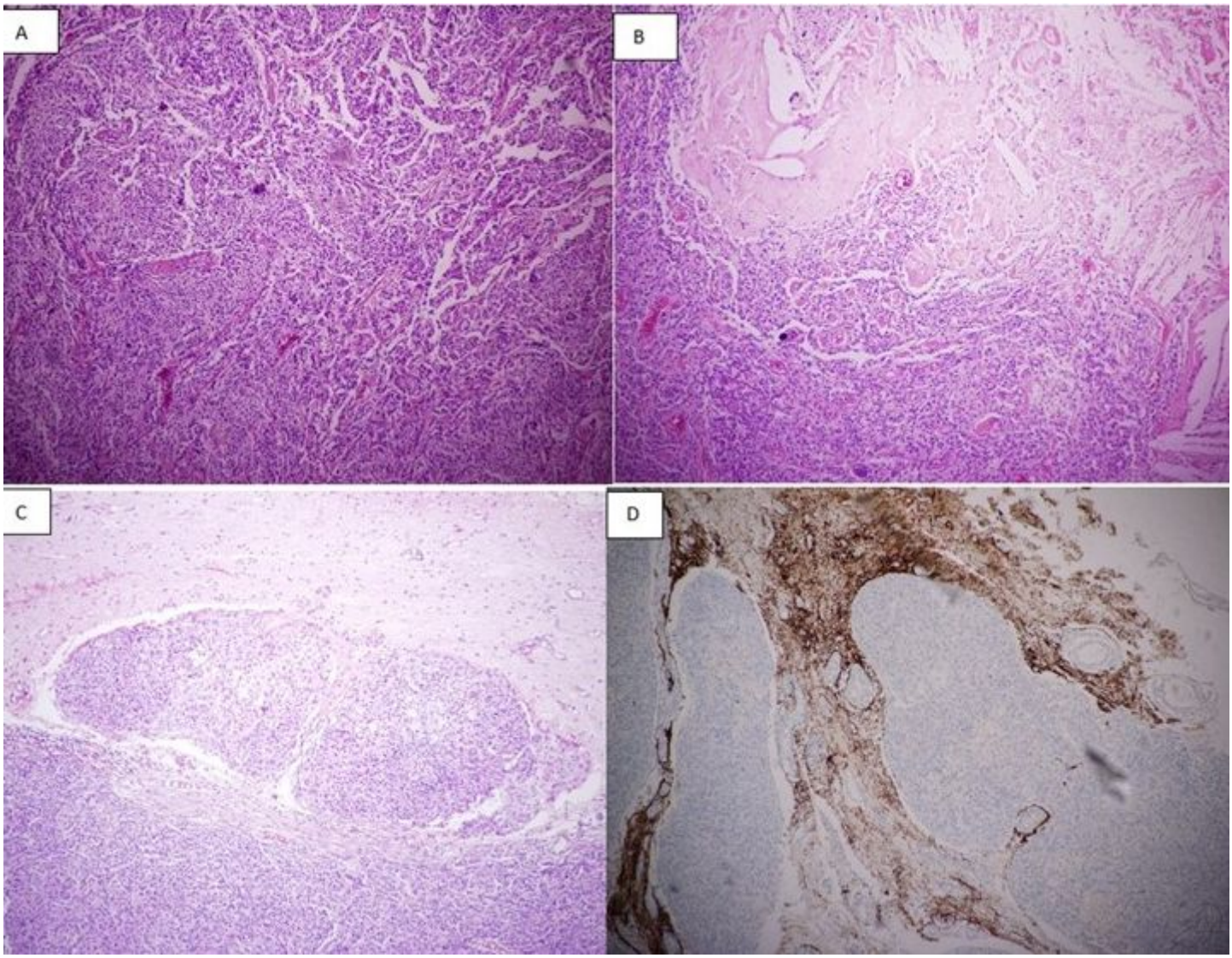

Figure 2

Sections from atypical meningioma show syncytial pattern along with areas of necrosis,10X(A&B).Brain invasion noted in H&; E stain and highlighted by GFAP immunostain,10X(C&D)

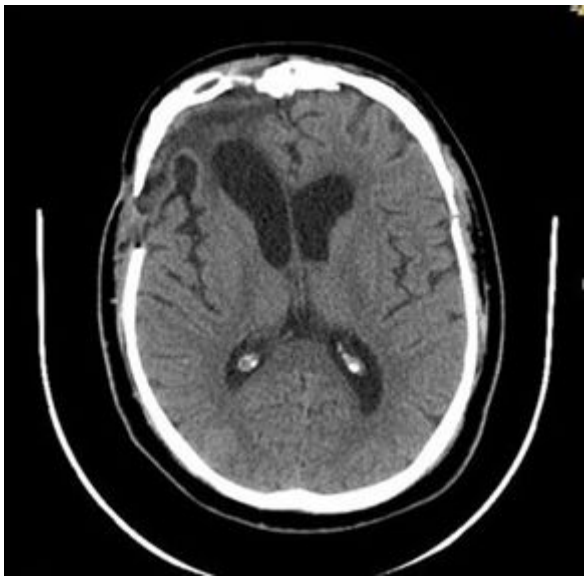

Figure 3

A Postoperative CT scan of the brain showing total excision of the tumor with regression of brain edema.

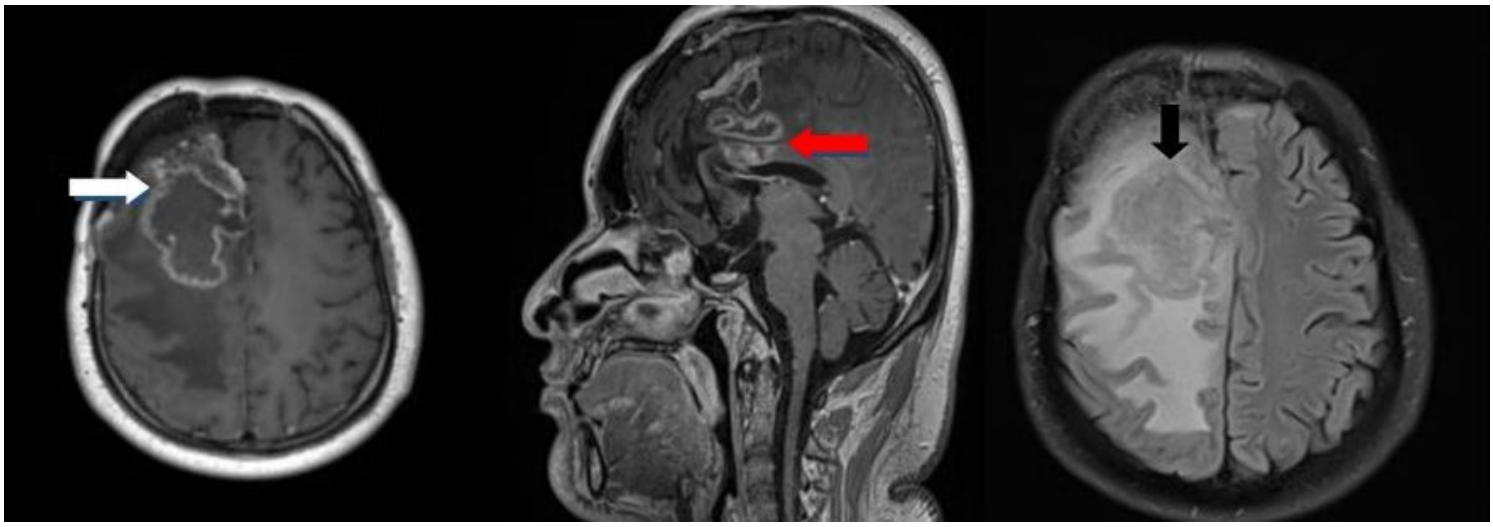

Figure 4

MRI brain of the lesion showing an ill-defined peripheral enhancing lesion (White arrow) with central necrosis in post-contrast, T1-weighted sequence. Enhancement of the genu of the corpus callosum was also noted (Red arrow)—the lesion was iso-intense (Black arrow) in the T2-weighted sequence, surrounded by extensive, vasogenic edema.

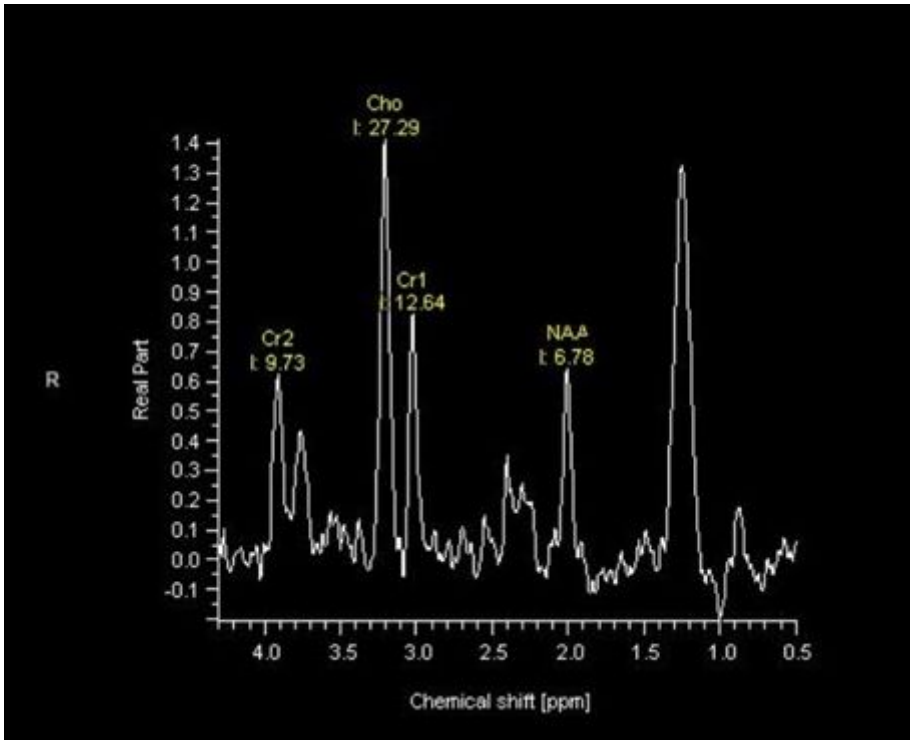

Figure 5

Magnetic resonant spectroscopy showed a high elevation of Cho and depression of NAA.

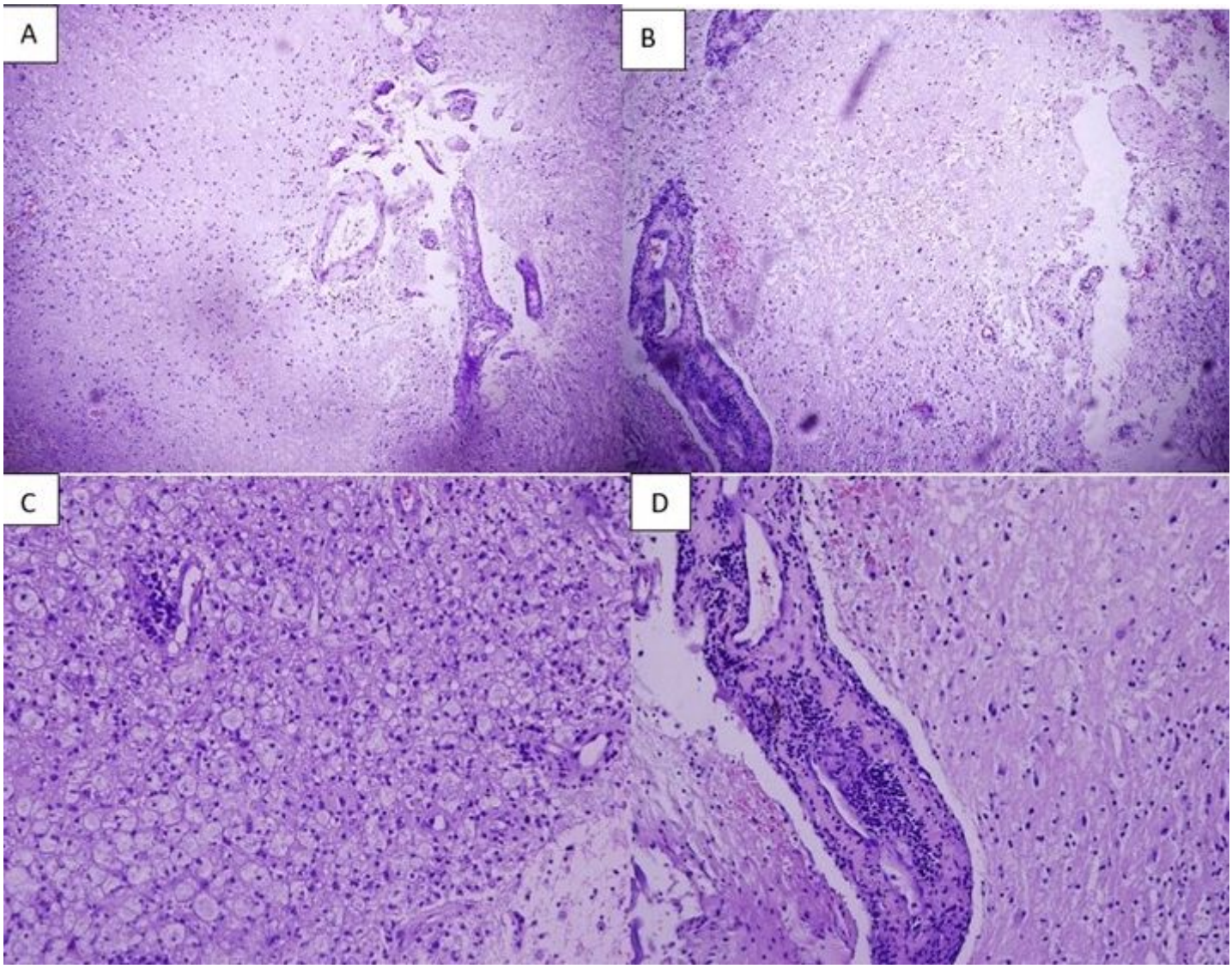

Figure 6

Post RT resection specimen is entirely submitted, and sections show areas of necrosis, mixed inflammation,10x(A&B).Infiltration by foamy histiocytes,20x(C) and vasculitis, 20x(D).No neoplastic pathology noted.

Supplementary Files

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