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PRIMARY INTRACEREBRAL MELANOMA: A CASE REPORT

Abstract: Primary intracranial malignant melanoma is an extremely rare entity These aggressive tumors are derived from the melanocytes of leptomeninges or their precursor cells and can give metastasis to other organs. It effects mostly middle aged males and represents a very poor prognosis with median survival less than 1 year. For proper diagnosis, melanoma of other localization must be excluded. Giving the rarity of this tumor, treatment of choice in unclear. We report a case of 43 year old patient with primary intracranial melanoma treated by supramarginal resection followed by whole brain RT, with disease free period of three years following treatment. We strongly advocate for aggressive treatment approach, supramarginal resection whenever safe, adjuvant therapy and frequent check-ups. We also hope to inspire future studies on larger sample to in order to establish an adequate therapy protocols.

Introduction

Primary intracerebral melanoma (PIM) is an extremely rare entity, representing 0.07% of all CNS tumors and 1% of all melanoma.(1) These aggressive tumors derive from the melanocytes of leptomeninges or their precursor cells - melanoblasts and can metastasize to other organs. It effects mostly middle aged males and carries a very poor prognosis with median survival of less than 1 year. Once there is leptomeningeal dissemination, the median survival is around 10 weeks.(2) In order to diagnose PIM, primary melanoma of other more common localization should be excluded. Brain MRI, fundoscopy, PET scan, CSF cytopathology, and thorough skin examination should be performed.

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Giving the rarity of this tumor, treatment of choice in unclear. Studies show than highly aggressive treatment including maximal safe resection, adjuvant HT and RT is associated with better prognosis. We report a case of 43-year-old patient with primary intracerebral melanoma.

Case Report

A 43-year-old male was referred to our Clinic with complains of worsening headaches. On admission no neurological deficit was observed. The brain magnetic resonance imaging with MR spectroscopy revealed a multilobular lesion in the right frontal lobe with perilesional edema and signs of subfalcine herniation, without signs of leptomeningeal dissemination. The lesion was enhanced by contrast medium and had heterogenic signal on T2 FLAIR weighted sequence, with hyperintensity on T1 weighted and hypointensity on T2 weighted MRI sequences. Metabolical index was Cho/Cr=2,00. The images prompted consideration of a intraneoplastic hemorrhage. None of the tumor markers has shown positive results. (Figures 1. and 2.)

The patient underwent right frontal craniotomy and supramarginal resection by transsulcal approach. Intraoperative findings included a pigmented, well-defined, good vascularized tumor. The postoperative course was uneventful.

Histopathological examination (HPE) revealed nervous tissue infiltrated by solid tumor tissue composed of densely compacted epitheloid cells with irregular hyperchromatic nuclei with mitotic activity (over 10 mitosis HPF). Tumour cells contained eosinophilic cytoplasm with brownish pigment resembling melanin. Tumor cells were positive on Vimentine , Pan CK (AE1/AE3), S100, HMB 45, Melan A and MITF and negative on GFAP Hystopathological finding was reported as melanoma. (Figure 3.)

In order to exclude primary skin melanoma, thorax and abdomen CT scan, colonoscopy and esophagogastroduodenoscopy were performed, followed by 2 whole body PET scan, fundoscopy and thorough whole body examination. No lesions were found outside the CNS. The CSF analysis showed no malignant cells. (Figure 4.)

The patient was discharged asymptomatic, ECOG PS 0. Concerning malignant histology, the patient was referred for whole-brain palliative radiotherapy. Radiation therapy with 30 Gy / 10 fractions / 18 days (at 3 Gy per fraction) was delivered to the brain. First check-up was 6 months after surgery. The patient had no symptoms or neurological deficits. (Figure 5.)

During follow-up, 16 months after completion of radiotherapy, the patient complained about paraesthesia in both arms and legs. Brain MRI showed postoperative changes, with no evidence of tumor residuum or recurrence. (Figure 6.) Total follow-up period lasts 3 years and regular examinations so far have not confirmed the residual or recidivant tumor.

Discussion

According to current understanding, prognosis depends on leptomeningeal dissemination, location of the tumor, extent of surgical excision and the number of mitosis. (3) Expressed symptoms depend on tumor localization. Most patients present with neurological findings related to the mass effect of the tumor. Most common symptoms include symptoms of intracranial hypertension - such as our patient's symptoms of worsening headaches.(3) Other symptoms such as blurred vision followed by focal neurologic deficits were also noted. Seizures were reported to be less common symptom. Primary intracranial melanoma in pineal region can be followed by symptoms including epilepsy, weight loss, tinnitus and memory loss.

Primary intracranial melanomas are derived from melanocytes present in the cerebral parenchyma, leptomeninges, human uvea, and the skin. In the cranium, melanocytes originating from the neural crest are distributed throughout the leptomeninges. Some authors claim that cells found in the reticular formation of the medulla and arachnoid cells usually located at the basal surface of the brain, optic chiasm and anterior surface of the brain stem can be transformed to tumor cells. (4) During embryonic development melanoblasts can migrate causing primary intracranial melanomas.(5) It is shown that melanoma in frontal lobe (36%) occurs twice as frequently as those in the parietal 26.4%, temporal 18.9%, or occipital lobe 10.6% , what can be explained by the size of surface of the frontal.

WHO 2016. classification divides central nervous system melanocytic tumors into meningeal melanocytoma ,meningeal melanocytosis, meningeal melanoma and meningeal melatomatosis.(6)

The diagnosis is based on brain MRI, thorough skin examination, PET scan, fundoscopy and CSF cytopathology in order to establish the right diagnosis and exclude the primary process in other body sites. CT scan in case of PIM is nonspecific due to the commonly present haemorrhage inside the tumor, therefore brain MRI is imperative. Typical MRI presentation demonstrates a lesion with hyperintensity on T1 weighted and hypointensity on T2 weighted MRI sequences with enhancing by contrast medium. Such neuroradiological findings are due to free radicals with unpaired electrons produced by melanin which cause a paramagnetic phenomenon, leading to a shortened T1 relaxation time.(7)

Our patient's brain MRI has shown the lesion in right frontal lobe which was enhanced by contrast medium and has heterogenic signal on T2W FLAIR, with hyperintensity on T1W and hypointensity on T2W MRI sequences. Metabolical index was Cho/Cr=2.00. In our case, there were no verified skin or eye melanoma. The diagno-

stic was complemented with PET scan followed by CT of the thorax and abdomen, however the primary malignant lesions were not detected in other body sites.

Because of the rarity of PIM, there is no standard treatment for these extremely malignant tumors. Accurate diagnosis is imperative for developing the appropriate treatment plan which can include surgical treatment, stereotactic radiotherapy, total brain radiotherapy, chemotherapy, immunotherapy and gene therapy.

It is shown that patients with enlarged tumor margin resection had a significantly longer survival time than patients undergoing subtotal removal, partial removal, or biopsy. (8)

Although in our case, there was no sign of leptomeningeal dissemination, number of mitosis was over 10 HPF which was not favourable prognostic factor. Regading the localization of the tumor in a non-eloquent zone, we conducted aggressive supramarginal resection.

The role of chemotherapy is still controversial. Due to its ability to cross blood-brain barrier, Temozolomide appears to show promising results, although significant difference in survival rates between treatment with Temozolomide and other chemotherapy combinations hasn't been observed.(2)

Since melanoma is considered to be radioresistant tumor, the efficacy of radiotherapy as an adjuvant therapy for primary intracranial melanomas is questionable. However the quality of life after stereotactic radiotherapy was reported to be higher than in whole brain radiotherapy. (9)

Althought the prognosis of PIM is very poor, it is reported to be better than in patients with metastatic CNS melanoma.(5) The median time of tumor recurrence is reported to be 6.5 months after the initial surgery with median time of death of 11 months.(10) However patient we report was disease free 3 years following treatment.

We believe that aggressive approach by conducting surgical supramarginal resection whenever safe and adjuvant therapy should be mandatory and formulated as official recommendation.

Conclusion

A thorough clinical and neuroradiological examination are essential for establishing the diagnosis and treatment plan. Although no valid conclusion regarding the official recommendation can be stated, given the solitary case, we believe that aggressive surgical treatment-total resection with surrounding brain tissue resection, followed by radiotherapy and chemotherapy offers better survival rates, and hope to inspire further studies on fairly larger scale required in order to confirm the efficacy of radiotherapy and chemotherapy as an adjuvant treatment for primary intracerebral melanomas and establish an adequate treatment guideline.

Declaration of interest

Authors declare no conflict of interest.

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FIGURES

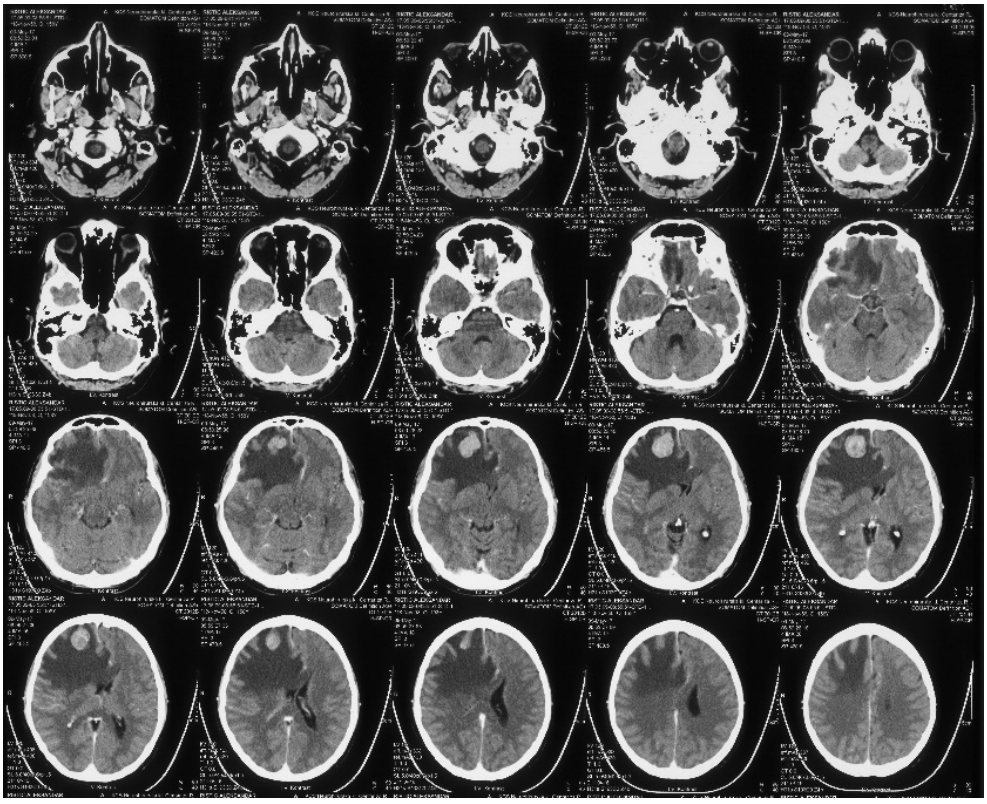

Figure 1. Preoperative brain CT images, Axial view

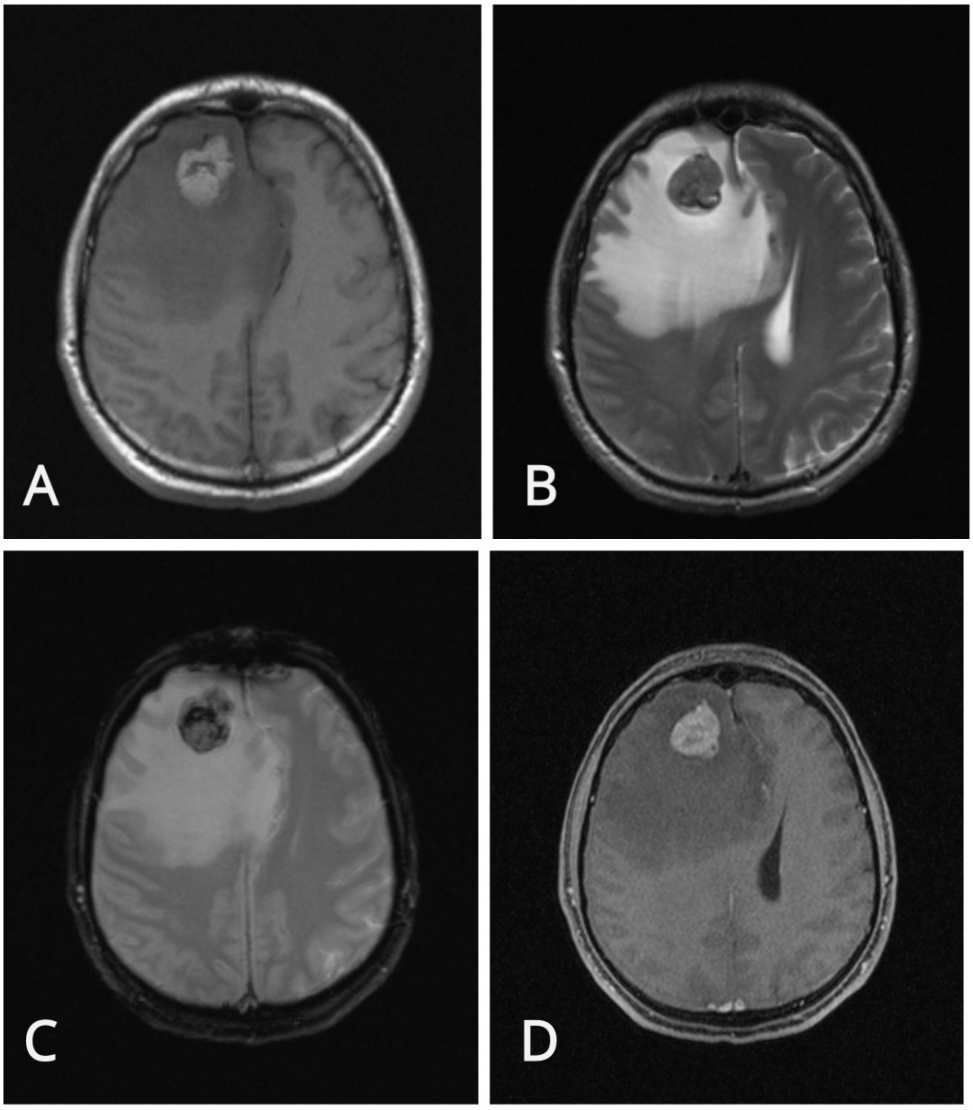

Figure 2. Preoperative brain MRI images, Axial view T1-weighed image (T1WI). (A) Axial view, T2WI. (B) ,) Axial view, T2 FLAIR weighted sequence (C) Axial view, contrast-enhanced T1WI (D). The right frontal lobe lesion appeared hyperdense on brain computed tomography (CT), short signal on T1-weighted magnetic resonance images (T1WI) and long signal on T2-weighted magnetic resonance images (T2WI) with heterogenic signal on T2 FLAIR weighted sequence

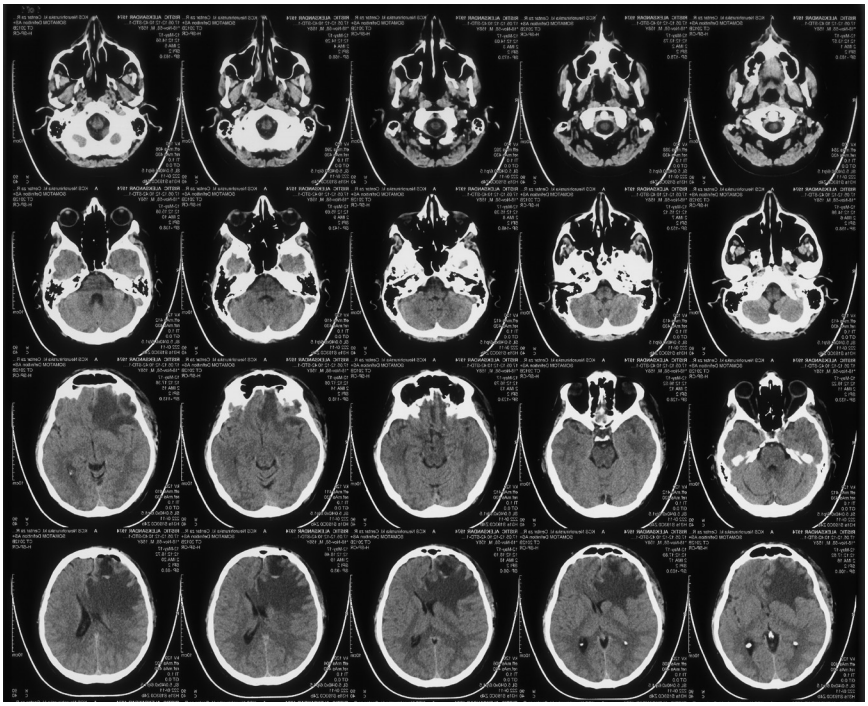

Figure 3. Postoperative brain CT images, axial view, showed no residual brain tumor.

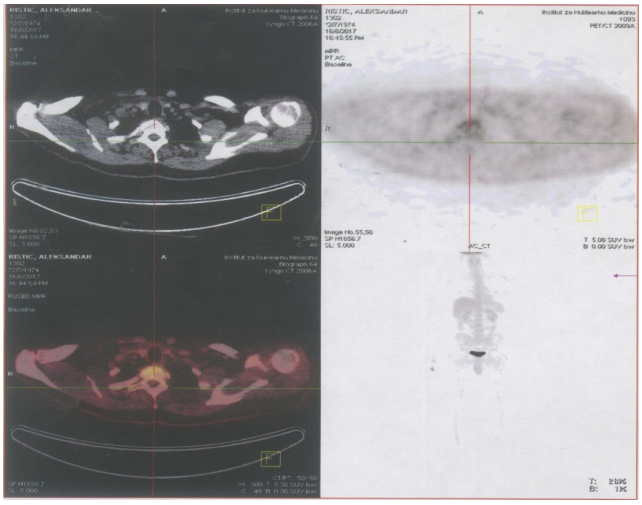

Figure 4. PET scan – primary process has not been revealed

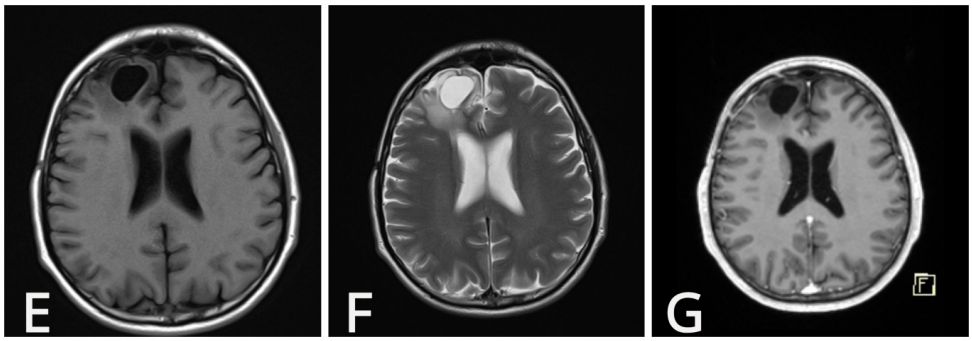

Figure 5. Postoperative brain MRI images on the first check-up, Axial view T1-weighed image (T1WI). (E) Axial view, T2WI. (F) Axial view, contrast-enhanced T1WI (G). A cystic formation in the operative regia, without any signs of tumor residuum

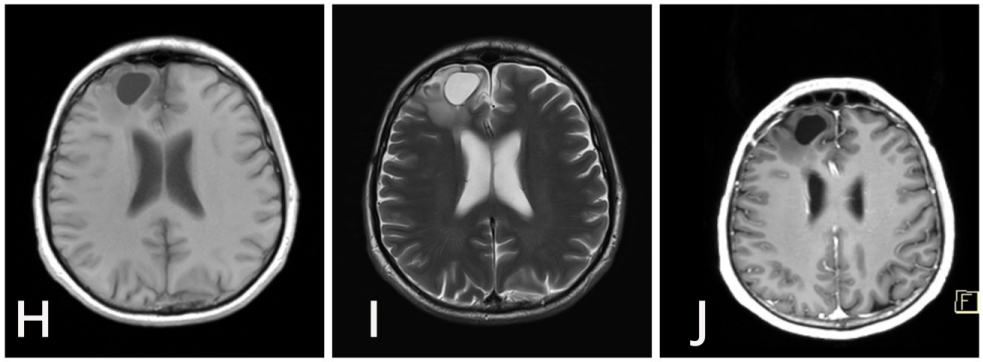

Figure 6. Postoperative brain MRI images on the last check- up. Axial view T1-weighed image (T1WI). (H) Axial view, T2WI. (I) Axial view, contrast-enhanced T1WI (J). Persisting non changing cystic formation in the operative regia, without any signs of tumor residuum