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PRIMARNI INTRACEREBRALNI MELANOM: IZVEŠTAJ SLUČAJA

Apstrakt: Primarni intrakranijalni maligni melanom je izuzetno redak entitet. Ovi agresivni tumori nastaju iz melanocita leptomeninge ili njihovih prekursorskih ćelija i mogu dati metastaze na drugim organima. Uglavnom pogađa muškarce srednjih godina i ima veoma lošu prognozu sa srednjim preživljavanjem manjim od 1 godine. Za pravilnu dijagnozu, melanom druge lokalizacije mora biti isključen.

S obzirom na retkost ovog tumora, tretman izbora nije jasan. Prijavljujemo slučaj 43-godišnjeg pacijenta sa primarnim intrakranijalnim melanomom lečenim supramarginalnom resekcijom praćenom RT celog mozga, sa periodom bez bolesti od tri godine nakon lečenja. Snažno se zalažemo za agresivan pristup lečenju, supramarginalnu resekciju kad god je bezbedna, pomoćnu terapiju i česte preglede. Takođe se nadamo da ćemo inspirisati buduće studije na većem uzorku kako bi se uspostavili adekvatni terapijski protokoli.

Uvod

Primarni intracerebralni melanom (PIM) je izuzetno redak entitet, koji predstavlja 0,07% svih tumora CNS-a i 1% svih melanoma (1). Ovi agresivni tumori potiču od melanocita leptomeninge ili njihovih prekursorskih ćelija – melanoblasta i mogu metastazirati na druge organe. Uglavnom pogađa muškarce srednjih godina i ima veoma lošu prognozu sa srednjim preživljavanjem manjim od 1 godine. Kada dođe do leptomeningealne diseminacije, medijan preživljavanja je oko 10 nedelja (2). Da bi se dijagnostikovao PIM, primarni melanom druge češće lokalizacije treba isklju-

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čiti. Treba obaviti MRI mozga, fundoskopiju, PET skeniranje, citopatologiju CSF i temeljni pregled kože.

S obzirom na retkost ovog tumora, tretman izbora nije jasan. Studije pokazuju da je visoko agresivan tretman, uključujući maksimalno bezbednu resekciju, adjuvantni HT i RT, povezan sa boljom prognozom. Prikazujemo slučaj 43-godišnjeg pacijenta sa primarnim intracerebralnim melanomom.

Izveštaj slučaja

Muškarac star 43 godine upućen je na našu kliniku sa žalbama na pojačane glavobolje. Prilikom prijema nije primećen neurološki deficit. Magnetna rezonanca mozga sa MR spektroskopijom otkrila je multilobularne lezije u desnom frontalnom režnju sa perilezijskim edemom i znacima subfalksne hernijacije, bez znakova leptomeningealne diseminacije. Lezija je pojačana kontrastnim medijumom i imala je heterogeni signal na T2 FLAIR ponderisanoj sekvenci, sa hiperintenzitetom na T1 ponderisanim i hipointenzitetom na T2 ponderisanim MRI sekvencama. Metabolički indeks je bio $\text{Cho/Cr}=2,00$. Slike su podstakle razmatranje intraneoplastičnog krvarenja. Nijedan od tumorskih markera nije pokazao pozitivne rezultate (slike 1. i 2).

Pacijentu je urađena desna frontalna kraniotomija i supramarginalna resekcija transsulkusnim pristupom. Intraoperativni nalazi uključivali su pigmentirani, dobro definisan, dobro vaskularizovan tumor. Postoperativni tok je protekao bez komplikacija.

Histopatološkim pregledom (HPE) otkriveno je nervno tkivo infiltrirano čvrstim tumorskim tkivom sačinjenim od gusto zbijenih epiteloidnih ćelija sa nepravilnim hiperhromatskim jezgrima sa mitotičkom aktivnošću (preko 10 mitozu HPF). Tumorske ćelije su sadržale eozinofilnu citoplazmu sa smeđkastim pigmentom koji podseća na melanin. Tumorske ćelije su bile pozitivne na Vimentin, Pan CK (AE1/AE3), S100, HMB 45, Melan A i MITF i negativne na GFAP. Histopatološki nalaz je prijavljen kao melanom (slika 3).

Da bi se isključio primarni melanom kože, urađeni su CT toraksa i abdomena, kolonoskopija i ezofagogastroduodenoskopija, zatim 2 PET skeniranja celog tela, fundoskopija i detaljan pregled celog tela. Nisu nađene nikakve lezije izvan CNS-a. Analiza CSF nije pokazala maligne ćelije. (slika 4).

Pacijent je otpušten asimptomatski, ECOG PS 0. Što se tiče maligne histologije, pacijent je upućen na palijativnu radioterapiju celog mozga. Radioterapija sa 30 Gy / 10 frakcija / 18 dana (sa 3 Gy po frakciji) je isporučena u mozak. Prvi pregled je bio 6 meseci nakon operacije. Pacijent nije imao simptome ili neurološke deficite. (Slika 5.)

Tokom praćenja, 16 meseci nakon završene radioterapije, pacijent se žalio na parestezije u obe ruke i noge. MRI mozga je pokazao postoperativne promene, bez dokaza o reziduumu tumora ili recidivu (slika 6). Ukupan period praćenja traje 3 godine i redovnim pregledima do sada nije potvrđen rezidualni ili recidivantni tumor.

Diskusija

Prema sadašnjem shvatanju, prognoza zavisi od leptomeningealne diseminacije, lokalizacije tumora, obima hirurške ekscizije i broja mitoza (3). Izraženi simptomi zavise od lokalizacije tumora. Većina pacijenata se javlja sa neurološkim nalazima vezanim za mass efekat tumora. Najčešći simptomi uključuju simptome intrakranijalne hipertenzije – kao što su simptomi pogoršanja glavobolje kod našeg pacijenta (3). Takođe su zabeleženi i drugi simptomi kao što je zamagljen vid praćen fokalnim neurološkim deficitima. Prijavljeno je da su napadi ređi simptom. Primarni intrakranijalni melanomi u epifizi mogu biti praćeni simptomima uključujući epilepsiju, gubitak težine, tinitus i gubitak pamćenja.

Primarni intrakranijalni melanomi potiču od melanocita prisutnih u cerebralnom parenhimu, leptomeningama, ljudskoj uveji i koži. U lobanji, melanociti koji potiču iz nervnog grebena su raspoređeni po leptomeningama. Neki autori tvrde da se ćelije koje se nalaze u retikularnoj formaciji medule i arahnoidnim ćelijama koje se obično nalaze na bazalnoj površini mozga, optičkoj hijazmi i prednjoj površini moždanog stabla mogu transformisati u tumorske ćelije (4). Tokom embrionalnog razvoja melanoblasti mogu da migriraju izazivajući primarne intrakranijalne melanome (5). Pokazano je da se melanom u frontalnom režnju (36%) javlja dvostruko češće od onih u parijetalnom 26,4%, temporalnom 18,9% ili potiljačnom režnju 10,6% , što se može objasniti veličinom površine čeonog režnja.

SZO 2016. klasifikacija deli melanocitne tumore centralnog nervnog sistema na meningealni melanocitom, meningealnu melanocitozu, meningealni melanom i meningealnu melatomatozu (6).

Dijagnoza se zasniva na MRI mozga, detaljnom pregledu kože, PET skeniranju, fundoskopiji i citopatologiji likvora kako bi se postavila prava dijagnoza i isključio primarni proces na drugim mestima tela. CT skeniranje u slučaju PIM je nespecifično zbog često prisutnog krvarenja unutar tumora, stoga je MRI mozga imperativ. Tipična MRI prezentacija pokazuje leziju sa hiperintenzitetom na T1 ponderisanim i hipointenzitetom na T2 ponderisanim MRI sekvencama sa pojačavanjem kontrastnim medijumom. Ovakvi neuroradiološki nalazi su posledica slobodnih radikala sa nesparenim elektronima koje proizvodi melanin koji izazivaju paramagnetni fenomen, što dovodi do skraćenog vremena relaksacije T1 (7).

MRI mozga našeg pacijenta je pokazao leziju u desnom frontalnom režnju koja je pojačana kontrastnim sredstvom i ima heterogeni signal na T2W FLAIR, sa hiperintenzitetom na T1W i hipointenzitetom na T2W MRI sekvencama. Metabolički indeks je bio $\text{Cho/Cr}=2,00$. U našem slučaju nije bilo verifikovanog melanoma kože ili oka. Dijagnostika je dopunjena PET skeniranjem praćenom

CT grudnog koša i abdomena, međutim primarne maligne lezije nisu otkrivene na drugim mestima na telu.

Zbog retkosti PIM-a, ne postoji standardni tretman za ove izuzetno maligne tumore. Tačna dijagnoza je imperativ za razvoj odgovarajućeg plana lečenja koji može uključivati hirurško lečenje, stereotaktičku radioterapiju, totalnu radioterapiju mozga, hemoterapiju, imunoterapiju i gensku terapiju.

Pokazalo se da su pacijenti sa resekcijom uvećane margine tumora imali značajno duže vreme preživljavanja od pacijenata koji su bili podvrgnuti subtotalnom uklanjanju, delimičnom uklanjanju ili biopsiji (8).

Iako u našem slučaju nije bilo znakova leptomeningealne diseminacije, broj mitotičkih ćelija bio je preko 10 HPF što nije bio povoljan prognostički faktor. U pogledu lokalizacije tumora u neelokventnoj zoni, izvršili smo agresivnu supramarginalnu resekciju.

Uloga hemoterapije je još uvek kontroverzna. Zbog svoje sposobnosti da pređe krvno-moždanu barijeru, čini se da Temozolomid pokazuje obećavajuće rezultate, iako značajna razlika u stopama preživljavanja između tretmana Temozolomidom i drugim kombinacijama hemoterapije nije primećena (2).

Pošto se melanom smatra radiorezistentnim tumorom, dovodi se u pitanje efikasnost radioterapije kao pomoćne terapije primarnih intrakranijalnih melanoma. Međutim, prijavljeno je da je kvalitet života nakon stereotaktičke radioterapije viši nego kod radioterapije celog mozga (9).

Iako je prognoza PIM-a veoma loša, prijavljeno je da je bolja nego kod pacijenata sa metastatskim CNS melanomom (5). Izveštava se da je srednje vreme recidiva tumora 6,5 meseci nakon inicijalne operacije sa srednjim vremenom smrti od 11 meseci (10). Međutim, pacijent kojeg smo prijavili je bio bez bolesti 3 godine nakon tretmana.

Smatramo da agresivni pristup izvođenjem hirurške supramarginalne resekcije kad god je bezbedna i adjuvantna terapija treba da bude obavezan i formulisan kao zvanična preporuka.

Zaključak

Za postavljanje dijagnoze i plana lečenja neophodan je temeljan klinički i neuroradiološki pregled. Iako se ne može izneti valjan zaključak u vezi sa zvaničnom preporukom, s obzirom na usamljeni slučaj, verujemo da agresivno hirurško lečenje – totalna resekcija sa resekcijom okolnog moždanog tkiva, praćeno radioterapijom i hemoterapijom, nudi bolje stope preživljavanja, i nadamo se da će inspirisati dalje studije u većem obimu da bi se potvrdila efikasnost radioterapije i hemoterapije kao pomoćnog tretmana primarnih intracerebralnih melanoma i uspostavila adekvatna smernica za lečenje.

Izjava o interesu

Autori izjavljaju da nema sukoba interesa.

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SLIKE

Slika 1. Preoperativne CT slike mozga, Aksijalni pogled

Slika 2. Preoperativne MRI slike mozga, aksijalni pogled T1-izmerena slika (T1WI). (A) Aksijalni pogled, T2WI. (B), Aksijalni prikaz, T2 FLAIR ponderisana sekvenca (C) Aksijalni prikaz, T1WI sa poboljšanim kontrastom (D). Lezija desnog frontalnog režnja je izgledala kao hiperdenza na kompjuterizovanoj tomografiji mozga (CT), kratki signal na T1-ponderisanim slikama magnetne rezonance (T1WI) i dug signal na T2-ponderisanim slikama magnetne rezonance (T2WI) sa heterogenim signalom na T2 FLAIR ponderisanoj sekvenci

Slika 3. Postoperativni CT snimci mozga, aksijalni pogled, nisu pokazali rezidualni tumor mozga

Slika 4. PET skeniranje – primarni proces nije otkriven

Slika 5. Postoperativne MRI slike mozga na prvom pregledu, aksijalni pogled T1-izmerena slika (T1WI). (E) Aksijalni pogled, T2WI. (F) Aksijalni pogled, T1WI sa kontrastom (G). Cistična formacija u operativnoj oblasti, bez znakova tumorskog reziduuma

Slika 6. Postoperativni MRI snimci mozga na poslednjoj kontroli. Aksijalni pogled T1-izmerena slika (T1WI). (H) Aksijalni pogled, T2WI. (I) Aksijalni pogled, T1WI sa kontrastom (J). Perzistirajuća nepromenljiva cistična formacija u operativnoj oblasti, bez znakova tumorskog reziduuma

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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 affects 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 is 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 in order to establish 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 affects 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 is unclear. Studies show that 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 complaints 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. Histopathological 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. Regarding 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)

Although 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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Figure 1 displays 15 axial CT scan images of the head, arranged in a 3x5 grid. The images show various cross-sections of the brain, including the skull base, lateral ventricles, and posterior horns. Each image is labeled with a number (1-15) and technical details such as 'CT HEAD' and 'AXIAL'.

Figure 1. Preoperative brain CT images, Axial view

Figure 2. Preoperative brain MRI images, Axial view T1-weighted 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-weighted image (T1WI). (E) Axial view, T2WI. (F) Axial view, contrast-enhanced T1WI (G). A cystic formation in the operative region, without any signs of tumor residuum

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