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PRIKAZ SLUČAJA

KRANIOFACIJALNE METASTAZE ADENOKARCINOMA GASTROINTESTINALNOG POREKLA: IZAZOV U DIJAGNOSTICI

Dražen Radanović[1,3,4], Dušan Micić[1,2], Ana Drakul[8], Marko Đurović[1,3], Mihajlo Ćurčić[1,3], Marija Rudić[1,4,6], Vanja Misić Mandić[1,4,6], Sonja Giljača[5], Emilija Manojlović Gačić[1,7]

[1]Medicinski fakultet, Univerzitet u Beogradu, Beograd, Republika Srbija
[2]Urgentni centar, Univerzitetski klinički centar Srbije, Beograd, Republika Srbija
[3]Neurohirurška klinika, Univerzitetski klinički centar Srbije, Beograd, Republika Srbija
[4]Institut za farmakologiju, kliničku farmakologiju i toksikologiju, Medicinski fakultet Univerzitet u Beogradu, Beograd
[5]Gradski zavod za javno zdravlje Beograda, Beograd, Republika Srbija
[6]Odeljenje za anesteziologiju i reanimaciju, Centar za anesteziologiju i reanimaciju, Univerzitetski Klinički Centar Srbije, Beograd, Republika Srbija
[7]Institut za patologiju, Medicinski fakultet Univerziteta Beograd, Beograd, Republika Srbija
[8]Institut za anatomiju, Medicinski fakultet Univerziteta Novi Sad, Novi Sad, Republika Srbija

Korespondirajući autor: dr Mihajlo Ćurčić, Neurohirurška klinika UKCS, 11000 Beograd, Republika Srbija; e-mail: curcicmihajlo5@gmail.com

SAŽETAK

Uvod/ciljevi: Adenokarcinomi gastrointestinalnog porekla retko metastaziraju u kraniofacijalnu regiju. Ovakve manifestacije, naročito uz sumnju na leptomeningealno širenje, odlikuju se visokom agresivnošću i lošom prognozom. Cilj rada je prikaz slučaja masivne kraniofacijalne metastaze adenokarcinoma atipične prezentacije i fulminantnog toka.
Prikaz bolesnika: Sprovedena je retrospektivna analiza medicinske dokumentacije 74-godišnje pacijentkinje. Pacijentkinja je primljena u Urgentni centar zbog naglog poremećaja stanja svesti. Radiološki je utvrđena masivna frontoparijetalna lezija sa destrukcijom kraniofacijalnih kostiju i invazijom orbite, sfenoidalne i temporalne kosti, te infratemporalne jame. Nisu uočene intraparenhimske lezije mozga, ali je postavljena sumnja na leptomeningealno zahvatanje. Otkrivene su i metastaze u jetri i kičmenim pršljenovima (Th1, L1, L3). Patohistološkom i imunohistohemijskom analizom biopsijskog uzorka kraniofacijalne mase potvrđen je adenokarcinom imunofenotipa koji ukazuje na gastrointestinalno poreklo. Uprkos intenzivnom multidisciplinarnom lečenju, klinički tok je bio fulminantan, sa letalnim ishodom četvrtog dana hospitalizacije.
Zaključak: Kraniofacijalne metastaze adenokarcinoma mogu biti prva manifestacija okultnog gastrointestinalnog maligniteta. Ekstenzivna koštana destrukcija i leptomeningealna diseminacija uslovljavaju izrazito nepovoljan ishod. Ovaj slučaj naglašava važnost brze dijagnostike i visokog stepena kliničke sumnje kod pacijenata sa atipičnim koštanim lezijama lobanje i akutnim neurološkim pogoršanjem.
Ključne reči: adenokarcinom, gastrointestinalni trakt, kraniofacijalne metastaze, leptomeningealna karcinomatoza, imunohistohemija, fulminantni tok

Uvod

Adenokarcinomi gastrointestinalnog (GI) porekla, prvenstveno kolorektalni karcinomi, predstavljaju značajan javnozdravstveni problem i treći su najčešći uzrok smrtnosti od maligniteta širom sveta. Iako ovi tumori uobičajeno metastaziraju u jetru, pluća i regionalne limfne čvorove, njihova diseminacija u centralni nervni sistem (CNS) javlja se u svega 1% do 4% slučajeva (1). Metastaze u kraniofacijalnoj regiji, koje obuhvataju bazu lobanje i paranazalne strukture, predstavljaju još ređi klinički entitet i često su povezane sa naprednim stadijumom osnovne bolesti.

Posebno agresivnu formu CNS diseminacije predstavlja leptomeningealna karcinomatoza (LMC), stanje u kojem maligne ćelije infiltrišu meke moždanice i subarahnoidalni prostor. Prevalencija LMC kod solidnih tumora GI trakta je izuzetno niska, procenjena na manje od 0,1%, ali je u stalnom porastu zbog produženja preživljavanja pacijenata usled savremene onkološke terapije i bolje radiološke dijagnostike (2). Patofiziološki mehanizam zahvatanja kraniofacijalnih kostiju i meninga najčešće podrazumeva hematogeno širenje putem Batsonovog venskog pleksusa ili direktno širenje iz koštanih meta-

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CASE REPORT

CRANIOFACIAL METASTASES OF GASTROINTESTINAL ADENOCARCINOMA: A DIAGNOSTIC CHALLENGE

Dražen Radanović[1,3,4], Dušan Micić[1,2], Ana Drakul[8], Marko Đurović[1,3], Mihajlo Ćurčić[1,3], Marija Rudić[1,4,6], Vanja Misić Mandić[1,4,6], Sonja Giljača[5], Emilija Manojlović Gačić[1,7]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia
[2]Emergency Center, University Clinical Center of Serbia, Belgrade, Republic of Serbia
[3]Clinic for Neurosurgery, University Clinical Center of Serbia, Belgrade, Republic of Serbia
[4]Institute of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia
[5]Belgrade City Institute of Public Health, Belgrade, Republic of Serbia
[6]Department of Anesthesiology and Resuscitation, Center for Anesthesiology and Resuscitation, University Clinical Center of Serbia, Belgrade, Republic of Serbia
[7]Institute of Pathology, Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia
[8]Institute of Anatomy, Faculty of Medicine, University of Novi Sad, Novi Sad, Republic of Serbia
Corresponding author: Mihajlo Ćurčić, MD, Clinic for Neurosurgery, University Clinical Center of Serbia, Belgrade, Republic of Serbia; Email: curcicmihajlo5@gmail.com

SUMMARY

Introduction/Aims: Adenocarcinomas of gastrointestinal origin rarely metastasize to the craniofacial region. Such manifestations, especially when associated with suspected leptomeningeal involvement, are characterized by high aggressiveness and a very poor prognosis. The aim of this paper is to present a rare case of a massive craniofacial metastasis from an adenocarcinoma with an atypical presentation and a fulminant clinical course.
Case Report: A retrospective analysis of the medical records of a 74-year-old female patient was performed. The patient was admitted to the Emergency Center due to a sudden disturbance in the level of consciousness. Radiology revealed a massive frontoparietal lesion with extensive destruction of craniofacial bones and invasion of the orbit, sphenoid and temporal bones, and the infratemporal fossa. No primary intraparenchymal brain lesions were observed, but radiological findings suggested leptomeningeal involvement. Metastases were also detected in the liver and vertebral bodies (Th1, L1, L3). Histopathological and immunohistochemical analysis of the craniofacial mass biopsy confirmed an adenocarcinoma with an immunophenotype indicative of gastrointestinal origin. Despite intensive multidisciplinary treatment, the clinical course was fulminant, resulting in a lethal outcome on the fourth day of hospitalization.
Conclusion: Craniofacial metastases of adenocarcinoma can be the first manifestation of an occult gastrointestinal malignancy. Extensive bone destruction and suspected leptomeningeal dissemination lead to an extremely unfavorable outcome. This case highlights the importance of rapid diagnosis and a high degree of clinical suspicion in patients presenting with atypical cranial bone lesions and acute neurological deterioration.
Keywords: adenocarcinoma, gastrointestinal tract, craniofacial metastases, leptomeningeal carcinomatosis, immunohistochemistry, fulminant course

Introduction

Adenocarcinomas of gastrointestinal (GI) origin, primarily colorectal cancers, represent a significant public health problem and the third most common cause of cancer-related deaths worldwide. Although these tumors usually metastasize to the liver, lungs and the regional lymph nodes, their dissemination to the central nervous system (CNS) occurs in only 1% to 4% of cases (1). Metastases in the craniofacial region, which involve the cranial base and paranasal structures, represent an even rarer clinical entity and are often associated with advance stages of the underlying disease.

A particularly aggressive form of CNS dissemination is leptomeningeal carcinomatosis (LMC), a condition in which malignant cells infiltrate the leptomeninges and the subarachnoid space. The prevalence of LMC in solid tumors of the GI tract is extremely low, estimated at less than 0.1%, but it is constantly increasing because of the prolonga-

staza baze lobanje (3).

Ovakve manifestacije bolesti odlikuju se visokom agresivnošću, fulminantnim kliničkim tokom i dramatičnim neurološkim simptomima, što dijagnostiku čini kompleksnom, naročito kada se metastaza prezentuje pre primarnog tumora (1,3).

Cilj ovog rada je prikaz slučaja pacijentkinje sa masivnom kraniofacijalnom metastazom i suspektnim leptomeningealnim zahvatanjem kao primarnom manifestacijom adenokarcinoma, uz analizu patofizioloških mehanizama i dijagnostičkih ograničenja u određivanju primarnog porekla tumora.

Prikaz bolesnika

Pacijentkinja starosti 74 godine primljena je u Urgentni centar zbog naglog poremećaja stanja svesti. Prethodno je pronađena bez svesti, a pri prijemu je bila u soporoznom stanju, spontano je disala uz devijaciju bulbusa udesno. Od ranijih oboljenja navode se arterijska hipertenzija, dijabetes mellitus tip 2 i hipotireoza nakon totalne tireoidektomije.

Lokalnim pregledom uočena je desna frontoparijetalna masa, meka na palpaciju, dimenzija 4 x 5 cm. CT endokranijuma otkrio je ekspanzivnu leziju sa ekstrakranijalnom propagacijom na krov orbite, frontalni procesus zigomatične kosti, skvamu temporalne kosti, veliko krilo sfenoidalne kosti, etmoidalne ćelije i optički kanal desno. Proces je zahvatio prednju i srednju lobanjsku jamu, uz proptozu desnog oka (slika 1-5). Sistemska evaluacija otkrila je osteolitične metastaze na pršljenovima Th1, L1 i L3, kao i metastatsku promenu u jetri promera 8 cm.

Zbog kritičnog stanja, pacijentkinja nije bila kandidat za hitnu operaciju. Multidisciplinarni pristup uključio je biopsiju supratentorijalne mase (slika 6). Patohistološki nalaz potvrdio je metastazu adenokarcinoma (glandularni i solidni angažman kockastih ćelija sa žarištima nekroze). Imunohistohemijskom analizom utvrđena je pozitivnost na panCK (AE1/AE3) i CK20 (difuzno), dok je CK7 bio samo fokalno pozitivan. Negativni su bili Vimentin, TTF-1, CDX-2, PAX8 i drugi specifični markeri. Uprkos intenzivnom lečenju, pacijentkinja je preminula četvrtog dana hospitalizacije.

Diskusija

Leptomeningealne metastaze adenokarcinoma gastrointestinalnog (GI) porekla predstavljaju izuzetno retku i klinički agresivnu manifestaciju malignitеta. Iako adenokarcinomi creva i drugih delova GI trakta uobičajeno metastaziraju u jetru, pluća i regionalne limfne čvorove, njihova invazija u centralni nervni sistem (CNS), uključujući leptomeninge i kraniofacijalne kosti, javlja se vrlo retko (4-6).

Kod naše pacijentkinje, primetna je akutna neurološka prezentacija sa poremećajem svesti, devijacijom bulbusa i izrazito proširenom ekstrakranijalnom masom u frontoparijetalnoj regiji. Radiološki nalazi su pokazali invaziju krovova orbite, frontalnog procesusa zigomatične kosti, temporalne skvame, velikog krila sfenoidalne kosti i infratemporalne fose, dok primarni intraparenhimalni tumor u mozgu nije bio prisutan. Ovako masivna i destruktivna prezentacija metastatskog adenokarcinoma, za koji se pretpostavlja da je intestinalnog porekla, podudarna je sa literaturnim opisima najagresivnijih formi diseminacije (7–9).

Leptomeningealne metastaze se obično manifestuju simptomima poput glavobolje, promene svesti, fokalnih neuroloških deficita i oftalmoloških tegoba, što je bio slučaj i kod naše pacijentkinje (4,5,10). Biopsija tumorske mase potvrdila je adenokarcinom, naglašavajući važnost histopatološke verifikacije kao zlatnog standarda u dijagnostici kod pacijenata sa nejasnim koštanim lezijama (4,11). Slični slučajevi u literaturi opisuju adenokarcinome kolona i duodenuma koji metastaziraju u intrakranijalne strukture, često udruženo sa sistemskom bolešću u jetri i skeletu (7,12).

Patofiziološki mehanizam metastaziranja adenokarcinoma u CNS je složen proces. Tumorske ćelije prolaze kroz lokalne i regionalne limfne čvorove, ulaze u sistemsku cirkulaciju i hematogenim putem dospevaju do mozga i kostiju lobanje (13). Ovaj proces zahteva da ćelije savladaju krvno-moždanu barijeru putem specifičnih interakcija adhezivnih molekula tumora sa endotelnim receptorima, uz sekreciju enzima koji razgrađuju bazalnu membranu kapilara (13). Tropizam tumorskih ćelija za kraniofacijalne kosti kod naše pacijentkinje može se objasniti širenjem kroz retikuloendotelne kapilare lobanjske baze, što dovodi do destruktivne ekspanzije i pritiska na okolne neurološke i oftalmološke strukture (8,9,13).

Prognoza ovih pacijenata ostaje izrazito loša. Prosečno preživljavanje nakon dijagnoze leptomeningealnih metastaza retko prelazi nekoliko nedelja, čak i uz primenu intenzivnih mera podrške vitalnim funkcijama (5,8,11). Ovaj slučaj naglašava potrebu za visokom kliničkom sumnjom kod bolesnika sa GI malignitetima koji razvijaju akutne neurološke simptome, jer rana dijagnostika putem CT, MRI i histopatološke analize ostaje ključna za planiranje palijativnog zbrinjavanja (3–12).

tion of patient survival due to modern oncological therapy and better radiological diagnostics (2). The pathophysiological mechanism of the involvement of craniofacial bones and meninges usually implies the hematogenous spread through the Batson venous plexus or direct spread from bone metastases of the cranial base (3).

Such manifestations of the disease are characterized by high aggressiveness, fulminant clinical course and dramatic neurological symptoms, which makes the diagnosis complex, especially when the metastasis is manifested before the primary tumor (1-3).

The aim of this paper is to present the case of a female patient with the massive craniofacial metastasis and suspected leptomeningeal involvement as the primary manifestation of adenocarcinoma, along with the analysis of pathophysiological mechanisms and diagnostic limitations in determining the primary origin of the tumor.

Case Report

A 74-year-old female patient was admitted to the Emergency Center due to a sudden disturbance in the state of consciousness. Previously, she was found unconscious and upon admission she was in a soporose state, breathing spontaneously with the deviation of the bulbus to the right. Among the earlier diseases, arterial hypertension, diabetes mellitus type 2 and hypothyroidism after total thyroidectomy are mentioned.

Local examination revealed a right frontoparietal mass, soft to palpation, measuring 4 x 5 cm. CT scan of the endocranium revealed an expansive lesion with the extracranial spread to the roof of the orbit, the frontal process of the zygomatic bone, the squama of the temporal bone, the greater wing of the sphenoid bone, ethmoid cells and optic canal on the right. The process affected the anterior and middle cranial fossa, with proptosis of the right eye (Figure 1-5). The systemic evaluation revealed osteolytic metastases on the Th1, L1 and L3 vertebrae, as well as a metastatic change in the liver with a diameter of 8 cm.

Due to the critical condition, the patient was not a candidate for an urgent operation. A multidisciplinary approach included biopsy of the supratentorial mass (Figure 6). The pathohistological findings confirmed the metastasis of adenocarcinoma (glandular and solid involvement of cuboidal cells with foci of necrosis. The immunohistochemical analysis revealed positivity for panCK (AE1/AE3) and CK20 (diffuse), while CK7 was only focally positive. Vimentin, TTF-1, CDX-2, PAX-8 and other specific markers were negative. Despite intensive treatment, the patient died on the fourth day of hospitalization.

Discussion

Leptomeningeal metastases of adenocarcinoma of gastrointestinal (GI) origin represent an extremely rare and clinically aggressive manifestation of malignancy. Although adenocarcinomas of the intestines and other parts of the GI tract commonly metastasize to the liver, lungs and regional lymph nodes, their invasion of the central nervous system (CNS), including the leptomeninges and craniofacial bones, occurs very rarely (4-6).

In our patient, an acute neurological presentation with impaired consciousness, deviation of the bulbus and a markedly enlarged extracranial mass in the frontoparietal region was noticeable. Radiological findings revealed the invasion of the roof of the orbit, the frontal process of the zygomatic bone, the temporal squama, the greater wing of the sphenoid bone and the infratemporal fossa, while the primary intraparenchymal brain tumor was not present. Such a massive and destructive presentation of metastatic adenocarcinoma, which is assumed to be of intestinal origin, is consistent with literature descriptions of the most aggressive forms of dissemination (7-9).

Leptomeningeal metastases are usually manifested by diverse symptoms such as headache, altered consciousness, focal neurological deficits and ophthalmological complaints, which was also the case with our patient (4,5,10). Biopsy of the tumor mass confirmed adenocarcinoma, emphasizing the importance of histopathological verification as the gold standard in diagnosis in patients with obscure bone lesions (4,11). Similar cases in the literature describe adenocarcinomas of the colon and duodenum that metastasize to intracranial structures, which is often associated with the systemic disease in the liver and skeleton (7,12).

The pathophysiological mechanism of adenocarcinoma metastases to the CNS is a complex process. Tumor cells pass through local and regional lymph nodes, enter the systemic circulation and reach the brain and bones of the skull via the hematogenous route (13). This process requires cells to overcome the blood-brain barrier through specific interactions of tumor adhesion molecules with endothelial receptors, with the secretion of enzymes that degrade the capillary basement membrane (13). Tumor cells' tropism for the craniofacial bones in our patient can be explained by the expansion

Snaga ovog prikaza slučaja ogleda se u detaljnoj radiološkoj i patohistološkoj dokumentaciji izuzetno retke kliničke prezentacije, koja doprinosi boljem razumevanju atipičnih metastatskih puteva gastrointestinalnih adenokarcinoma. Multidisciplinarni pristup omogućio je brzu dijagnostičku trijažu u urgentnim uslovima, uprkos kritičnom stanju bolesnice. Ipak, fulminantni klinički tok i letalni ishod četvrtog dana hospitalizacije predstavljali su glavno ograničenje u radu, jer su onemogućili sprovođenje dodatne dijagnostike, poput endoskopskih pregleda ili citološke analize likvora, radi definitivne potvrde primarnog ishodišta i leptomeningealne infiltracije. Takođe, iako imunohistohemijski profil (CK20+, CK7 fokalno+) snažno sugeriše gastrointestinalno poreklo, negativnost markera CDX2 ukazuje na potencijalno nisku diferentovanost tumora, što naglašava dijagnostičku kompleksnost kod metastaza nepoznatog primarnog porekla.

Zaključak

Leptomeningealne i kraniofacijalne metastaze GI adenokarcinoma su retke forme diseminacije sa izrazito nepovoljnom prognozom. Ovaj slučaj ilustruje da metastaze mogu biti prva manifestacija okultnog maligniteta, izazivajući dramatičnu kliničku sliku. Iako imunohistohemija (pozitivnost na CK20) sugeriše gastrointestinalno poreklo, negativnost CDX2 ukazuje na potrebu za širim panelom markera (MUC2, SATB2) u sličnim slučajevima. Pravovremena radiološka dijagnostika i multidisciplinarni pristup ostaju ključni za planiranje palijativnog zbrinjavanja pacijenata sa agresivnim sekundarnim depozitima u CNS-u.

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through the reticuloendothelial capillaries of the skull base, which leads to destructive expansion and pressure on the surrounding neurological and ophthalmic structures (8,9,13).

The prognosis of these patients remains very poor. The average survival after the diagnosis of leptomeningeal metastases rarely exceeds a few weeks, even with the application of intensive measures to support vital functions (5,8,11). This case highlights the need for high suspicion in patients with GI malignancies who develop acute neurological symptoms, as early diagnosis using CT, MRI and histopathological analysis remains crucial for planning the palliative care (3-12).

The strength of this case report is reflected in the detailed radiological and pathohistological documentation of an extremely rare clinical presentation, which contributes to a better understanding of the atypical metastatic pathways of gastrointestinal adenocarcinomas. The multidisciplinary approach enabled the rapid diagnostic triage in emergency conditions, despite the patient's critical condition. However, the fulminant clinical course and the fatal outcome on the fourth day of the hospitalization represented the main limitation of the study, because they made it impossible to carry out additional diagnostics, such as endoscopic examinations or cytological analysis of the cerebrospinal fluid, for the definitive confirmation of the primary origin and leptomeningeal infiltration. Also, although the immunohistochemical profile (CK20+, CK7 focal+) strongly suggests the gastrointestinal origin, the negativity of the CDX2 marker indicates a potentially low differentiation of the tumor, which emphasizes the diagnostic complexity in metastases of unknown primary origin.

Conclusion

Leptomeningeal and craniofacial metastases of GI adenocarcinoma are rare forms of dissemination with an extremely unfavorable prognosis. This case illustrates that metastases can be the first manifestation of an occult malignancy, causing a dramatic clinical picture. Although immunohistochemistry (CK20 positivity) suggests a gastrointestinal origin, the negativity of CDX2 indicates the need for a wider panel of markers (MUC2, SATB2) in similar cases. Timely radiological diagnostics and a multidisciplinary approach remain crucial for planning the palliative care of patients with aggressive secondary deposits in the CNS.

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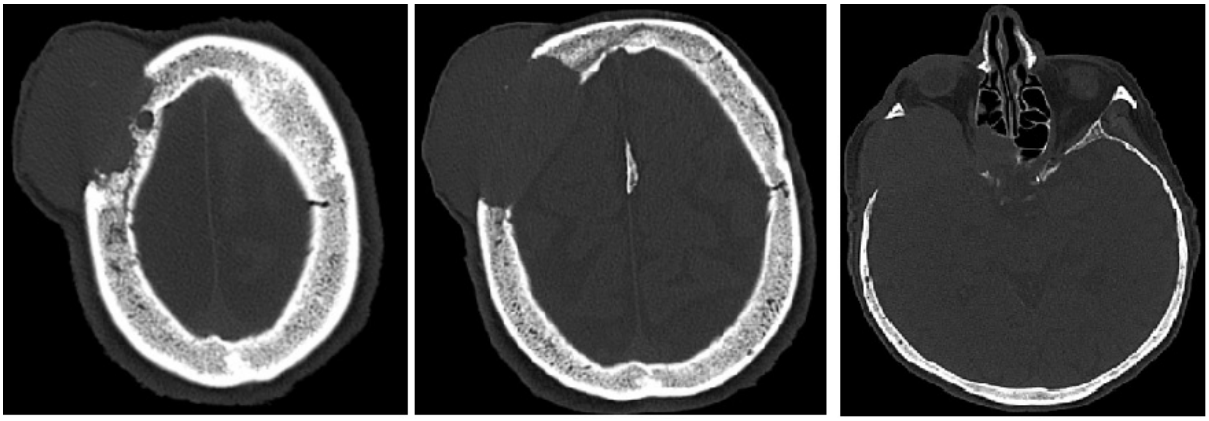
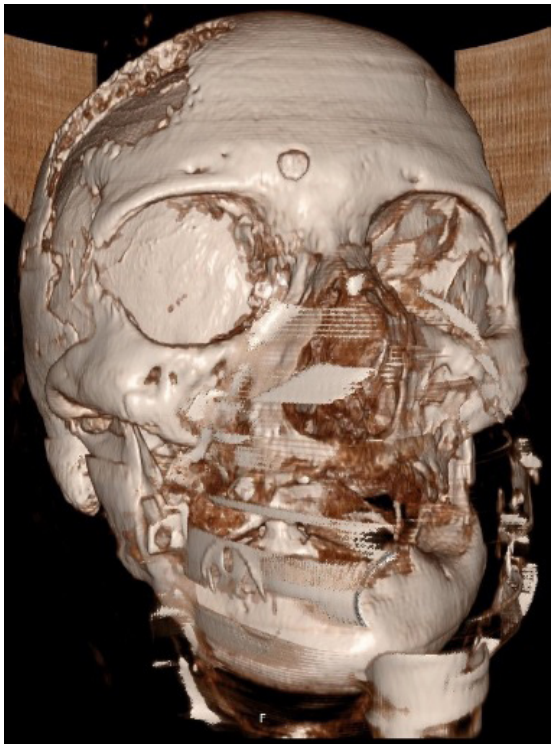
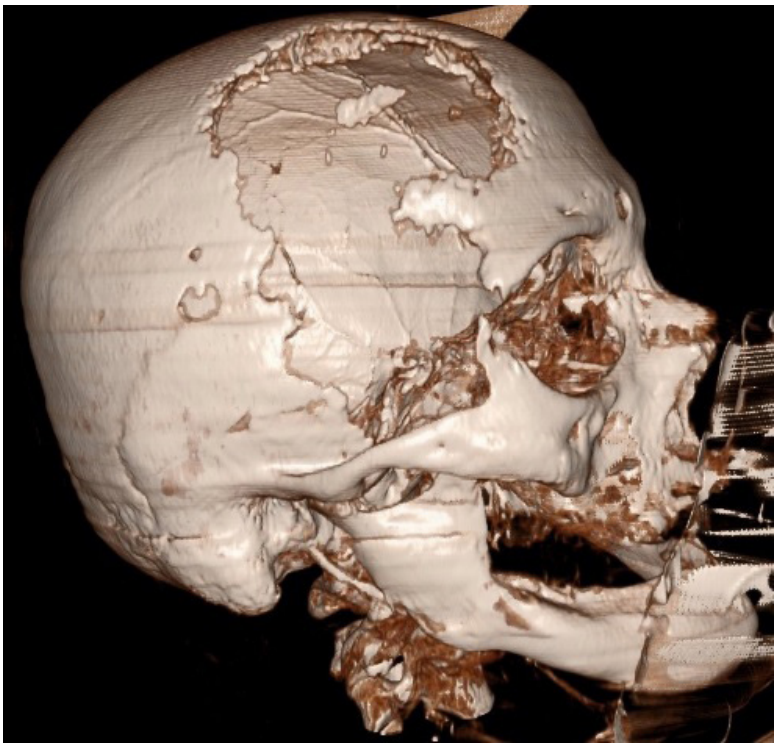


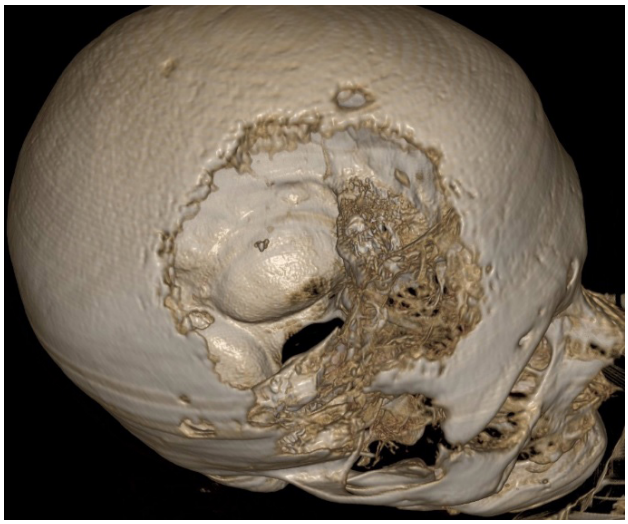
Slika 1. CT endokranijuma sa prikazom koštanog dela gde se uočava osteolitički proces kao posledica metastatskog efekta adenokarcinoma



Slika 2. 3D rekonstrukcija kraniofacijalne regije na kojoj se uočava desnostrana destrukcija koštanog segmenta



Slika 3. 3D rekonstrukcija kranijofacijalne regije. Desni profil.



Slika 4. 3D rekonstrukcija na osnovu koje se uočava intrakranijalni prostor i baza lobanje

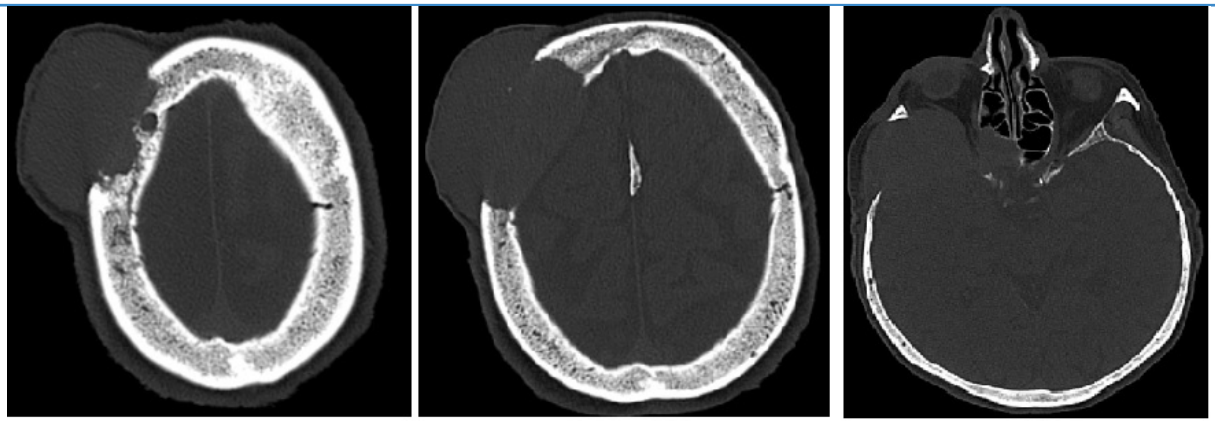


Figure 1. CT scan of the endocranium showing the bony component, where an osteolytic process is observed as a consequence of the metastatic effect of adenocarcinoma

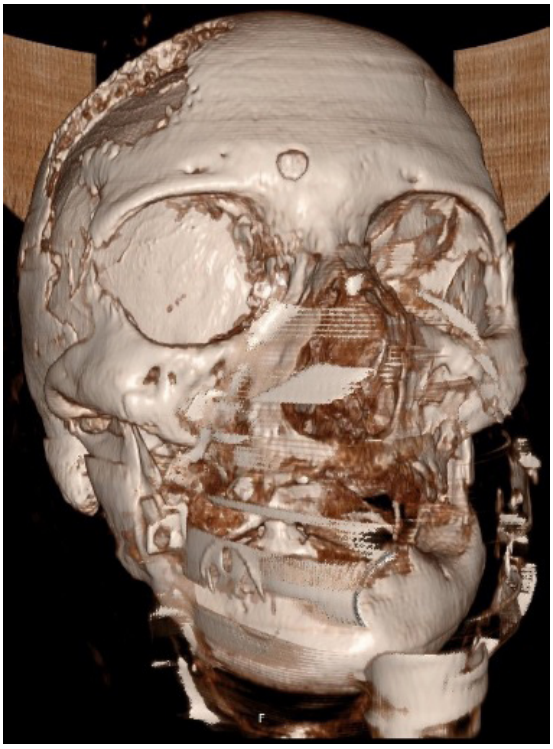


Figure 2. Three-dimensional reconstruction of the craniofacial region demonstrating right-sided destruction of a bony segment

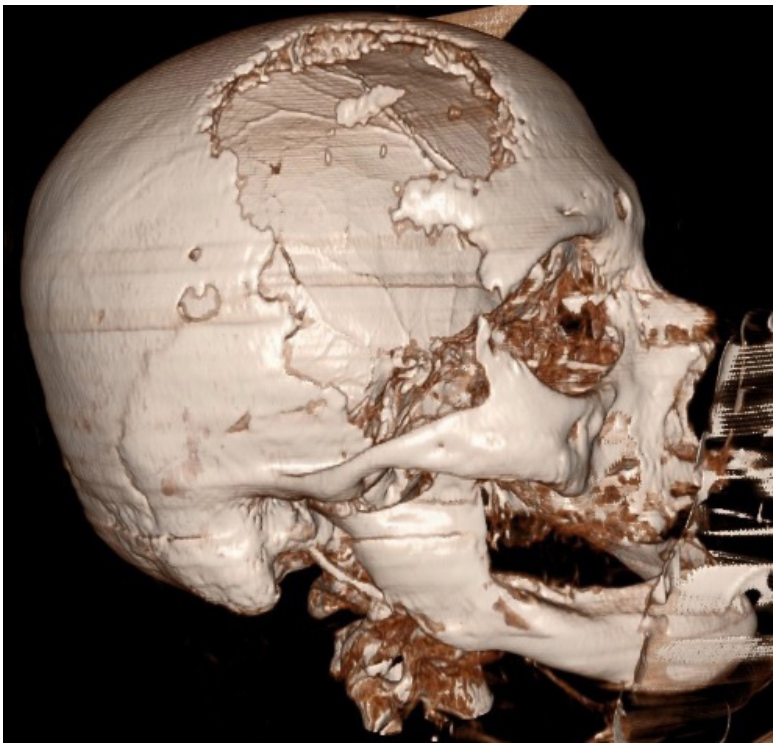


Figure 3. Three-dimensional reconstruction of the craniofacial region. Right profile view.

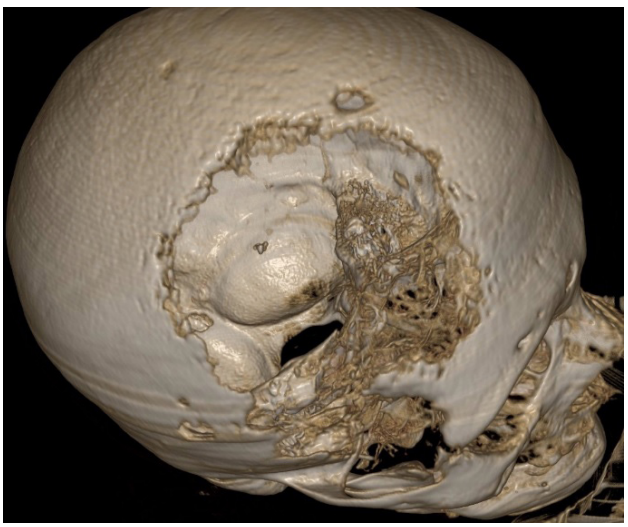
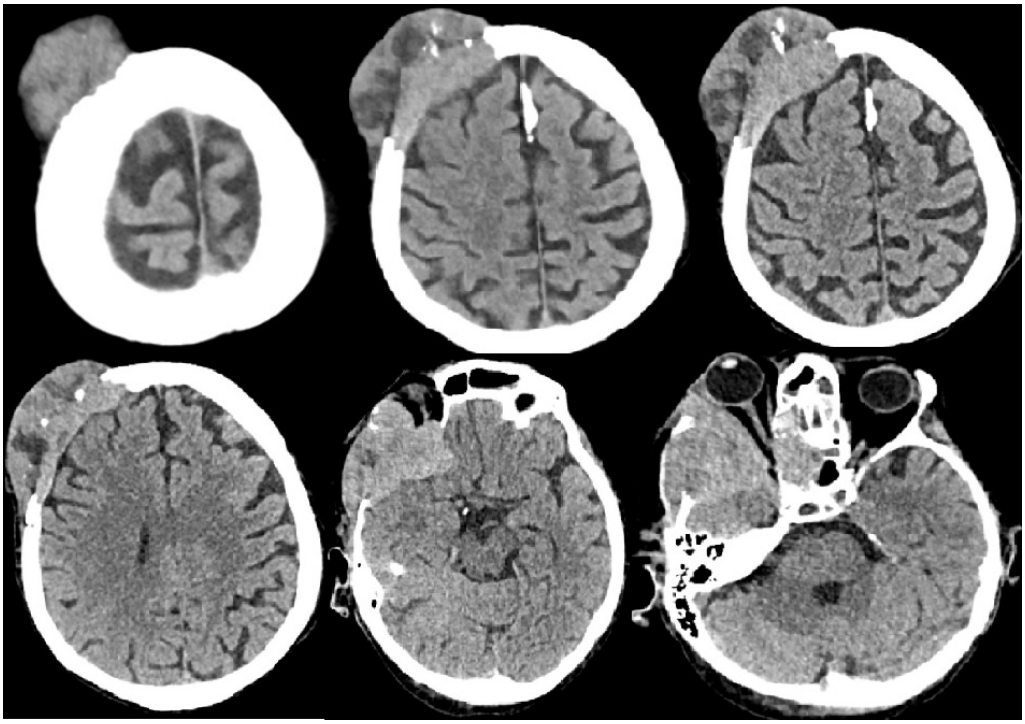
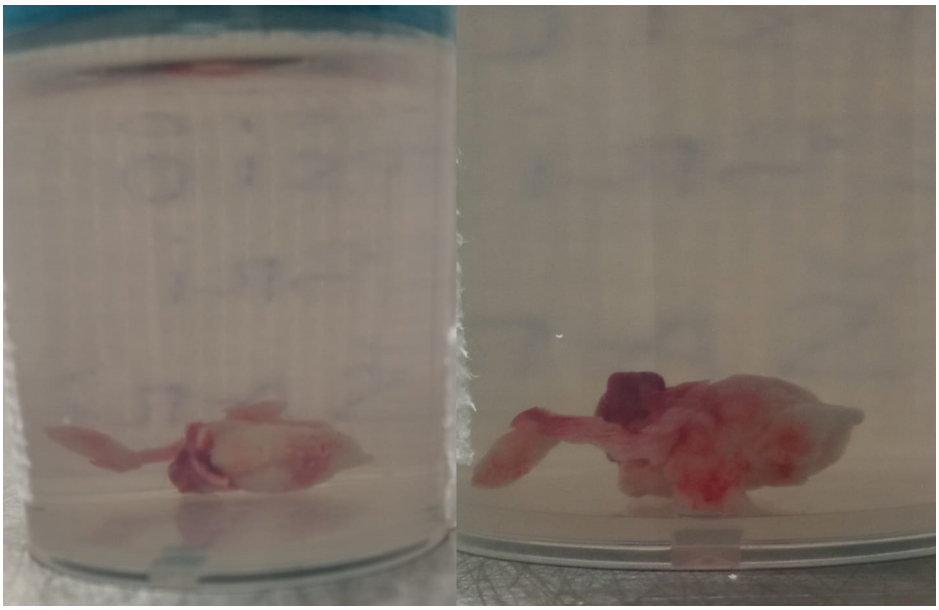


Figure 4. Three-dimensional reconstruction illustrating the intracranial space and the skull base



Slika 5. CT endokranijuma, prikaz parenhima



Slika 6. Bioptirani preparat metastatske promene. Fragment tkiva beličaste boje, umereno meke konzistencije, ukupnih dimenzija 13x9x4 mm. Sav materijal uzet u rad u jedan kalup.

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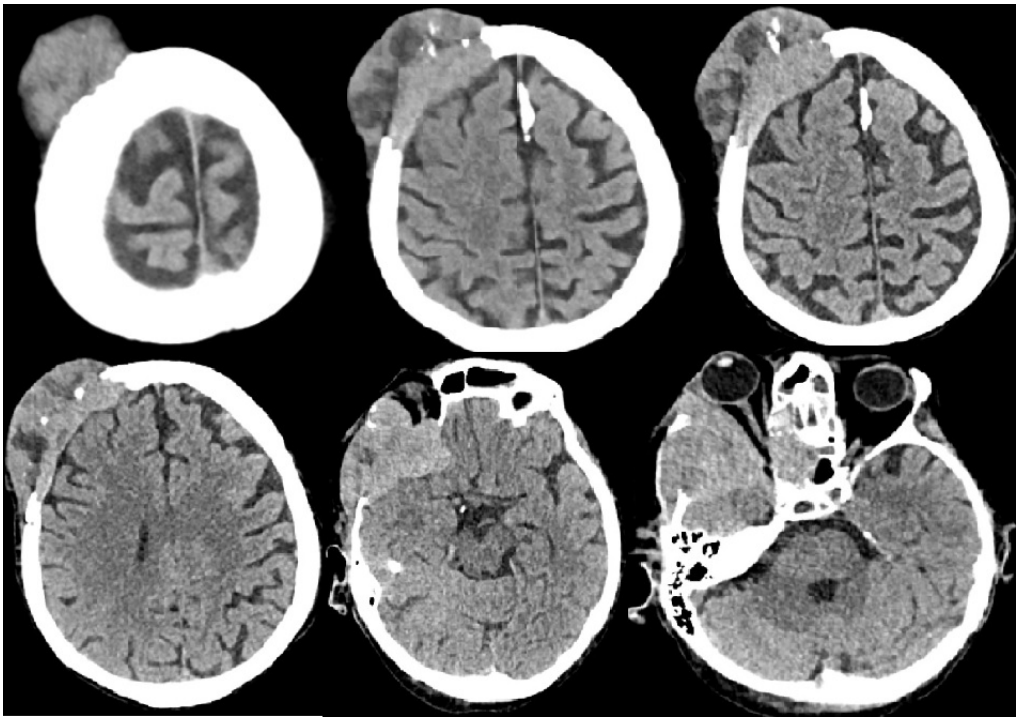

Figure 5. CT scan of the endocranium showing the brain parenchyma

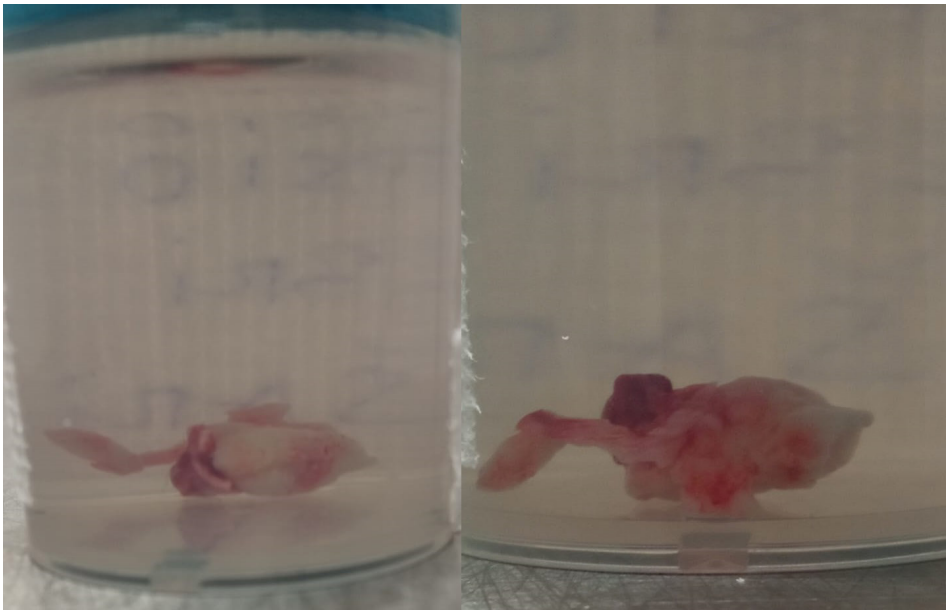

Figure 6. Biopsy specimen of a metastatic lesion. A fragment of whitish tissue with moderately soft consistency, measuring 13 × 9 × 4 mm in total. All material was processed in a single paraffin block.

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