Baskurt *et al.*
Egyptian Journal of Neurosurgery (2022) 37:25
https://doi.org/10.1186/s41984-022-00163-z

Egyptian Journal of Neurosurgery

REVIEW

Open Access

Extracranial metastasis of recurrent glioblastoma to the parotid gland: a case report and review of the literature

Ozan Baskurt[1*], Yunus Kurtulus[2], Ahmed Yasin Yavuz[3] and İdris Avci[4]

Abstract

Background: Glioblastomas are the most common and highly malignant primary brain tumors in adults with a median survival of 15 months even with appropriate treatment. Extracranial metastases are extremely rare due to the poor prognosis not allowing sufficient time to spread. We report an extremely rare case of extracranial metastasis of supra-tentorial glioblastoma involving the skin, subcutaneous and muscular layers, periauricular region and parotid gland, and review the literature. A total of 13 glioblastoma parotid gland metastases cases have been hitherto described.

Main body of the abstract: A 42-year-old man underwent surgery for right temporal glioblastoma and received 60 Gy/30 fractions radiotherapy together with temozolomide at 75 mg/m^2. Seven months later, the tumor relapsed and the patient underwent a second surgery while chemotherapy continued. Fifteen months later, he complained of swelling in the right neck region. Fine needle aspiration and tru-cut biopsy revealed a high-grade malignant tumor infiltration within the parotid gland. Despite salvage chemotherapy and adjuvant radiotherapy, in his follow-up after 6 months neck swelling increased. The patient declined any treatment modality and continues his life 39 months after the primary diagnosis of intracranial glioblastoma.

Short conclusion: Due to the recurrence rate of intracranial glioblastoma and its malignant nature; close imaging follow-up is highly crucial. The increase in reported cases of its extracranial metastases is generally due to the modern diagnostic tools and prolonged survival attributed to the improvement in treatment modalities where now radical surgery with adjuvant radiotherapy and chemotherapy is standard protocol. Patients with glioblastomas presenting with swelling in the cervical region should be investigated to rule out parotid gland metastasis.

Keywords: Extracranial metastasis, Glioblastoma, Parotid gland, Recurrent glioblastoma

Background

Glioblastoma are the most common and aggressive primary brain tumor in adults. Histopathologically, it is characterized by necrosis and endothelial proliferation and is classified as grade IV, the highest grade according to the World Health Organization (WHO) classification of brain tumors [1]. Patients diagnosed with these tumors have a poor prognosis, even with appropriate treatment like total resection followed by whole brain radiotherapy and adjuvant chemotherapy [2]. Due to an aggressive clinical course, extracranial metastases are very rare and are only reported in 2% of all patients with glioblastoma [3]. We report an extremely rare case of extracranial metastasis of supra-tentorial glioblastoma

*Correspondence: ozanbskrt@gmail.com

[1] Department of Neurosurgery, Kiziltepe Public Hospital, Kızıltepe, Mardin, Turkey
Full list of author information is available at the end of the article

involving the skin, subcutaneous and muscular layers, periauricular region and parotid gland and review the literature. A total of 13 glioblastoma parotid gland metastases cases have been hitherto described.

Main text

A 42-year-old male patient presented to our outpatient clinic with headache, syncope and tinnitus. Magnetic resonance imaging (MRI) scan revealed a mass lesion approximately 5*4 cm in size, with central hypointensity and peripheral contrast involvement located in the right temporal lobe causing a midline shift. The patient underwent subtotal resection of the tumor via temporal craniotomy as intense vascularization made a total removal impossible and was discharged without any neurological deficits a week later (Fig. 1). Pathological biopsy was reported as glioblastoma grade IV-NOS (not otherwise specified) (Fig. 2). The patient received 60 Gy/30 fractions radiotherapy (RT) with concurrent temozolomide at 75 mg/m^2 one month after surgery.

Seven months later, while continuing his chemotherapy, the patient developed left hemiparesis with muscle strength of 2/5. MRI demonstrated a recurrence approximately 6*5 cm in size, with a midline shift in the right temporal region. Emergency total removal of the tumor was made within temporal lobectomy (Fig. 3). Again, the biopsy was reported as glioblastoma (WHO Grade

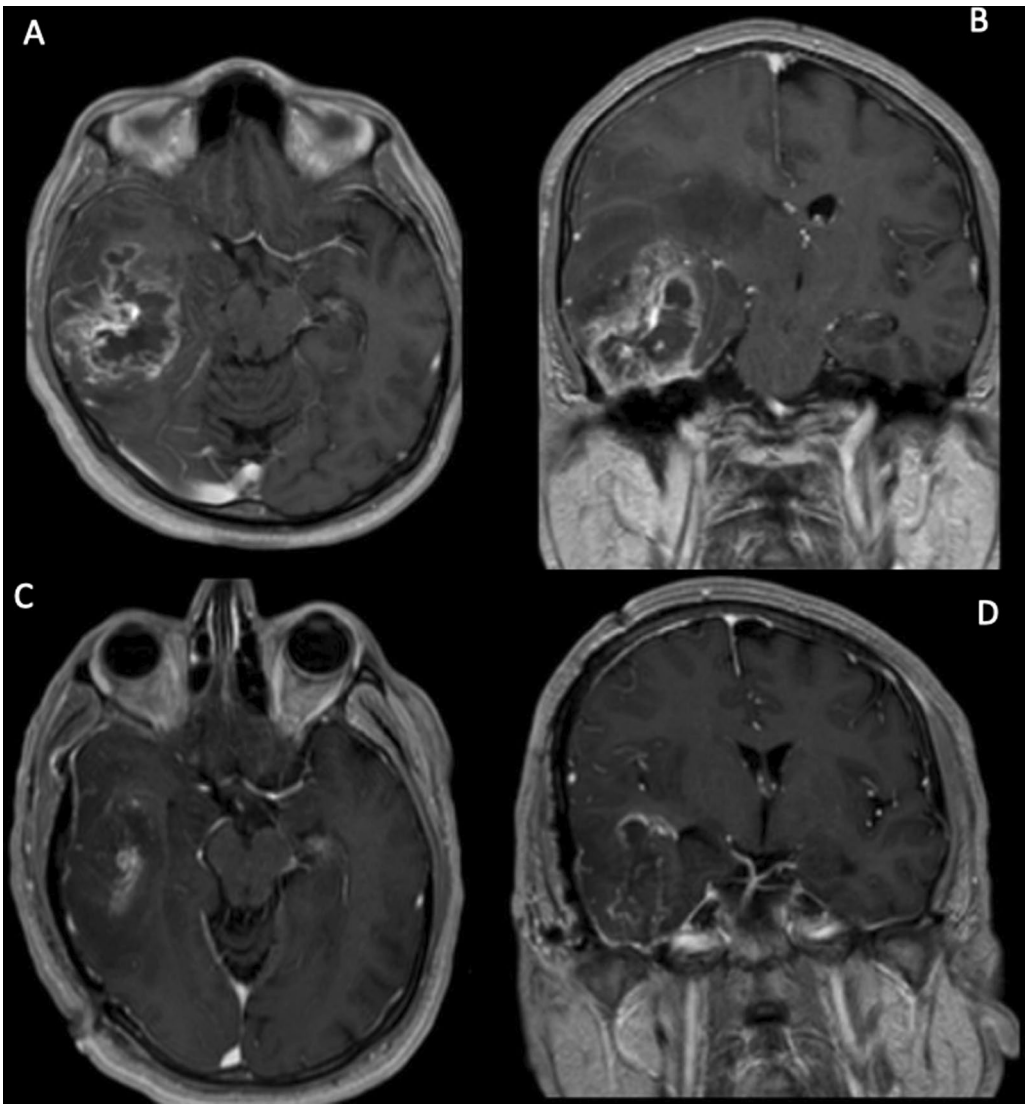

Fig. 1 Primary glioblastoma. **A**, **B** Preoperative axial and coronal cranial MRI scan. **C**, **D** Postoperative axial and coronal cranial MRI scan

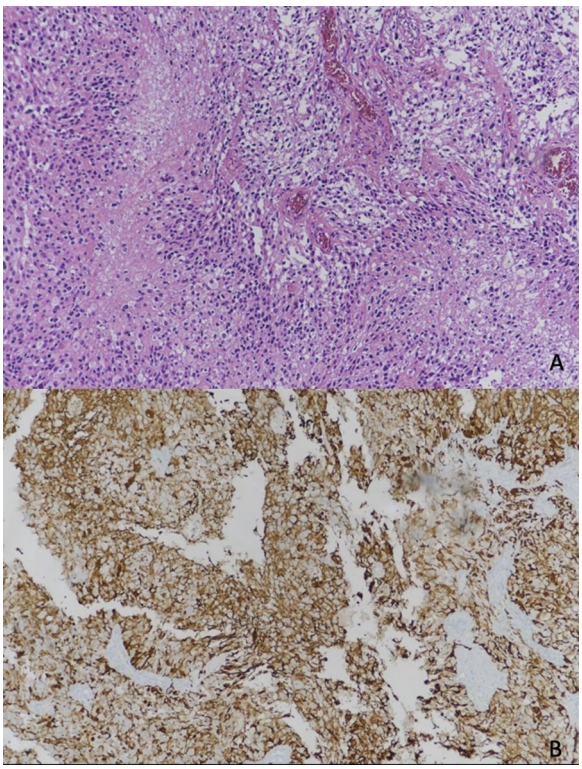

Fig. 2 Cellular tumor with palisading necrosis and vascular endothelial proliferation. **A** Haematoxylin and eosin (H&E*100). **B** GFAP positivity (IHC*100)

IV-NOS) (Fig. 4). The patient was discharged with left hemiparesis with muscle strength 3/5 and transferred to the physical rehabilitation unit. After the second surgery, chemotherapy was continued with bevacizumab irinotecan.

Fifteen months later, the patient complained of swelling in the right neck region. On ultrasonography (USG), a lesion with a heterogeneous internal structure with lobulated contours was observed in the right preauricular region. Intense vascularization was noted in the Doppler USG examination in which the superficial temporal artery passed through the lesion. On MRI, a heterogeneous internal mass lesion with lobulated contours infiltrating toward the superficial lobe of the parotid gland was observed. The mass extended to the upper part of the previous craniotomy border. Also, multiple pathological lymphadenopathies were detected in the right submandibular area (Fig. 5). Fine needle aspiration biopsy and tru-cut biopsy revealed a high-grade malignant tumor (Fig. 6). In the immunohistochemical (IHC) study; glial fibrillary acidic protein (GFAP) (Leica/ GA5) was positive in a small number of cells and Pan-cytokeratin (BioGenex/ AE1-AE3) was negative. The findings were evaluated with the diagnosis of glioblastoma in the patient's anamnesis and radiological features, and they were considered to be compatible with glioblastoma.

Despite salvage chemotherapy and adjuvant RT, on the 6 months follow-up, the neck swelling increased and the patient developed subcutaneous nodules in his scalp of the prior craniotomy scar. Cranial MRI revealed cortico-subcortical cystic encephalomalacia in the right temporal lobe, multiple new distinct lesions and recurrent intracranial tumor growth (Fig. 7). The patient declined any further treatment and continues his life 39 months after the primary diagnosis of intracranial glioblastoma.

Discussion

Glioblastoma are highly malignant primary brain tumors with a median survival of 15 months despite standard treatment which consists of debulking surgery, followed by RT and chemotherapy in selected patients [4]. Extracranial metastases are extremely rare with incidences between 0.2 and 2.7% due to the poor prognosis not allowing sufficient time to spread [5–7]. The implantation of tumor cells into extracranial blood vessels and lymphatics during the surgery is postulated as its main mechanism of spread [8]. In addition, postoperative neovascularization of the surgical field; especially the dura is estimated to lead to dissemination of these tumor cells [5]. Subependymal seeding or drop metastases via the cerebrospinal fluid are also considered as a possible cause [5, 7]. With all these pathophysiological theories, the physical disruption of the blood–brain barrier; scalp metastasis adjacent to the craniotomy, leptomeningeal spread to the spine, metastases to lymph nodes, to the abdomen via ventriculoperitoneal shunt or seeding along the biopsy tract has been documented. Also, there are reports presenting extracranial metastases of glioblastoma to the lungs, heart, pleura, liver and bone marrow [9, 10]. The parotid gland is the largest of the salivary glands in the head and neck. Its major function is to secrete saliva to participate in lubrication, digestion and immunity in the human body. It contains lymph nodes draining the lymph of the forehead, nasal root, upper lip, cheek, temple and external ear [11]. The majority of metastases in the parotid gland

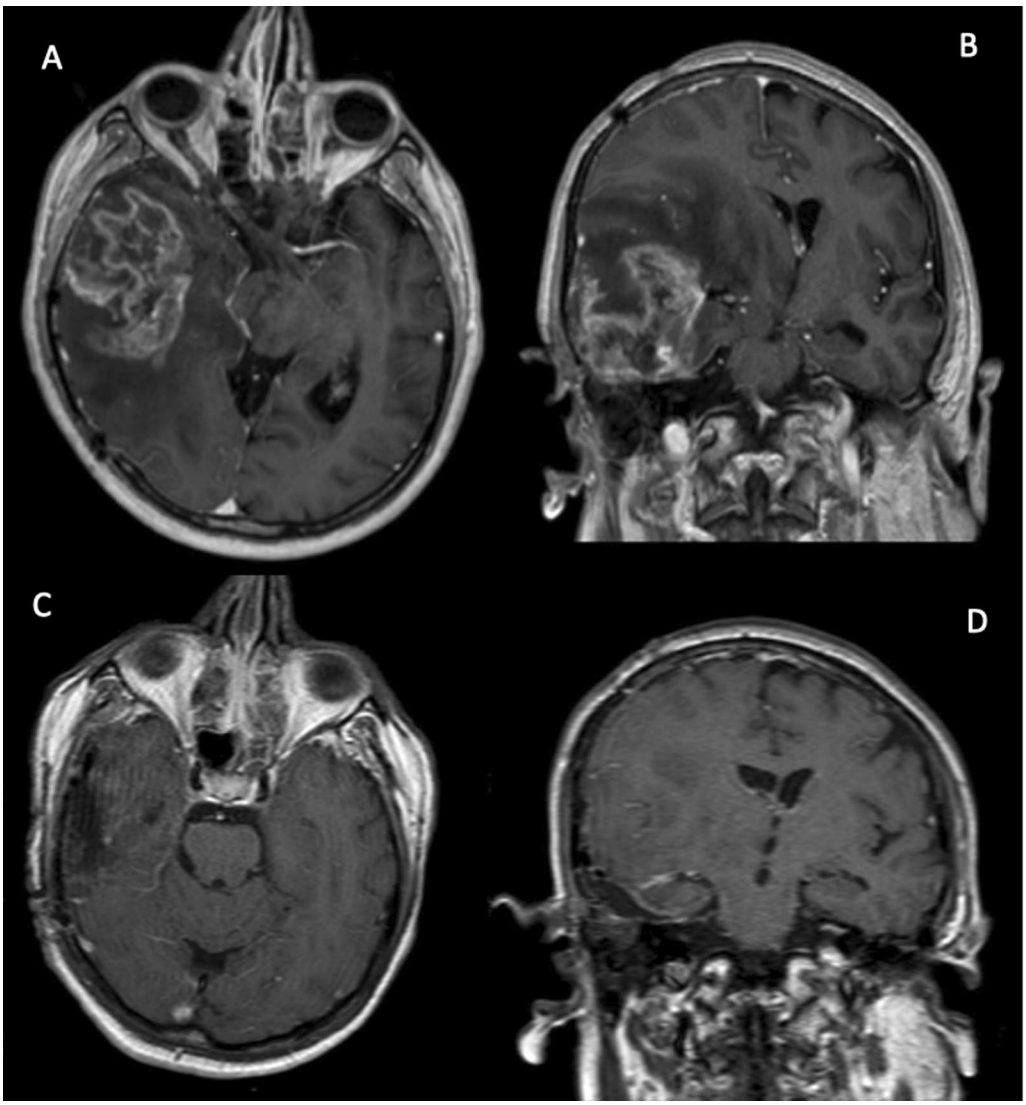

Fig. 3 Recurrence of the glioblastoma. **A**, **B** Preoperative axial and coronal cranial MRI scan. **C**, **D** Postoperative axial and coronal cranial MRI scan

arise from primary tumors of the head and neck which mostly develop by lymphomatous spread and rarely by hematogenously [12]. However, the exact mechanisms for metastases of glioblastoma to the parotid gland remain unknown. Despite some authors considering tumor seeding being a logical consequence to neighboring tissues near the surgical site, Nguyen et al. reported subgaleal metastasis on the contralateral side which can be an indication for possibly local vascular invasion of tumor cells [13]. In addition to this, Willis postulated that the thin-walled and poorly supported dura mater; central nervous system venules may permit metastatic spread [14]. But this theory does not explain how metastases to more distant organs work. We believe that the leptomeningeal dissemination and invasion of the superficial temporal artery by dural

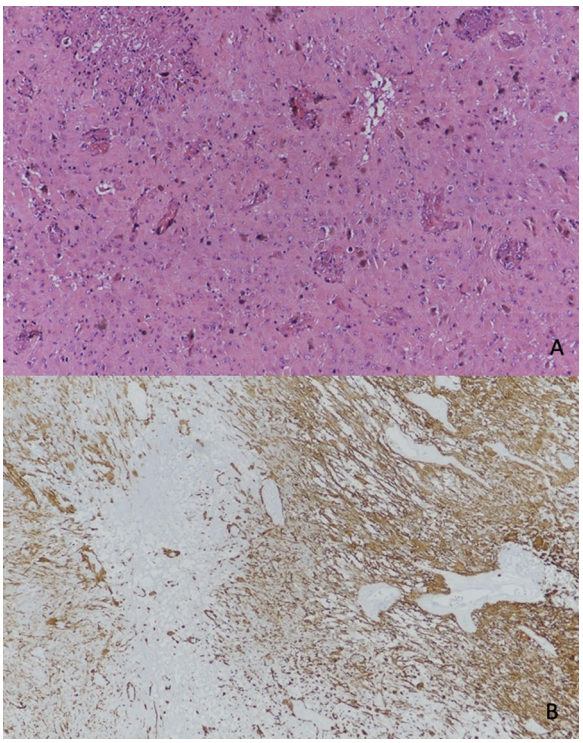

Fig. 4 Gemistocytic cells, areas of necrosis and vascular endothelial proliferation. **A** H&E*100. **B** GFAP positivity (IHC*100)

extension through the craniotomy defect are the most likely way of seeding in our patient. By reviewing the literature, the number of parotid gland metastases of glioblastoma is 13 together with our case (Table 1) [6, 15–25]. Age distribution ranged from 25 to 66 years, with an average of 46.15 years. Nine cases were men and four were women. In all cases, the location of the primary tumor was supra-tentorial; temporal in six cases, frontal in four and frontoparietal, temporoparietal and occipital in one case. The time between the diagnosis of the glioblastoma and spread to the parotid gland ranged from 3 months to 2 years with an average of 9.2 months which is almost identical to extracranial metastases to other organs. The onset of the symptoms ranged from immediately postoperatively to 14 months [26].

Cervical lymph nodes were noted as the area of concomitant metastasis which supports our pathophysiological theory. For the diagnosis of parotid gland metastases; authors have used different methods: cervical lymph node biopsy, parotid biopsy, fine needle aspiration cytology or parotidectomy. Likewise, it was seen that there was no consensus on the treatment. Only surgery, RT and/or chemotherapy in addition to surgery were among the options for palliative purposes. No standard treatment protocol is currently available for glioblastoma spreading to the parotid gland, whereas no significant difference in clinical efficacy has been observed between these treatment modalities [27].

Overall survival times in glioblastoma that develop extracranial metastases are not different from the expected survival in patients without metastatic disease; are which is roughly estimated as 12 months. It has been reported that the average life expectancy of patients with local intracranial tumor recurrence is 7.5 months [2, 3, 27]. Furthermore, according to data with parotid gland metastases, the median survival time from the time of extracranial disease diagnosis was found between 2 months and 2.5 years with an average of 9 months. Our patient was the patient who was found to have survived the longest.

Conclusions

Due to the recurrence rate of the intracranial glioblastoma and its malignant nature; close imaging follow-up is highly crucial. The increase in reported cases of extracranial metastases is generally due to the modern diagnostic tools and prolonged survival attributed to the improvement in treatment modalities, where now radical surgery with adjuvant RT and chemotherapy is the standard protocol. Patients with glioblastoma who experience enlargement of cervical lymph nodes developing mass lesions in the neck area should undergo further investigation to rule out parotid gland metastasis.

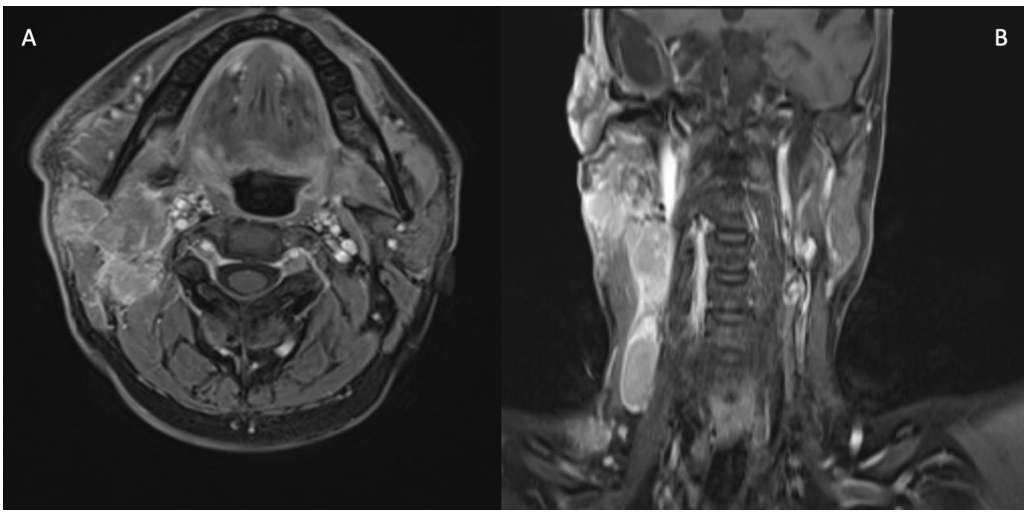

Fig. 5 Neck MRI scan (**A** axial- **B** coronal sections)

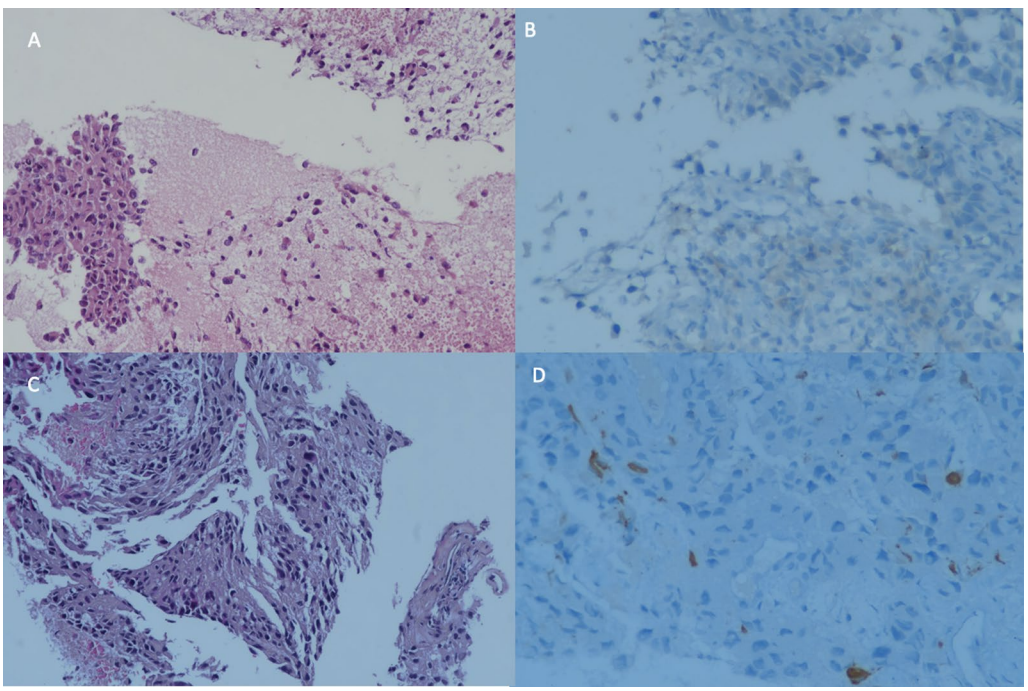

Fig. 6 Subcutaneous soft tissue biopsy. **A** Tumor cells in liquid-based cytology cell block (H&E*100). **B**. GFAP positivity in tumor cells in liquid-based cytology cell block (IHC*400). **C** Subcutaneous soft tissue tru-cut biopsy: pleomorphic tumoral infiltration with hyperchromatic nuclei within the fibrous stroma (H&E*100). **D**. Subcutaneous soft tissue tru-cut biopsy: GFAP circulating positivity (IHC*400)

Table 1 Metastasis of glioblastoma to the parotid gland reported in the literature

Authors, year	Cases								
	Sex	Age	Primary tumor	Site of tumor	Treatments	Metastasis timing	Concomittant metastasis (Other than parotid gland)	Treatments	Prognosis (Dx after metastasis)
Moghtader and Washington [15]	M	64	Astrocytoma (grade II WHO)	Temporal	Macroscopic total removal + postoperative RT (5070 r with Cobalt 60)	3 months	Intracranial, cervical lymph nodes, cheek,	Cervical node biopsy + Radical parotidectomy + radical neck dissection + Local RT	Died after 6 months
Megele et al. [16]	M	66	Malignant, protoplasmic astrocytoma (grade III WHO)	Temporal	Macroscopic total removal + postoperative RT (60 Gy)	9 months	Intracranial, cervical lymph nodes, mouth	Partial parotidectomy + Recurrence macroscopic total removal + Radical parotidectomy + radical neck dissection + The facial nerve reconstruction	Died after 4 months
Waite et al. [6]	M	40	Glioblastoma	Frontal	Macroscopic total removal + frontal lobectomy + postoperative RT (60 Gy)	2 years	Intracranial, cervical lymph nodes, submandibular	Tru-cut biopsy of the parotid mass	Died after 2 months
Park et al. [17]	F	25	Glioblastoma	Frontoparietal	Subtotal resection + external beam radiation therapy to 59.4 Gy	9 months	Intracranial, Scalp	Re- resection + external beam radiation therapy to scalp + Chemotherapy + VP shunt	Died after 1 year
Kühn et al. [18]	M	58	Glioblastoma	Temporal	Macroscopic total removal + temporal lobectomy + subsequent RT	9 months	Intracranial	Total parotidectomy	Unknown
Taha et al. [19]	M	33	Glioblastoma (grade IV WHO)	Frontal	Postoperative RT (60 Gy) + chemotherapy	6 months	Lymph nodes	Parotide biopsy (Local RT + PCV Chemotherapy)	Died after 3 months
Ogungbo et al. [20]	F	49	Glioblastoma (grade IV WHO)	Occipital	Postoperative RT (total 30 Gy) + chemotherapy (CCNU + Procarbazine)	5 months	Intracranial	Parotide biopsy	Died after 11 months
Kraft et al. [21]	M	58	Glioblastoma (grade IV WHO)	Temporal	Postoperative RT + palliative chemotherapy (Temozolomide)	15 months	Intracranial, orbita, lung and pleura, mediastinal lymph nodes, thoracic spine, femur, liver, left auricle heart	Total parotidectomy	Died after 2 months

Table 1 (continued)

Authors, year	Cases								
	Sex	Age	Primary tumor	Site of tumor	Treatments	Metastasis timing	Concomittant metastasis (Other than parotid gland)	Treatments	Prognosis (Dx after metastasis)
Taskapılıoglu et al. [22]	F	30	Glioblastoma (grade IV WHO)	Frontal	Postoperative RT + palliative chemotherapy (Temozolomide)	10 months	Bones, Lymph nodes	Radical parotidectomy + radical neck dissection	Died after 6 months
Romero-Rojas et al. [23]	M	26	Glioblastoma (grade IV WHO)	Frontal	Postoperative RT + palliative chemotherapy (Temozolomide)	6 months	Lymph nodes, bones	Fine needle aspiration cytology (FNAC)	Documented 2-year survival after diagnosis
Swinnen et al. [24]	F	56	Glioblastoma (grade IV WHO-IDH wildtype)	Temporal	Postoperative RT + palliative chemotherapy (Temozolomide + Axitinib + Avelumab)	3.5 months	Intracranial, lymph nodes, lung	Fine needle aspiration cytology (FNAC)	Died after 11 months
Alhoulaiby et al. [25]	M	53	Glioblastoma (grade IV WHO)	Temporoparietal	Postoperative RT (total 60 Gy) + chemotherapy (Temozolomide)	6 months	Intracranial, bones	Parotide biopsy	Died after 4 months
Başkurt et al. this study	M	42	Glioblastom (grade IV WHO—NOS)	Temporal	Microscopic grosstotal removal + postoperative RT (60 Gy) + chemotherapy (Temozolomide)	15 months	Intracranial, cervical lymph nodes,	Parotide biopsy Fine needle aspiration cytology (FNAC)	Still alive

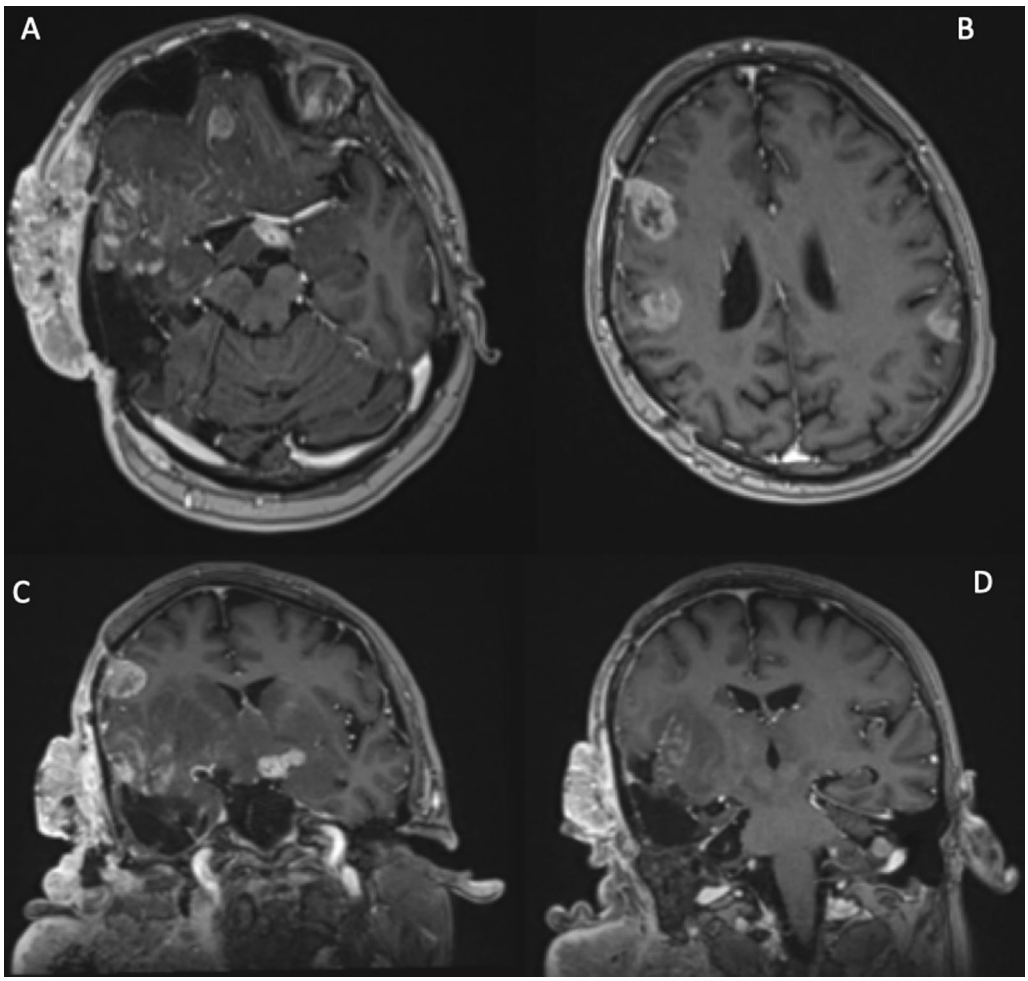

Fig. 7 Cranial MRI scan. **A**, **B** axial sections. **C**, **D** coronal sections

Abbreviations
GFAP: Glial fibrillary acidic protein; H&E: Haematoxylin and eosin stain; IHC: Immunohistochemical; MRI: Magnetic resonance imaging; NOS: Not otherwise specified; RT: Radiotherapy; USG: Ultrasonography; WHO: World Health Organization.

Acknowledgements
Not applicable.

Author contributions
OB and YK performed literature research and analysis of the originality of the case. The writing phase was done by the whole team. AYY and IA were supervised. All authors read and approved the final manuscript.

Funding
No funding.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Informed consent was obtained from the patient included in this study.

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

Author details
[1]Department of Neurosurgery, Kiziltepe Public Hospital, Kızıltepe, Mardin, Turkey. [2]Department of Neurosurgery, Adiyaman Training and Research Hospital, Adiyaman, Turkey. [3]Department of Neurosurgery, Prof. Dr. Cemil Tascioglu State Hospital, Istanbul, Turkey. [4]Department of Neurosurgery, Mehmet Akif Inan Training and Research Hospital, Sanliurfa, Turkey.

Received: 4 August 2021 Accepted: 17 May 2022
Published online: 18 July 2022

References

1. Wirsching HG, Galanis E, Weller M. Glioblastoma. Handb Clin Neurol. 2016;134:381–97.
2. Campos B, Olsen LR, Urup T, Poulsen HS. A comprehensive profile of recurrent glioblastoma. Oncogene. 2016;35(45):5819–25. https://doi.org/10.1038/onc.2016.85.

3. Lun M, Lok E, Gautam S, Wu E, Wong ET. The natural history of extracranial metastasis from glioblastoma multiforme. J Neurooncol. 2011;105(2):261–73.
4. Alexander BM, Cloughesy TF. Adult glioblastoma. J Clin Oncol. 2017;35(21):2402–9.
5. Buhl R, Barth H, Hugo HH, Hutzelmann A, Mehdorn HM. Spinal drop metastases in recurrent glioblastoma multiforme. Acta Neurochir (Wien). 1998;140(10):1001–5.
6. Waite KJ, Wharton SB, Old SE, Burnet NG. Systemic metastases of glioblastoma multiforme. Clin Oncol. 1999;11(3):205–7.
7. Amitendu S, Mak SKD, Ling JM, Ng WH. A single institution experience of the incidence of extracranial metastasis in glioma. J Clin Neurosci. 2012;19(11):1511–5. https://doi.org/10.1016/j.jocn.2011.08.040.
8. Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA - J Am Med Assoc. 2013;310(17):1842–50.
9. Yokoyama H, Ono H, Mori K, Kishikawa M, Kihara M. Extracranial metastasis of glioblastoma with sarcomatous component. Surg Neurol. 1985;24(6):641–5.
10. Allan RS. Scalp metastasis from glioblastoma. J Neurol Neurosurg Psychiatry. 2004;75(4):559.
11. Kochhar A, Larian B, Azizzadeh B. Facial nerve and parotid gland anatomy. Otolaryngol Clin North Am. 2016;49(2):273–84.
12. Franzen AM, Günzel T, Lieder A. Parotid gland metastases of distant primary tumours: a diagnostic challenge. Auris Nasus Larynx. 2016;43(2):187–91.
13. Nguyen B, Samara J, Lee A, Fadia M, Ngu C, Pranavan G. A case of subgaleal metastasis from glioblastoma multiforme. Intern Med J. 2018;48(6):741–2.
14. Willis RA. The spread of tumours in the human body, vol. 29, Postgraduate Med J. 1953. p. 160.
15. Moghtader A. Cervical and parotid metastasis secondary to cerebral astrocytoma. Report Case Laryngoscope. 1966;76(11):1834–41.
16. Megele R, Gruß P, Biihrmonni K. Fallberichte - Case reports Das extr akr aniell metastasierende maligne Gliom-iatrogen ?. 157–9.
17. Park CC, Hartmann C, Folkerth R, Loeffler JS, Wen PY, Fine HA, et al. Systemic metastasis in glioblastoma may represent the emergence of neoplastic subclones. J Neuropathol Exp Neurol. 2000;59(12):1044–50.
18. Kühn U, Köhler HH, Jecker P. Seltene parotistumoren: Talgdrüsenlymphadenom und extrakranielle glioblastommetastase. HNO. 2003;51(5):417–20.
19. Taha M, Ahmad A, Wharton S, Jellinek D. Extra-cranial metastasis of glioblastoma multiforme presenting as acute parotitis. Br J Neurosurg. 2005;19(4):348–51.
20. Ogungbo BI, Perry RH, Bozzino J, Mahadeva D. Report of GBM metastasis to the parotid gland [4]. J Neurooncol. 2005;74(3):337–8.
21. Kraft M, Lang F, Braunschweig R, Janzer RC. Parotid gland metastasis from glioblastoma multiforme: A case report and review of the literature. Eur Arch Oto-Rhino-Laryngol. 2008;265(6):709–11.
22. Taskapilioglu MO, Aktas U, Eser P, Tolunay S, Bekar A. Multiple extracranial metastases from secondary glioblastoma: a case report and review of the literature. Turk Neurosurg. 2013;23(6):824–7.
23. Romero-Rojas AE, Diaz-Perez JA, Amaro D, Lozano-Castillo A, Chinchilla-Olaya SI. Glioblastoma metastasis to parotid gland and neck lymph nodes: fine-needle aspiration cytology with histopathologic correlation. Head Neck Pathol. 2013;7(4):409–15.
24. Swinnen J, Gelin G, Fransis S, Vandevenne J, Van Cauter S. Glioblastoma with extracranial parotid, lymph node, and pulmonary metastases: a case report. Radiol Case Rep. 2019;14(11):1334–47. https://doi.org/10.1016/j.radcr.2019.08.011.
25. Alhoulaiby S, Abdulrahman A, Alouni G, Mahfoud M, Shihabi Z. Extra-CNS metastasis of glioblastoma multiforme to cervical lymph nodes and parotid gland: a case report. Clin Case Reports. 2020;8(9):1672–7.
26. Vertosick FTJ, Selker RG. Brain stem and spinal metastases of supratentorial glioblastoma multiforme: a clinical series. Neurosurgery. 1990;27(4):512–6.
27. Piccirilli M, Brunetto GMF, Rocchi G, Giangaspero F, Salvati M. Extra central nervous system metastases from cerebral glioblastoma multiforme in elderly patients: clinico-pathological remarks on our series of seven cases and critical review of the literature. Tumori. 2008;94(1):40–51.

Publisher's Note