

Abscess Formation in Metastatic Brain Tumor with History of Immune Checkpoint Inhibitor: A Case Report

Takeshi Takayasu,¹ Fumiyuki Yamasaki,¹ Takeo Shishido,² Motoki Takano,¹ Hirofumi Maruyama,² Kazuhiko Sugiyama,³ and Kaoru Kurisu¹

We present the case of a 68-year-old man with brain metastasis from lung cancer and a history of immune checkpoint inhibitor administration, with overlapping abscess within the metastatic lesion. He initially received antibiotic treatment under a diagnosis of brain abscess because of a hyper-intense area on diffusion-weighted imaging inside the gadolinium-enhanced wall. The size of the enhanced lesion did not change much, but the extent of perifocal edema decreased after antibiotic treatment. After 2–4 months, the lesion gradually enlarged, and imaging characteristics changed from single cyst to multiple cysts. Surgical resection was performed and pathological examination revealed the lesion as metastasis from the lung tumor. Smear preparation of the tumor contents detected Gram-positive bacilli, confirming the dual pathology of metastasis and brain abscess. Discussing the pathogenesis, we speculated that therapy with durvalumab (MEDI4736), an anti-PD-L1 antibody, induced immune status modification including immunosuppressive regulation, which might have promoted abscess formation.

Keywords: brain abscess, metastatic brain tumor, dual pathology, immune checkpoint inhibitor

Introduction

Signal hyper-intensity on diffusion-weighted imaging (DWI) inside a gadolinium-enhanced rim is the most well-known and important imaging characteristic of brain abscess, and is useful for differentiating this pathology from other ring-enhancing lesions.^{1–3} However, some acutely necrotic or hemorrhagic malignant brain tumors have been reported to show high intensity on DWI with restricted diffusion of contents.^{3–5} Furthermore, we must keep in mind the rare clinical condition of abscess formation within a tumor.^{6–11} Even using

advanced magnetic resonance (MR) imaging techniques including DWI, precise preoperative diagnosis of co-existing abscess and brain tumor seems difficult.

We present a case of metastatic brain tumor with a history of immune checkpoint inhibitor administration, accompanied by intratumoral abscess formation, initially treated as brain abscess because of a hyper-intense appearance on DWI.

Case

A 68-year-old man with lung pleomorphic carcinoma had received durvalumab (MEDI4736) therapy in a clinical trial. The patient had undergone resection of the original lung cancer about 9 months earlier (day–280). He had received two cycles of carboplatin and paclitaxel chemotherapy (1st cycle on day–238: carboplatin AUC6 and PTX 200 mg/m², 2nd cycle on day–205: carboplatin AUC5 and PTX 160 mg/m²) and 1 cycle of cisplatin (64 mg/m²) and vinorelbine (20 mg/m²) chemotherapy (on day–154) at another hospital before undergoing treatment with durvalumab (MEDI4736). Screening whole-body computed tomography (CT) before the clinical trial had not detected any abnormal lesions (day–106) and tumor markers showed: carcinoembryonic antigen (CEA), 1.8 ng/ml; and cytokeratin subunit 19 fragment (CYFRA), 1.4 ng/ml. Four administrations of durvalumab had been performed every 4 weeks (days–97, –69, –41, and –13) and had not caused any clinical complications other than sustained lymphocytopenia. However, CYFRA increased successively to 6.9 ng/ml (day–69), 8.9 ng/ml (day–41), and 19.7 ng/ml (day–13). A metastatic lesion in the left femur was then detected on CT (day–17) and positron emission tomography (day–6). Screening brain MR imaging (day–3) with contrast enhancement then revealed a 1.3-cm ring-enhancing mass lesion in the left medial temporal lobe (Figs. 1A and 1B). The internal part of the enhanced rim appeared hyper-intense on DWI (Fig. 1C) and hypo-intense on an apparent diffusion coefficient (ADC) map (Fig. 1D). Body temperature was 36.6°C. Laboratory testing (day–1) showed: white blood cells, 3560/μl; neutrophils, 3100/μl; lymphocytes, 420/μl; monocytes, 20/μl; hemoglobin, 10.1 g/dl; platelets, 290 × 10³/μl; C-reactive protein (CRP), 2.89 mg/dl; procalcitonin (PCT), 0.03 ng/ml; and beta-D-glucan, <6 pg/ml. The patient showed no neurological manifestations. He also had no recent history of infectious diseases such as middle otitis, paranasal sinusitis, gingivitis, or bronchitis.

Because of the typical imaging characteristics, we diagnosed the lesion as brain abscess. As a result, administration

¹Department of Neurosurgery, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Hiroshima, Japan

²Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Hiroshima, Japan

³Department of Clinical Oncology & Neuro-oncology Program, Hiroshima University Hospital, Hiroshima, Hiroshima, Japan

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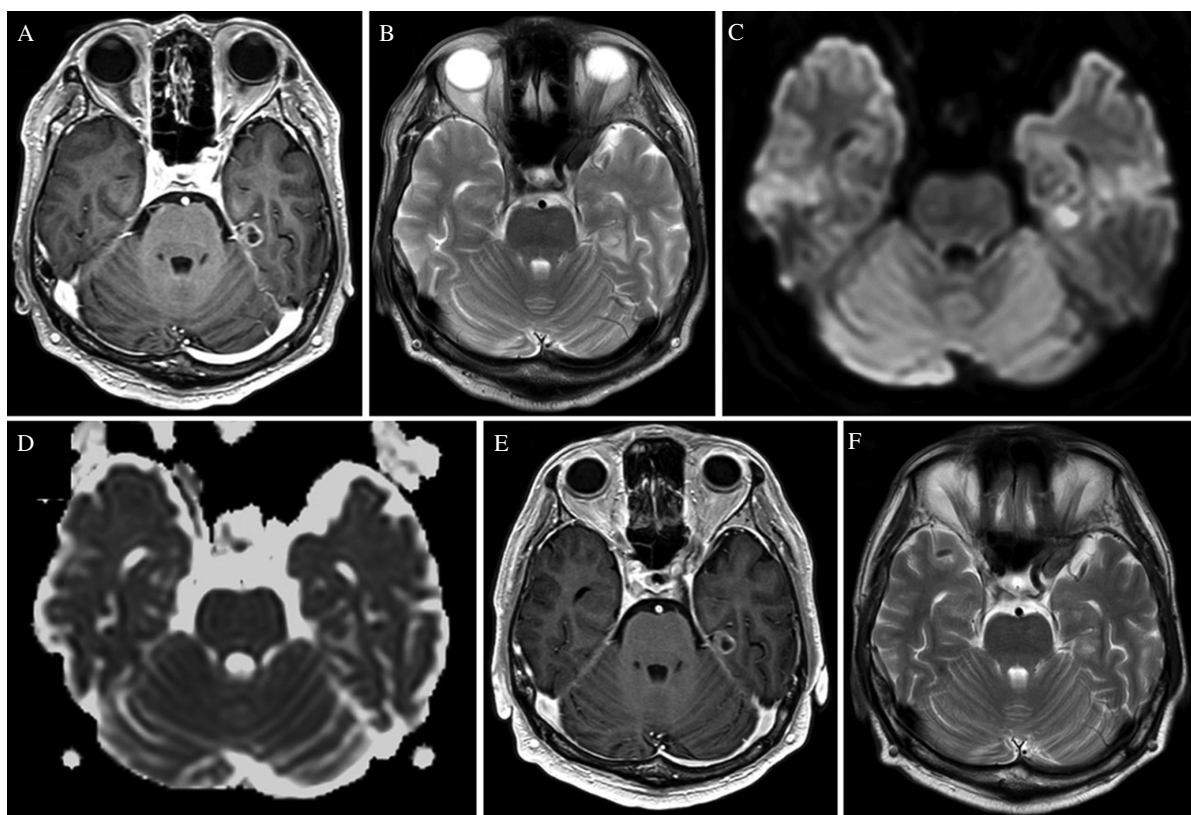


Fig. 1 A ring-enhanced lesion in the left medial temporal lobe (A), accompanied by edema around the lesion (B). The inside appears hyper-intense on diffusion-weighted imaging (C) and hypo-intense on the apparent diffusion coefficient map (D). A week after beginning antibiotic therapy (day 7), the lesion has reduced in size slightly (E) and the edematous area around the lesion has decreased (F).

of meropenem (2 g every 8 h) and vancomycin (1.0–1.5 g every 12 h) was started (day 1). After 1 week, MR images suggested the efficacy of antibiotics (Figs. 1E and 1F). We therefore continued antibiotic treatment. Nevertheless, the patient developed fever (maximum body temperature, 39.3°C), and blood testing showed that CRP was 5.38 mg/dl on day 12, while CRP was 17.83 mg/dl and PCT was 0.9 ng/ml on day 14. Cerebrospinal fluid (CSF) examination from lumbar tap on day 15 revealed: cell count, <1/μl; glucose, 75 mg/dl; and protein, 43 mg/dl, although this was after beginning antibiotics. Culture of the CSF had not detected any bacteria, and cytology had demonstrated no malignant cells. Tumor markers were still high, with CEA at 6.7 ng/ml and CYFRA at 16 ng/ml on day 15. The clinical course is shown in Fig. 2.

For a metastatic lesion in the left femur, the patient received radiation (39 Gy/13 fr) from day 20 to day 42, and three cycles of docetaxel (48 mg/m²) and ramucirumab (8 mg/kg) chemotherapy on days 48, 76, and 103. Until day 116, we also continued antibiotic administration while changing drugs. Fever improved during treatment and CRP decreased to 1.14 mg/dl on day 103. The fever was thus considered to be neoplastic fever. Both CEA and CYFRA decreased to 2.3 ng/ml on day 103, and follow-up CT on day 120 showed partial response of the left femoral metastasis. However, the left temporal lobe lesion gradually enlarged, reaching 1.6 cm on day 78, 2.2 cm on day 106, and 2.6 cm on day 119 (Fig. 3). Imaging

characteristics changed from a single cyst to multiple cysts (Fig. 3). We then reconsidered whether the lesion was a metastatic brain tumor. The elevated tumor markers could conceivably have been largely attributable to the left femoral metastasis. Although the patient still showed no neurological symptoms, we decided to perform surgical resection. The lesion was slightly harder than the brain parenchyma and contained whitish creamy fluid (Fig. 4). Total removal of the lesion was achieved. The pathological diagnosis was metastatic squamous cell carcinoma (Fig. 5A). In addition, smear preparation of the whitish creamy fluid detected Gram-positive bacilli (Fig. 5B). Finally, we diagnosed that the lesion as a dual pathology comprising metastatic brain tumor associated with abscess formation.

Discussion

Ring enhancement on gadolinium contrast-enhanced T1-weighted imaging (T1WI) is a feature of a variety of intracranial pathologies, including brain metastases, brain abscess, glioma, infarct, encephalitis, and demyelinating diseases, radiation necrosis, and lymphoma. Differentiating between these ring-enhancing lesions is difficult with conventional MRI sequences. DWI provides information about water diffusion and many studies have confirmed the utility of DWI in distinguishing between brain abscesses and other lesions with ring enhancement, since brain abscess shows markedly high intensity on DWI.^{1–3,5} Accordingly, we initially

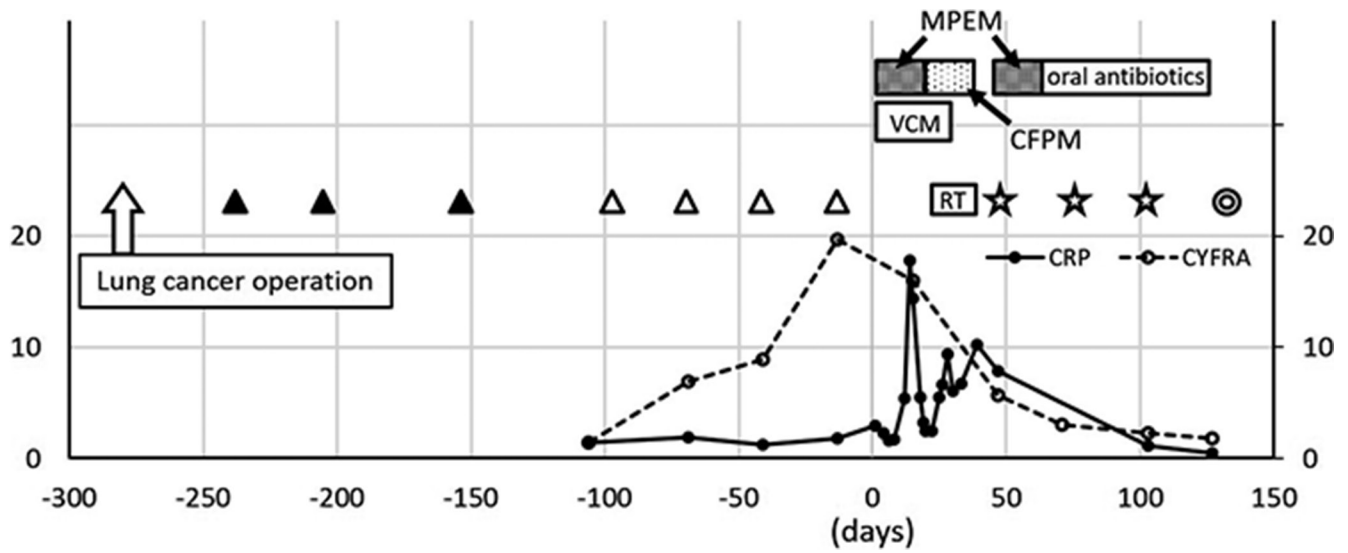


Fig. 2 Summarized clinical course. Each symbol indicates clinical events as follows: closed triangle, first-line chemotherapy for lung cancer; open triangle, administration of durvalumab (MEDI4736); star, chemotherapy for the left femoral metastasis; and double circle, surgical resection of the left temporal lesion. Time courses of CRP (mg/dl) and CYFRA (ng/ml) are also shown. Data before durvalumab are unavailable because previous treatments were provided at another hospital. MEPM: meropenem, VCM: vancomycin, CFPM: cefepime, RT: radiotherapy for the left femoral metastasis. Oral antibiotics consisted of levofloxacin and metronidazole.

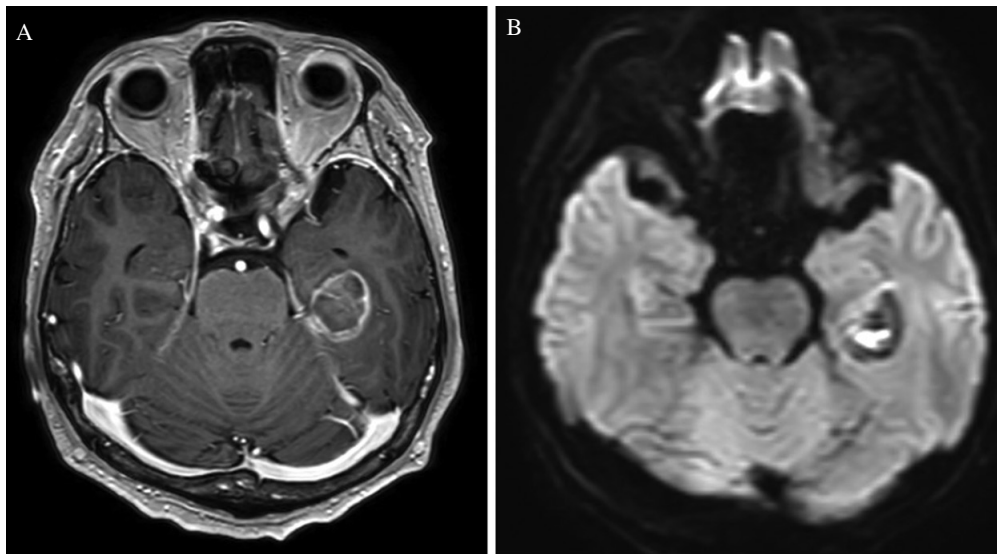


Fig. 3 Post-contrast MRI on day 119 demonstrates an enlarged lesion (A), and the contents show heterogeneous hyper- and hypointensity on DWI (B).

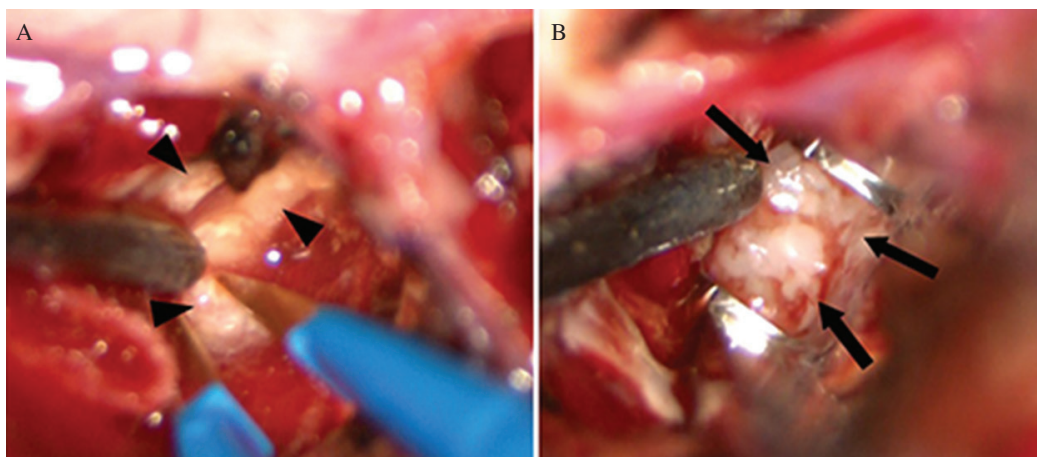


Fig. 4 Operative view of the lesion containing whitish, pus-like fluid (arrowheads) (A). Tumor shows a slightly grayish appearance (arrows) (B).

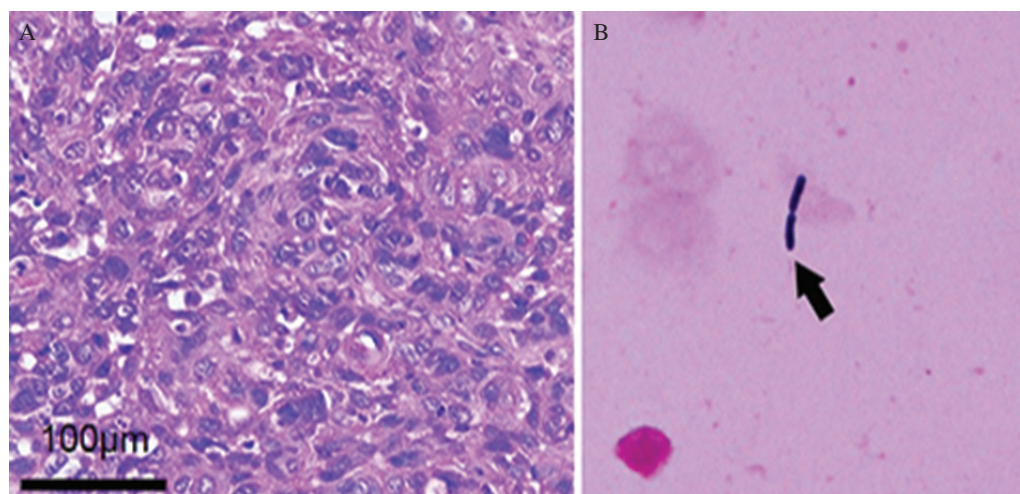


Fig. 5 Hematoxylin and eosin staining of tumor sections. Pathological findings indicate metastatic squamous cell carcinoma. The tumor cells are arranged in a trabecular pattern with focal squamous differentiation. Large tumor cells contain highly pleomorphic and hyperchromatic nuclei (A). Microscopic examination of the content smear shows Gram-positive bacilli (arrow) (B).

diagnosed the lesion in this case as brain abscess based on the high intensity on DWI and low intensity on the ADC map. Improvement of the edema around the lesion after first-line antibiotic therapy, fever, and elevated CRP supported this diagnosis. Nevertheless, the lesion grew from 1.3 to 2.6 cm in diameter within about 4 months. We corrected the diagnosis to metastatic brain tumor, because several cases of necrotic brain metastasis or high-grade glioma with signal hyper-intensity on DWI have been reported. The reasons for restricted diffusion might include early necrosis with intracellular edema of the region and high viscosity of content fluid with proteinaceous degradation products. In lesions with ring enhancement, restricted diffusion might be characteristic, but does not always indicate brain abscess.^{3,4)} Although DWI shows difficulty in differentiating between brain tumor and abscess or co-existing tumor with abscess, Campenni et al.⁶⁾ reported the utility of immunoscintigraphy with ^{99m}Tc-labeled sulesomab (LeukoScan). LeukoScan binds to an antigen of activated neutrophils, and infectious lesions can be detected as an uptake of tracer.

Surgical resection of the lesion surprisingly demonstrated the dual pathology of metastatic tumor and abscess formation in our case. The co-existence of brain abscess and metastatic brain tumor is a rare clinical condition, but some cases have been reported.^{7,8,10)} The pathogenesis of abscess formation within brain tumor is considered to be related to both systemic and local factors. Systemic factors include immunodeficiency due to steroid therapy, poor nutrition, or chemotherapy. Local factors include failure of the blood–brain barrier (BBB), tumor bleeding and intratumoral necrosis. Deterioration of the BBB due to tumor invasion and neovascularization could lead to invasion of bacteria into a tumor. Tumor bleeding or central necrosis would act as a culture medium for bacteria.^{6–11)} Those authors seem to be considering the mechanism of abscess formation as involving a metastatic brain tumor arising earlier and infection occurring there. In our case, we also thought that the initial lesion was a metastasis. The patient was without any recent history of infectious disease that could have caused brain abscess as a primary lesion, but was in an immunocompromised condition. Due to the previous chemotherapy he had shown sustained lymphocytopenia and monocytopenia. In addition, he had received

durvalumab (MEDI4736) therapy. Durvalumab is an anti-PD-L1 antibody, and an immune checkpoint inhibitor. Immune checkpoint inhibitors are thought to have favorable toxicity profiles compared to cytotoxic chemotherapy. Common adverse effects of immune checkpoint inhibitors are known as immune-related adverse events, and can include endocrine, cutaneous, hepatic and gastrointestinal toxicities. However, some reports have documented the PD-1 antibody nivolumab causing severe neutropenia or opportunistic infections.^{12–15)} Wang et al.¹⁶⁾ reported that nivolumab caused immunosuppressive regulation, possibly due to feedback mediated by blockade of the PD-1/PD-L1 signaling pathway. We thus speculated that the brain metastasis formed first, then PD-L1 blockade and subsequent immunosuppressive regulation might have promoted abscess formation at the same site in this case.

Conclusion

Preoperative diagnosis of dual pathologies such as metastatic brain tumor and abscess is difficult even with advanced MR sequences. In cases with lesion growth after antibiotic treatment for suspected brain abscess, we should consider the possibility of abscess overlapping brain tumor.

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Conflicts of Interest Disclosure

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The other authors have nothing to disclose.

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Corresponding author:

Takeshi Takayasu, Department of Neurosurgery, Institute of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima734-8551, Japan.

✉ ttakayasu-nsu@umin.ac.jp