

CASE REPORT

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Antibody-Drug Conjugates as a Potential a Systemic Treatment Strategy for Brain Metastases in Cases of Solid Tumors

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ABSTRACT Large molecular antibody–drug conjugates (ADCs) are able to easily access the site of metastasis in the brain due to the edematous structure of brain metastases, facilitating considerably high concentrations of the cytotoxic component of these ADCs in the intracellular and peritumoral environment. The present study discusses the cases of two different patients. The first patient had lung adenocarcinoma with asymptomatic brain metastases, visceral metastases, and bone metastases, and was treated with Sacituzumab govitecan. The second patient had HER2-positive breast cancer with lung and brain metastases, received treatment with Trastuzumab deruxtecan. The use of ADC achieved a complete response in brain metastases in both cases. Accordingly, it is suggested that efficacy evaluations regarding brain metastases should be investigated as a separate secondary endpoint in studies conducted on the use of ADC and that brain metastases should be included as a special research topic in antibody drug design and development.

Keywords: Immunoconjugates; brain neoplasms; brain edema

Brain metastases are common in solid tumors, with lung and breast cancers among the most common cancers with brain metastases. Brain metastases develop in 10%-36% of all cases of lung cancer and 10%-16% of all cases of breast cancer, affecting the prognosis of these patients negatively.¹⁻³ The incidence of brain metastasis is particularly higher in the cases of non-small cell lung cancer (NSCLC) with EGFR or ALK mutation, with metastasis observed in 50%-60% of these patients.^{4,5} Median survival in patients of lung cancer with brain metastases ranges from 3 months to 46.8 months, and this variation is attributed to the potent effects of ALK and EGFR inhibitors on brain metastases in eligible NSCLC patients.⁶ A meta-analysis of patients with breast cancer revealed that 31% of HER2-positive patients, 32% of triple-negative patients, and 15% of hormone recep-

tor-positive and HER2-negative patients with metastatic breast cancer developed brain metastases.⁷ Median survival in breast cancer patients with brain metastases is just 14.4 months.⁸ The prognosis is worse in triple-negative breast cancer patients with brain metastases, who present a median survival of just 3.4 months, while the corresponding duration is 20.3 months in HER2-positive patients.^{9,10} Significant advances have been achieved in the systemic treatment of brain metastases in cases of certain tumors such as ALK and EGFR-positive NSCLC. The cases of brain metastases in most solid tumors, on the other hand, remain to achieve improvements in this regard.

Antibody-drug conjugates (ADCs) are prepared by combining an antibody and a cytotoxic agent developed against an antigen of cancer cells with a strong bond. When the ADCs reach the antigen-ex-

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pressing tumor cells, cytotoxic molecules are released. After the destruction of the target tumor cells, these cytotoxins are released into the cellular environment, which affects the neighboring tumor cells as well. This phenomenon is referred to as a bystander effect, in which the cells that do not express the antigen are also killed.¹¹

Since brain metastases have an edematous structure, large molecular ADCs have easy access to the site of metastasis in the brain. This facilitates reaching considerably high doses of the cytotoxic component in the intracellular and peritumoral environment, causing brain metastases to be exposed to intense cytotoxicity. This mechanism enables achieving deeper responses in brain metastases with the use of ADCs.

In the text ahead, the cases of two patients treated with ADCs are presented in the context stated above.

CASE REPORT

CASE 1

A 56-year-old woman was admitted to the emergency department when she had an epileptic seizure in July 2021. Mass excision was performed after the cranial magnetic resonance imaging (MRI) results revealed a solitary left temporal mass. The results of pathological analysis were consistent with lung adenocarcinoma. Thorax abdominal computed tomography (CT) revealed a T3Nx mass in the right lung. The pa-

tient underwent whole-brain radiotherapy after surgery. The systemic treatments used for the patient and the results achieved are presented in Figure 1.

In November 2022, Sacituzumab govitecan was administered at a dosage of 10 mg/kg on Day 1, and 8 q21 was commenced for this patient with multiple asymptomatic brain metastases, visceral metastases, and bone metastases. Complete response was achieved after 6 weeks, as revealed in the control cranial MRI analysis. Thorax and abdominal CT revealed partial response, and similar findings were obtained in the follow-up (Figure 2).

CASE 2

A 47-year-old woman with ER and PR-negative, HER2-positive invasive breast carcinoma along with *de novo* bone metastases and multiple liver metastases was treated with docetaxel, pertuzumab, trastuzumab, followed by maintenance treatment with trastuzumab and pertuzumab. Imaging performed 21 months after the diagnosis revealed a 1.5 cm metastatic nodular lesion in the left lung and a 35*17 mm metastatic mass lesion in the left cerebral hemisphere. Trastuzumab deruxtecan at a dosage of 5.4 mg/kg q21 was commenced. Control imaging after treatment revealed regression of the metastatic lesion in the lung and complete response to treatment in the cranial metastases. The systemic treatments used for the patient and the results achieved are presented in Figure 3.

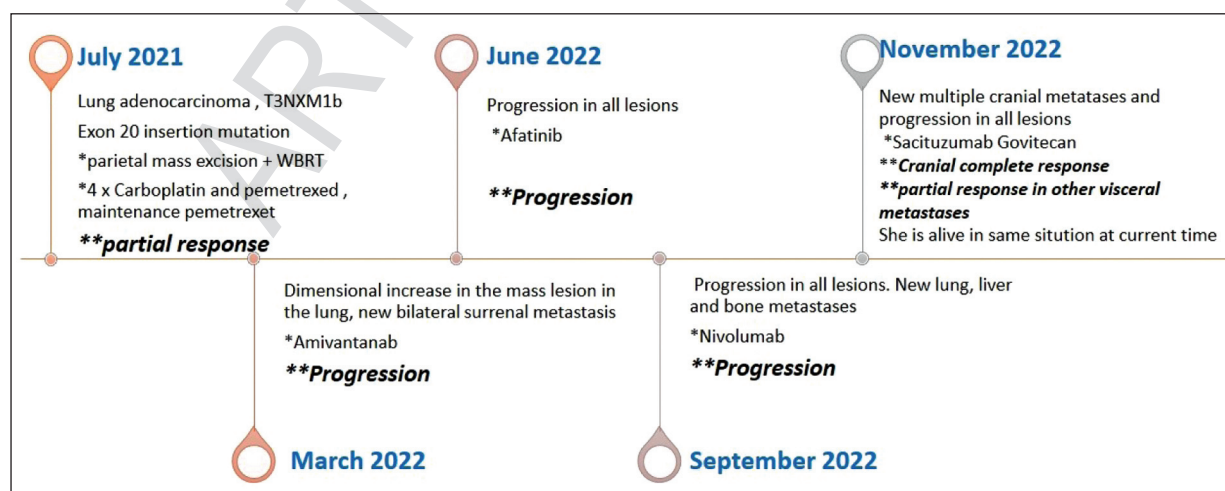


FIGURE 1: Systemic treatments used and the results achieved for the patient who underwent whole brain radiotherapy after surgery.

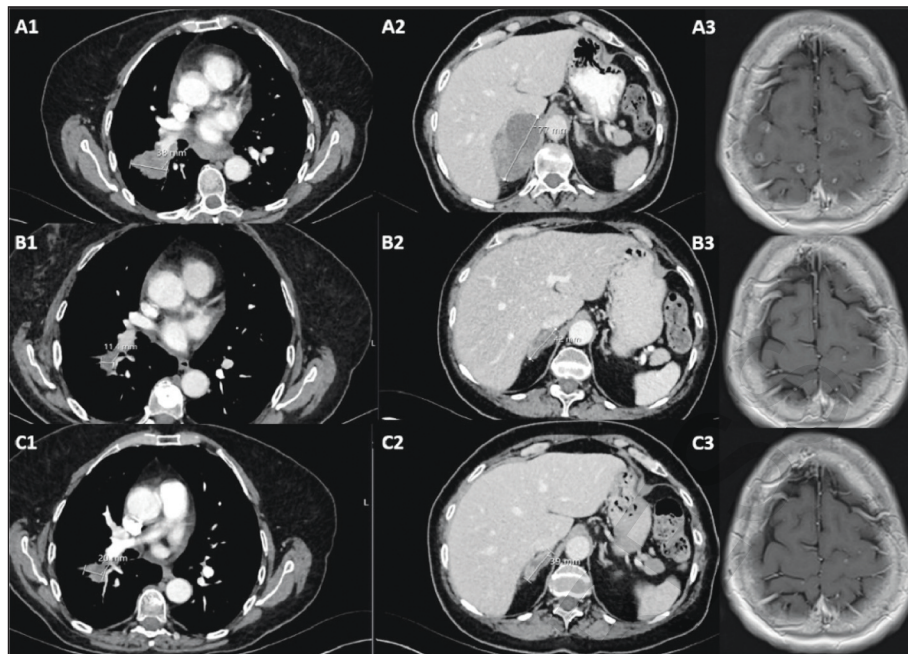


FIGURE 2: Thorax and abdominal computed tomography revealing partial response, and similar findings obtained in the follow-up.

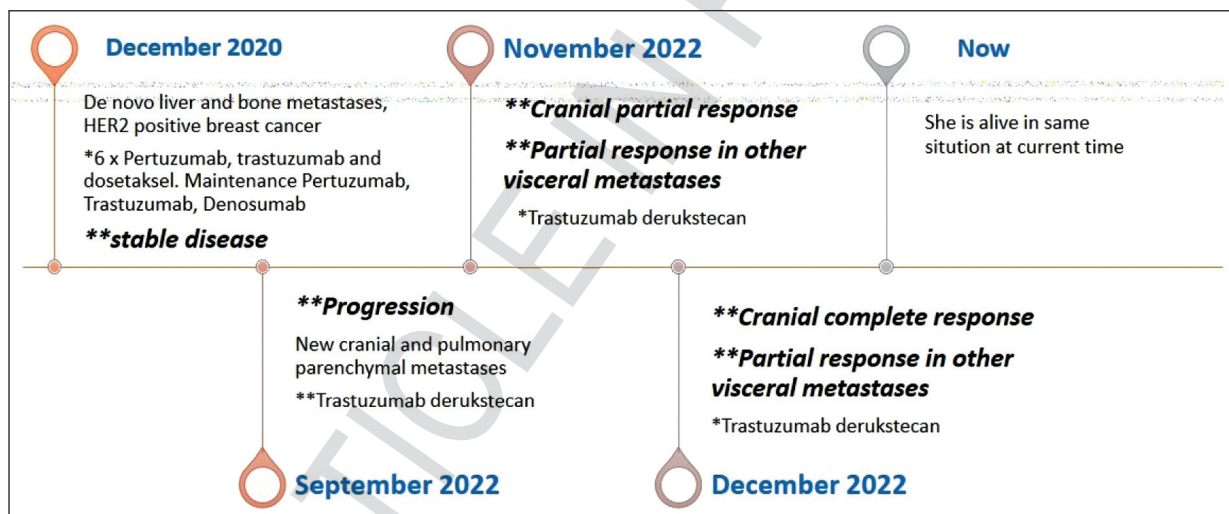


FIGURE 3: Systemic treatments used and the results achieved for the patient.

Figure 4 presents the rapid deep and complete promotions after treatment with Trastuzumab deruxstecan.

Informed consent was obtained from the people who participated in the study.

DISCUSSION

Brain metastases are common in solid tumors, and lung and breast cancers are among the most common cancers with brain metastases. Brain metastases, unlike other solid organ metastases, have a more intra-

tumoral and peritumoral edematous structure. This edematous structure observed in brain tumors and metastases is vasogenic edema that occurs due to impaired blood-brain barrier function and increased vascular permeability.¹² The production of factors that increase tumor vascular permeability, such as VEGF, glutamate, and leukotrienes, and the lack of tight endothelial cell connections within tumor blood vessels are two major factors that cause tumor-related blood-brain barrier disruption and increased permeability.¹³ Neovascularization is ob-

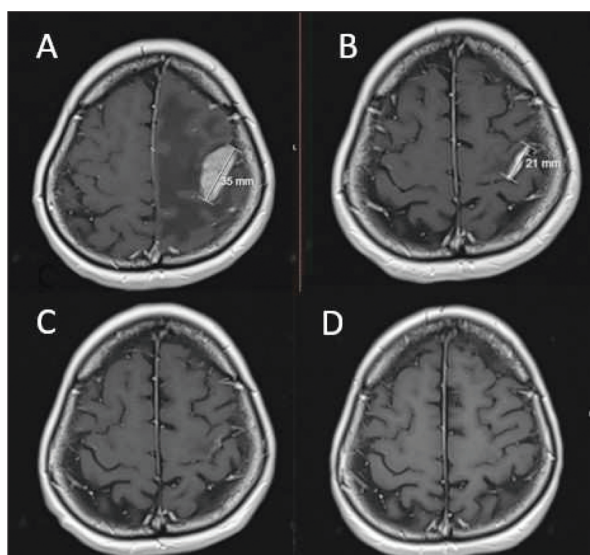


FIGURE 4: Rapid deep and complete promotions after treatment with Trastuzumab deruxtecan.

served in response to angiogenic factors such as VEGF and fibroblast growth factors (bFGF and FGF2).¹⁴ VEGF is largely responsible for the disruption of blood-brain barrier integrity in gliomas, meningiomas, and metastatic brain tumors, usually through VEGF upregulation.¹⁵ VEGF is released by both tumor cells and stromal cells and is capable of binding to VEGFR1 and VEGFR2, which are receptors located on the surface of endothelial cells.¹⁶ VEGF stimulates the formation of gaps in the endothelium, resulting in fluid passage across the brain parenchyma, thereby causing vasogenic edema.¹⁷ The newly formed vessels are different from those already present in normal brain tissue, with the former having inadequate expression of the transmembrane proteins occludin and claudin and the intracellular zonula occludin proteins ZO-1, ZO-2, and ZO-3, which are key molecules associated with the abnormalities responsible for the increased permeability of tumor endothelial tight junctions.¹⁸⁻²¹ Numerous studies have reported a reduced number of normal astrocytes in brain tumor tissue and the lack of astrocyte-derived factors necessary for the formation of a normal blood-brain barrier as the other causes of defective endothelial tight junctions.^{22,23} In addition, high expressions of both aquaporin-1 and aquaporin-4 are reportedly associated with the development of brain edema.^{24,25}

Brain metastases are differentiated from other solid organ metastases in terms of their intense edematous structure, which is characterized by the unique factors stated above. Therefore, different systemic treatment options may be used for treating brain metastases with different targets and hemodynamic mechanisms.

Trastuzumab deruxtecan and Sacituzumab govitecan reportedly exhibit efficacy in both breast cancer and NSCLC.²⁶⁻²⁹ However, these reports were based on studies that did not evaluate brain metastases separately from systemic diseases. The cases discussed in the present report, however, suggest that efficacy evaluations on brain metastases should be investigated as a separate secondary endpoint in studies conducted on the use of ADCs. In addition, it is recommended that brain metastases, due to their unique pathophysiology and structural features, should be included as a special research topic in the field of antibody-drug design and development.

Brain metastases are among the most detrimental consequences noted in solid tumors, and ADCs may serve as suitable candidates to achieve the solution in this regard.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Didem Divriklioğlu, İrfan Çiçin; **Design:** İrfan Çiçin, İsmail Bayrakçı; **Control/Supervision:** İrfan Çiçin, Didem Divriklioğlu, İsmail Bayrakçı; **Data Collection and/or Processing:** Didem Divriklioğlu, Erkan Özcan; **Analysis and/or Interpretation:** İrfan Çiçin, İsmail Bayrakçı; **Literature Review:** Didem Divriklioğlu, Erkan Özcan; **Writing the Article:** Didem Divriklioğlu, İsmail Bayrakçı; **Critical Review:** İrfan Çiçin, Didem Divriklioğlu; **References and Fundings:** Erkan Özcan; **Materials:** İsmail Bayrakçı, Erkan Özcan.

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