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CASE REPORT

Fatal herpetic encephalitis during brain radiotherapy in a cerebral metastasized breast cancer patient

Tatiana Koudriavtseva · Emanuela Onesti · Riccardo Tonachella · Lorella Pelagalli · Antonello Vidiri · Bruno Jandolo

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Abstract Herpes simplex encephalitis (HSE) is a life-threatening condition with high mortality. The pathogenesis underlying the reactivation of latent herpes simplex virus (HSV) remains undefined. We present the case of a 55-year-old female who developed HSE type 1 during brain irradiation and antioedematous dexamethasone treatment for leptomeningeal metastasized breast tumor with epileptic seizures. During the radiotherapy (RT), after a total of 32 Gray administrated in 16 fractions, our patient developed cognitive impairment and partial epileptic status without fever. Two days later the patient's clinical conditions had deteriorated and high fever manifested. A diagnosis of HSE type 1 was made by a positive cerebrospinal fluid polymerase chain reaction. Antiviral therapy with high doses of acyclovir was practiced for four weeks but the comatose state persisted. The patient died 59 days after the last RT fraction. The temporal relationship of RT to the occurrence of HSE suggests that cranial irradiation may play a role in the reactivation of latent HSV. Although antiviral therapy resistance is infrequent in immunocompetent patients, it is one of the main problems in immunocompromized patients.

Keywords Herpes simplex · Encephalitis · Radiotherapy · Leptomeningeal metastases · Breast cancer

T. Koudriavtseva (✉) · E. Onesti · B. Jandolo
Department of Neuroscience and Cervical-Facial Pathology, Neurology, National Cancer Institute Regina Elena, Via Elio Chianesi 53, 00144 Rome, Italy
e-mail: koudriavtseva@ifo.it

R. Tonachella
Department of Medical Oncology, Geriatric Oncology, National Cancer Institute Regina Elena, Via Elio Chianesi 53, 00144 Rome, Italy

L. Pelagalli
Department of Pain Therapy and Palliative Care, Intensive Care Unit, National Cancer Institute Regina Elena, Via Elio Chianesi 53, 00144 Rome, Italy

A. Vidiri
Department of Diagnostic Imaging, National Cancer Institute Regina Elena, Via Elio Chianesi 53, 00144 Rome, Italy

Introduction

Herpes simplex encephalitis (HSE) is a life-threatening consequence of herpes simplex virus (HSV) brain infection. Its incidence has been estimated at about one case per million per year and in most cases HSV-1 is responsible for the disease [1]. Although HSE is rare, mortality reaches 70% in the absence of therapy. A variety of immunosuppressive factors, for example stress, ultraviolet light, hyperthermia, dental extraction, and surgery, have been implicated in the reactivation of latent HSV but the pathogenesis of this process remains undefined [2]. Brain radiotherapy (RT) may reactivate HSV, probably by induction of a localized immunosuppressive state.

Case report

A 55-year-old postmenopausal woman had diagnosis of left breast cancer in February 1995. Histopathological examination revealed a ductal T2N1 carcinoma. She received total left mastectomy with axillary lymphoadenectomy and chemotherapy according to CMF 1-21 for eight cycles in the same year, and the following year a right quadrantectomy, RT, and hormonotherapy with tamoxifen, toremifene, and letrozole for a new breast tumor presentation

reported as ductal T1N0 carcinoma. New surgical intervention and, subsequently, chemo and hormonotherapy with adriamycin, megestrol, and anastrozole were performed in 2002 for a left breast cutaneous cancer recurrence.

After four years, follow-up examinations detected supraclavicular nodes and bone dissemination (at the level of the sternum, dorsal vertebra and fronto-parietal cranial bone), and a relapse in the left breast. The patient was treated by hormonotherapy with fulvestrant.

In January 2008 the patient presented a generalized epileptic seizure, and antiepileptic therapy with levetiracetam was introduced successfully. An MRI showed two meningeal metastases with perilesional oedema in right frontal region (Fig. 1), thus in March 2008 she started focal right cranial fronto-parietal irradiation (total 40 Gray in 20 fractions) and antioedematous dexamethasone treatment. After 16 fractions of RT, with a total 32 Gray, the patient presented subacute cognitive impairment without fever. The next day she developed sub-continuous left partial epileptic seizures which required increased antiepileptic therapy. Two days later a high fever with mild meningitis reaction was manifested and the patient's clinical condition deteriorated. On admission to hospital an increase of urea levels (59 mg/dl), a reduction of natremia levels (127 mmol/l), and mild leucocytosis (WBC 12.7 × 103/μl) with lymphopenia and invert CD4/CD8 cells ratio were recorded. Urgent CT was almost unchanged compared with recent control. A chest X-ray revealed suspected pneumonia and therapy with imipenem and teicoplanine was promptly started. Electroencephalography (EEG) revealed a pattern of delta and triphasic waves with burst suppression. Lumbar cerebrospinal fluid (CSF) analysis showed a slightly elevated protein level (50 mg/dl) and mild pleocytosis (26 white blood cells/μl) with prevalence of native CD4-positive T lymphocytes, and excluded the presence of neoplastic cells. A diagnosis of HSE was made by positive CSF polymerase chain reaction (PCR). Intravenous treatment with acyclovir (ACV) 10 mg/kg every 8 h was continued for four weeks. Two weeks after the sixteenth RT dose, MRI showed frontal, parietal, and temporal diffuse bilateral lesions (Fig. 2). At the end of antiviral therapy, HSV PCR of CSF was again positive. The comatose state persisted throughout the period of hospitalization and tracheal intubation soon became necessary. The patient died 59 days after the last RT fraction.

Discussion

Breast cancer is the second most common cause of brain metastases [3]. Recently, the recurrence of secondary CNS diffusion has been increased to 25–34% from historical rates of 10–20% [3]. The estimated frequencies of leptomeningeal metastases (LM) from breast cancer in clinical and autopsy series are 2–5% and 3–6%, respectively [4].

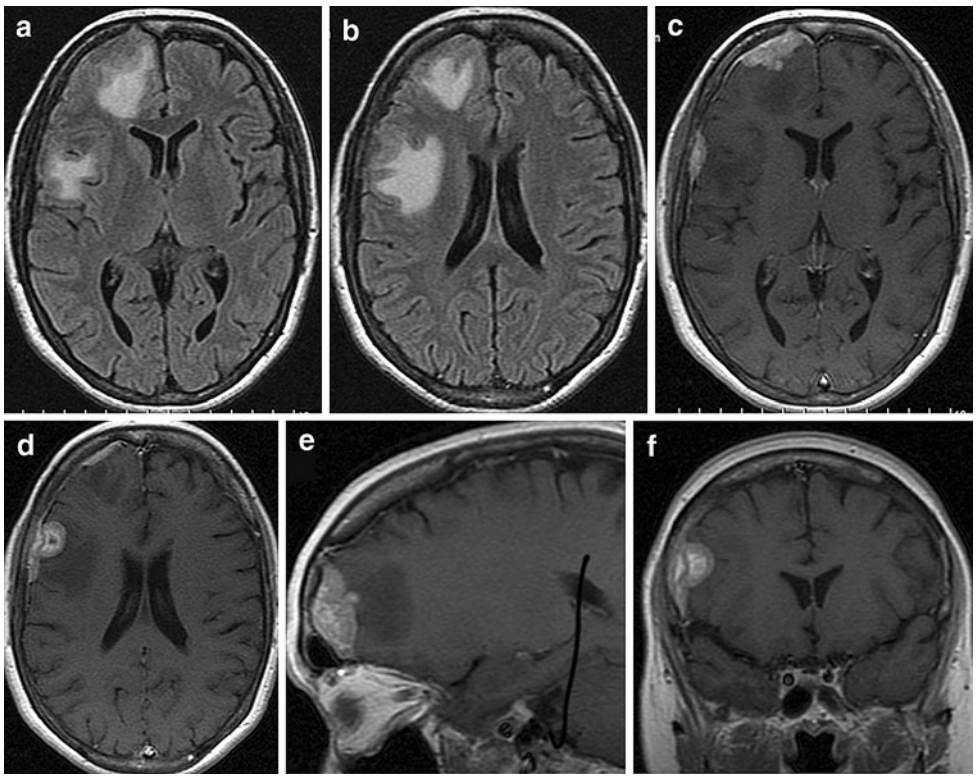

Fig. 1 MRI performed with the FLAIR sequence in the axial plain (**a**, **b**), and spin–echo T1 after gadolinium–DTPA infusion sequences in the axial (**c**, **d**), sagittal (**e**), and coronal (**f**) planes, shows two dural metastases with perilesional oedema in the right frontal lobe

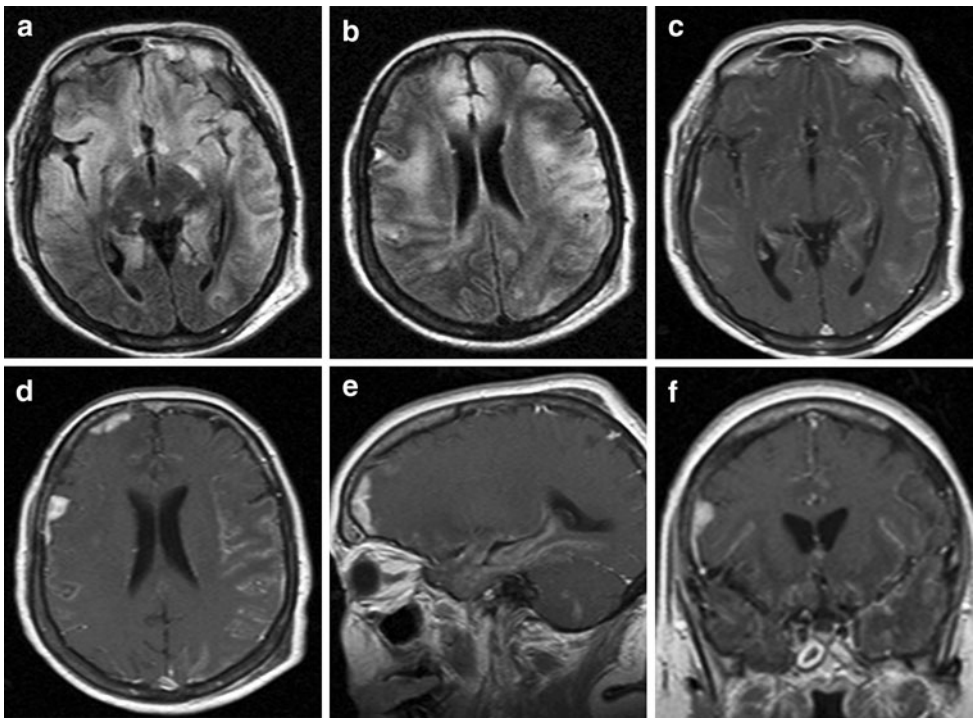

Fig. 2 MRI performed with the FLAIR sequence in the axial plain (**a**, **b**), and spin–echo T1 after gadolinium–DTPA infusion in the axial (**c**, **d**), sagittal (**e**), and coronal (**f**) planes shows a diffuse hyperintensity signal in the frontal, parietal, and temporal lobe bilaterally. A bilateral leptomeningeal enhancement is shown after gadolinium–DTPA infusion

The increased frequency of brain metastases may be a consequence of the induction of more sensitive diagnostic methods and increased survival as a result of improved systemic chemotherapy with only partial efficacy on CNS metastases because of the blood–brain barrier [3].

Whole-brain radiation therapy (WBRT) is considered a well-established treatment for patients with brain metastases; the role of chemotherapy has not been defined [5–7]. However, the prognosis for patients with brain metastases usually associated with aggressive tumor behavior remains poor with median survival ranging from 4.2 to 6.5 months [5, 6].

Our patient's case, in addition to some case reports, suggests that RT could be a contributory factor in the occurrence of HSV infection, especially in the immunocompromized host [8–13]. Moreover the combined use of RT and antioedematous corticosteroids more easily induces an immunosuppressive condition, so cellular immunosuppression with a inverted CD4/CD8 ratio was present in our patient on admission in hospital after radio and steroid therapy. Hughes et al evaluated a group of 70 patients with primary brain tumors treated with high doses of corticosteroids for prolonged periods and demonstrated that patients with CD4 cell counts less than 200/mm^3 were significantly more likely to be hospitalized for infections during RT [14]. They suggested the need to assess the occurrence of low CD4 counts and to monitor CD4 counts during and after RT.

Early diagnosis and treatment are essential for HSE. The International Herpes Management Forum has issued guidelines to aid the diagnosis and treatment of HSE [15]. HSE is diagnosed using clinical symptoms, EEG, CT, MRI, and CSF analysis with HSV-specific PCR, the most reliable diagnostic method, which can verify the elimination of the replicating virus after completion of therapy, aiding further management of the patient.

However, the early symptoms of this disease are various, and the laboratory diagnostic criteria are sometimes unclear. In particular, immunocompromized patients may have unusual presentations, negative initial neuroimaging, and absent or mild CSF pleocytosis with the risk of underrecognition of HSE. Consequently incidence of HSE is underestimated in these patients. In our patient cognitive impairment without fever during the first days was ascribed to cerebral oedema worsened by RT. CSF examination showed slight pleocytosis (26/μl) which is usually higher (about 100/μl) in HSE, but six-color flow cytometry immunophenotyping of the CSF demonstrated the presence of native CD4 positive T lymphocytes. Initially the CT was unchanged compared with the previous examination and only after two weeks did the MRI show diffuse cerebral damage. Therefore, the patient's immunocompromized state may possibly have limited the initial degree of clinical and laboratory manifestations.

Therapy with ACV (10 mg/kg every 8 h for 14–21 days) should be started as soon as HSE is suspected. In fact, the main prognostic factor affecting the outcome seems to be early administration of antiviral treatment [16]. In immunocompetent patients, HSV infections are controlled rapidly whereas the response to antiviral treatment

is variable in immunocompromized patients with the highest CD4+ cell counts and poor in those with more severe immunosuppression [17]. Treatment of immunocompromized patients is, furthermore, limited by the frequent development of resistence to antiviral drugs. The prevalence of ACV resistance has been estimated at about 0.5% in immunocompetent patients, at around 5% in immunocompromized patients, and at 14–30% in allogenic bone marrow transplant patients [18, 19]. Resistance to ACV is associated with mutations located in one of the two genes involved in the ACV mechanism of action: the thymidine kinase (TK) gene, which is involved in 95% of cases, and the DNA polymerase gene [18]. Antiviral resistance should be suspected in all immunocompromized patients when there is no prompt response to ACV, and alternative treatments with different mechanisms of action may be considered. The resistant infections could be managed with foscarnet or cidofovir, drugs which also inhibit viral DNA polymerase but with greater renal toxicity than ACV [20].

Conclusions

These results suggest that HSE should be considered in differential diagnosis of acute neurological decline in patients undergoing cranial RT, and in cases of atypical clinical presentation and unclear laboratory and neuroimaging findings.

Empirical ACV therapy should be started as soon as possible when HSE is suspected and antiviral resistance should be suspected in immunocompromized patients if an expected response to ACV does not occur. In these patients alternative treatments should be evaluated, and use of other antiviral drugs should be considered, even at the risk of greater toxicity than ACV.

Moreover, accurate assessment of the occurrence of low CD4 counts before RT and monitoring of CD4 counts during and after this treatment may be useful for identifying patients at high risk of infective complications.

References

1. Kennedy PG, Chaudhuri A (2002) Herpes simplex encephalitis. J Neurol Neurosurg Psychiatry 73(3):237–238
2. Roizman B, Sears AE (1993) Herpes simplex virus and their replication. In: Roizman B, Whitley RJ, Lopez C (eds) The human herpes viruses. Raven Press, New York, pp 11–68
3. Lee SS, Ahn JH, Kim MK, Sym SJ, Gong G, Ahn SD, Kim SB, Kim WK (2008) Brain metastases in breast cancer: prognostic factors and management. Breast Cancer Res Treat 111(3):523–530
4. Chang EL, Lo S (2003) Diagnosis and management of central nervous system metastases from breast cancer. Oncologist 8(5):398–410 Review
5. Fokstuen T, Wilking N, Rutqvist LE, Wolke J, Liedberg A, Signomklao T, Fernberg JO (2000) Radiation therapy in the management of brain metastases from breast cancer. Breast Cancer Res Treat 62(3):211–216
6. Mahmoud-Ahmed AS, Suh JH, Lee SY, Crownover RL, Barnett GH (2002) Results of whole brain radiotherapy in patients with brain metastases from breast cancer: a retrospective study. Int J Radiat Oncol Biol Phys 54(3):810–817
7. Mir O, Ropert S, Alexandre J, Lemare F, Goldwasser F (2008) High-dose intrathecal trastuzumab for leptomeningeal metastases secondary to HER-2 overexpressing breast cancer. Ann Oncol 19(11):1978–1980
8. Dragoje S, Tolnay M, Dalquen P, Probst A (1995) Brain irradiation an antioedematous dexamethasone treatment-risk factors for herpes simplex encephalitis? Schweiz Arch Neurol Psychiatr 146(6):277–280
9. Jacobs DH (1999) Herpes simplex virus encephalitis following corticosteroids and cranial irradiation. Neurology 52(5):1108–1109
10. Molloy S, Allcutt D, Brennan P, Farrell MA, Perryman R, Brett FM (2000) Herpes simplex encephalitis occurring after chemotherapy, surgery and stereotactic radiotherapy for medulloblastoma. Arch Pathol Lab Med 124(12):1809–1812
11. Riel-Romero RM, Baumann RJ (2003) Herpes simplex encephalitis and radiotherapy. Pediatr Neurol 29(1):69–71
12. Spacca B, Mallucci C, Riordan A, Appleton R, Thorp N, Pizer B (2007) HSV encephalitis in a child with brain stem glioma: a rare complication of therapy. Case report and review of the neurosurgical literature. Childs Nerv Syst 23(11):1347–1350 Review
13. Silvano G, Lazzari G, Resta F, Buccoliero G, Pezzella G, Pisconti S (2007) A Herpes simplex virus-1 fatal encephalitis following chemo-radiotherapy, steroids and prophylactic cranial irradiation in a small cell lung cancer patient. Lung Cancer 57(2):243–246
14. Hughes MA, Parisi M, Grossman S, Kleinberg L (2005) Primary brain tumors treated with steroids and radiotherapy: low CD4 counts and risk of infection. Int J Radiat Oncol Biol Phys 62(5):1423–1426
15. Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, Kennedy PG (2005) Viral encephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol 12(5):331–343 Review
16. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, Lebon P, Canton P, Rozenberg F (2002) Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. Clin Infect Dis 35(3):254–260
17. Cinque P, Vago L, Marenzi R, Giudici B, Weber T, Corradini R, Ceresa D, Lazzarin A, Linde A (1998) Herpes simplex virus infections of the central nervous system in human immunodeficiency virus-infected patients: clinical management by polymerase chain reaction assay of cerebrospinal fluid. Clin Infect Dis 27(2):303–309
18. Morfin F, Thouvenot D (2003) Herpes simplex virus resistance to antiviral drugs. J Clin Virol 26(1):29–37
19. Stránská R, Schuurman R, Nienhuis E, Goedegebuure IW, Polman M, Weel JF, Wertheim-Van Dillen PM, Berkhout RJ, van Loon AM (2005) Survey of acyclovir-resistant herpes simplex virus in the Netherlands: prevalence and characterization. J Clin Virol 32(1):7–18
20. Pöhlmann C, Schetelig J, Reuner U, Bornhäuser M, Illmer T, Kiani A, Ehninger G, Jacobs E, Rohayem J (2007) Cidofovir and foscarnet for treatment of human herpesvirus 6 encephalitis in a neutropenic stem cell transplant recipient. Clin Infect Dis 44(12):118–120