Bone Marrow Transplantation (2003) 31, 57–60
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www.nature.com/bmt

Case report

Fatal chemotherapy-induced encephalopathy following high-dose therapy for metastatic breast cancer: a case report and review of the literature

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Summary:

Chemotherapy-induced encephalopathies occur in a variety of clinical settings and the most detailed accounts have been described following combination methotrexate and radiation therapy. The case described herein developed severe encephalopathy following a high-dose chemotherapy protocol used in the treatment of metastatic carcinoma of the breast. Visual symptoms developed 3 weeks after completing high-dose chemotherapy and peripheral blood hematopoietic stem cell transplantation. Over the next several weeks, additional neurologic deficits developed and continued to progress despite various treatment interventions. Diffuse deep gray matter damage was identified on MR imaging and a brain biopsy revealed pathological findings similar in many respects to those described for methotrexate/radiation, cisplatin, BCNU and/or 5 FU/levamisole-related leukoencephalopathy. The patient succumbed to complications resulting from the CNS disorder, 8 weeks after the onset of symptoms. This case is unusual for two reasons. First, the patient developed severe encephalopathy following a high-dose chemotherapy protocol commonly used in the treatment of metastatic breast carcinoma and second, the encephalopathy involved primarily deep gray matter structures rather than white matter.
Bone Marrow Transplantation (2003) **31,** 57–60. doi:10.1038/sj.bmt.1703768
Keywords: encephalopathy

High-dose chemotherapy has been widely used for the treatment of metastatic breast cancer. Treatment regimens typically utilize combinations of two to three drugs with hematopoietic stem cell support. These procedures are associated with various transplant-related mortalities and morbidity. The major complications include infections, bleeding, pulmonary damage, veno-occlusive disease of the liver and other gastrointestinal disorders. Although the complication rate associated with autologous transplantation is lower than with allogeneic transplantation, significant complications do occur in a small proportion of patients undergoing autologous transplantation. Central nervous system complications have been alluded to in breast cancer patients, but have not been well documented. Changes including cognitive dysfunction with memory problems and ophthalmologic disorders including retinitis have been described.[1]

The ophthalmic disorders that have been reported include retinopathy, optic neuritis and rare cases of cortical blindness.[2,3] Patients typically present with decreasing visual acuity, visual field blurring, visual field shadows, visual field loss or global visual loss. Fundal findings include retinopathy with cotton-wool spots, retinal hemorrhages, macular exudates and edema, arteriolar occlusion, and optic neuropathy with disc swelling and optic atrophy. The defects may present unilaterally or bilaterally and do not necessarily occur at the same point in time in each eye.

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Received 15 June 2001; accepted 10 August 2002

Case report

A 37-year-old woman had Stage III-A infiltrating poorly differentiated ductal carcinoma T2N2M0, G3, ER/PR −/− with DNA index 1.12 and 1.89 and 70% of tumor cell nuclei Ki67 (proliferation marker) positive. The initial diagnosis was made via lumpectomy. She subsequently underwent a modified radical mastectomy 13 months prior to high-dose chemotherapy and PSC transplantation. Multiple foci of comedo carcinoma were found and angiolymphatic tumor invasion was present. Metastases to 20 of 31 axillary lymph nodes with perinodal extension into fat and matting of lymph nodes were present. There was no evidence of distant metastatic disease as demonstrated by chest X-ray, isotopic bone scan, and chemistry profile. The patient underwent three cycles of CAF chemotherapy (Cytoxan 100 mg/m^2/day p.o. for 14 days, Adriamycin 30 mg/m^2 i.v. days 1 and 8, and 5 FU 500 mg/m^2 i.v. days 1 and 8), followed by stem cell harvest 4 weeks later. Three more cycles of CAF were completed over the following 2 months. Local radiation therapy to the right anterior chest wall and regional lymph nodes was administered at 5040 cGy with 6 MeV photon beam and 720 cGy boost with 10 MeV electron beam to the anterior

chest wall and 1440 cGy boost with 10 MeV electron beam to the axilla were completed over the following 3 months. Despite chemotherapy and radiation treatments, a CT scan of the chest 1 month later demonstrated bilateral nodules in the lung, which were found via thoracotomy and excisional biopsy to be ER/PR-/- poorly differentiated metastatic carcinoma. Overexpression of HER-2/neu was not present as measured by immunocytochemistry. Bone scan was negative at that time.

The patient was treated with Taxotere 100 mg/m^2 every 3 weeks for 3 doses without evidence of clinical response on repeat CT scans of the chest. She then underwent high-dose induction therapy with the STAMP I regimen consisting of cisplatin 55 mg/m^2/day continuous infusion $\times$ 3 days, cyclophosphamide 1875 mg/m^2 $\times$ 3 days and BCNU 600 mg/m^2 $\times$ 1 day. Immediate post-transplant recovery was uneventful, and she was discharged home on day 10. Three weeks following the PSC transplant, blurring of vision with visual field defects in the left eye were noted; these were followed by similar symptoms involving the right eye 3 days later. Five days later paresthesiae involving the anterior and posterior torso began below the breast line spreading down to the thighs and progressing to the feet. These were associated with unsteadiness on standing and walking. There was a feeling of incomplete bowel evacuation and difficulty with initiation of urination. MRI of the head showed bilateral symmetric areas of abnormal signal within the deep gray matter including the caudate nuclei, globus pallidi, putamina, thalami and habenula (Figure 1a). Abnormal signal was also identified within the left tegmentum of the midbrain and medial left cerebellum. After administration of gadolinium, there was mild enhancement within the globus pallidi, putamina and caudate nuclei, as well as intense enhancement within the habenula and left midbrain tegmentum (Figure 1b). There was no hemispheric white matter involvement. Retinal examination showed extensive ischemia and 'cotton wool' exudates throughout the posterior poles of both eyes (Figure 2).

Prednisone, 50 mg p.o. q.d., was started at that time. However, symptoms and signs continued to evolve with development of weakness in the lower extremities and decreased light touch and pinprick sensation below the T4 spinal cord level as well as the lateral portion of the neck. Reflexes were symmetric and 2+/4 except the right brachioradialis, which was 1+/4. Finger-to-nose testing was normal and the gait was normal but unsteady with tandem walking. Rhomberg and Babinski testings were negative. Visual blurring and diplopia progressed over the next 11 days. This was associated with the development of bilateral lower extremity weakness, memory disturbance, hallucinations and bowel/bladder incontinence. The patient became chair/bed bound with motor 4+/5 in the upper extremities, and 3+/5 in the lower extremities. Reflexes were 2+/4 throughout and Babinski testing remained downgoing. Lumbar puncture revealed WBC 0, RBC 0, protein 119 without foreign cells present. Cultures and special stains for bacteria, fungi and viral infections did not indicate an infectious etiology. Echocardiogram was normal. A cerebral arteriogram was normal and repeat MRI of the head demonstrated significant progression of disease when compared with the previous MRI study done 3 weeks earlier (Figure 1c and d). There was extensive involvement of the brain stem and medial cerebellar hemispheres (dentate nuclei). There continued to be a relative lack of hemispheric white matter involvement. The MRI of the spine was normal.

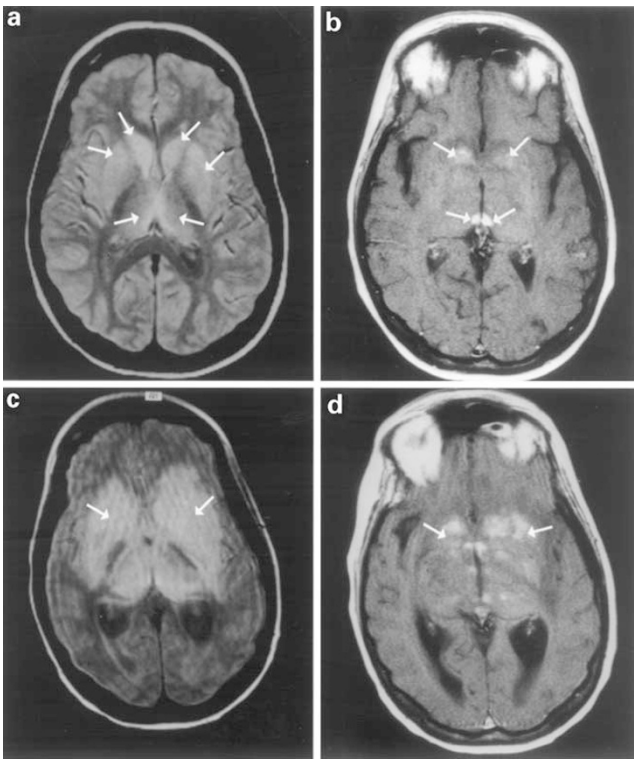

Figure 1 (a) Proton-density-weighted MRI scan demonstrates abnormal increased signal intensity within the caudate nuclei, lentiform nuclei and medial thalami. (b) TI-weighted MRI scan after the administration of gadolinium demonstrates areas of contrast enhancement within the basal ganglia and intense enhancement within the habenular region. (c) Repeat proton-density-weighted MRI scan and (d) TI-weighted MRI scan demonstrate dramatic progressive, confluent abnormal signal intensity within the deep gray matter nuclei and relative lack of involvement of the hemispheric white matter. Administration of gadolinium demonstrates extensive enhancement within the deep gray matter nuclei.

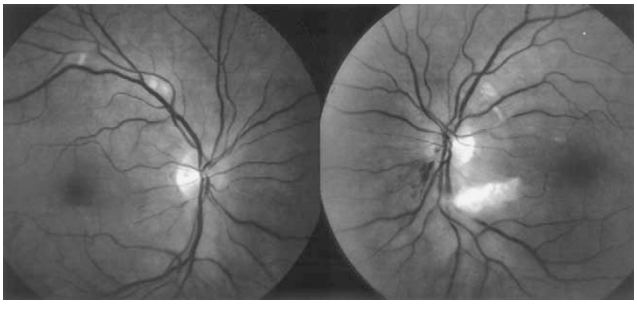

Figure 2 Retinal findings: cotton wool exudates involving the retinae of both right and left eyes. Retinal hemorrhage noted infero-nasal to the left optic disc.

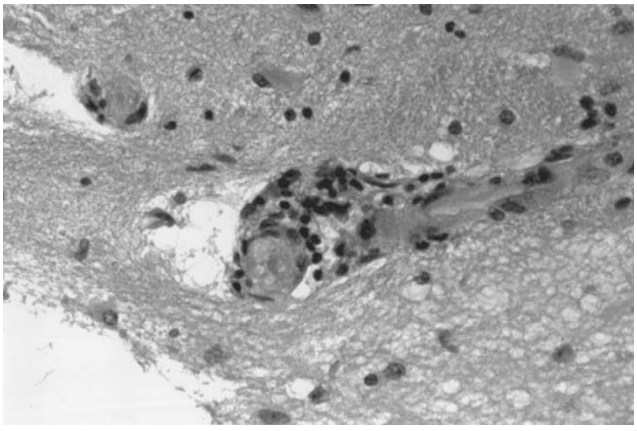

Figure 3 Histologic section of the stereotactic brain biopsy shows perivascular lymphocytes, capillary luminal narrowing and gliosis.

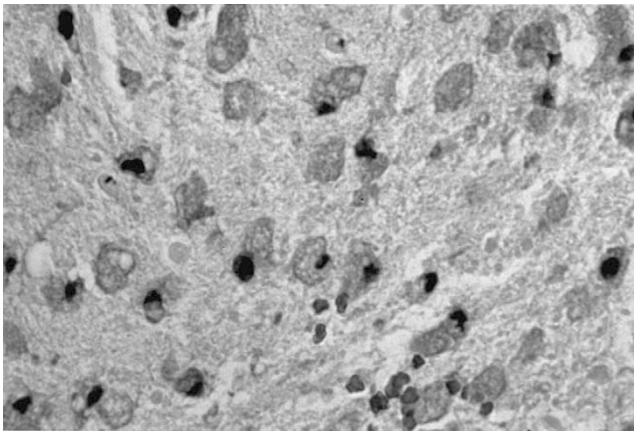

Figure 4 A microscopic region of brain showing extensive infiltration with foamy macrophages.

Stereotactic core needle biopsies of the brain revealed perivascular lymphocytes and microscopic fibrin thrombi in small capillaries (Figure 3). Gliosis and necrosis of brain tissue with macrophage infiltration were noted. Focal zones of severe axonal and myelin loss were seen in microscopic regions of apparent white matter; however, myelin loss was not out of proportion to axonal loss. Microscopic regions showing necrosis with prominent macrophage infiltration were observed (Figure 4). Some small capillaries showed endothelial atypia with luminal narrowing and perivascular fibrinoid accumulations (Figure 5). Lymphocytes were seen surrounding and sometimes infiltrating blood vessel walls. These changes were present both within necrotic and relatively intact regions of brain. Fibrinoid degeneration of blood vessels was identified, suggesting that a primarily small vessel vasculitis was part of the initiating process. Several larger blood vessels showed prominent hyalinization similar to that seen with radiation effect. Reactive astrocytosis was a prominent feature throughout, both in severely damaged and less damaged regions.

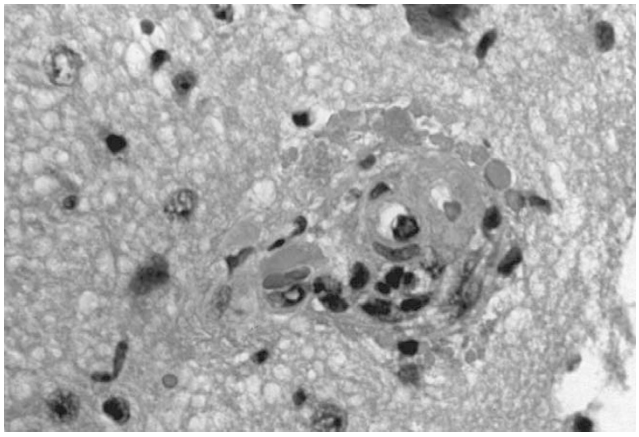

Figure 5 Capillary showing endothelial atypia, luminal narrowing and granular perivascular fibrinoid material.

Because cerebral vasculitis was the presumed etiology for the clinical presentation, coumadin was administered as well as decadron 8 mg i.v. q 8 h and then escalated to 24 mg i.v. b.i.d. for 7 days; the dose was gradually tapered over the following month. A 60 g dose of intravenous gamma globulin was administered without response 4 weeks after the initial symptoms had began and a 5-day course of 1.5 blood volume/day plasma exchange was performed. No response was observed to any therapy and clinical deterioration continued. The patient developed dysphagia and subsequent aspiration pneumonia with oxygen desaturation and she died in a vegetative state, 2 months after the initial visual changes had begun.

Discussion

Delayed encephalopathies secondary to combination cranial irradiation and chemotherapy have been designated 'disseminated necrotizing leukoencephalopathy'[4] or alternatively 'subacute encephalopathy'.[5] A variety of chemotherapeutic agents have been implicated in this process. The lesions characteristically consist of discrete or confluent foci of demyelination and coagulative necrosis scattered throughout white matter. The distribution of white matter lesions ranges from isolated optic chiasm, or optic nerve involvement, to multifocal white matter abnormalities to confluent symmetrical subcortical involvement. Primary deep gray matter involvement such as seen in our patient is not typical of this entity. The onset of chemotherapy-associated encephalopathy ranges from acute/subacute to delay, and clinical outcomes are variable. Patients have been described with reversible visual abnormalities following cisplatin therapy and others have died from chemotherapy-induced disseminated necrotizing leukoencephalopathy.[6] Therapeutic interventions such as steroid therapy have been used, but are usually not effective.

The changes observed in the cerebral microvasculature in our patient suggest a pathogenic mechanism for the diffuse

MRI abnormalities. Although white matter demyelination was not seen histologically and gray matter lesions were most prominent on MRI, many of the histopathologic features of this case were analogous to those previously described for combination radiation/chemotherapy toxicity.[7] For example, endothelial cell atypia with narrowing of capillary lumina and associated red blood cell extravasation was present. Fibrinoid blood vessel wall degeneration, perivascular hyalinization and vasculitis have also been described with radiation- and drug-induced toxicity. Similar findings have been described for 5 FU plus levamisole therapy.[8,9] The histopathologic changes in this case support the conclusion that microvascular changes rather than toxic effects on myelin contributed to the disease process.

Although many of the published reports of chemotherapy/radiation-induced leukoencephalopathy have not included pathologic descriptions, reported histopathologic changes have ranged from myelin pallor with foamy macrophages and gliosis to severe vasculitis with necrosis. The current case represents the severe end of this histopathological spectrum. Features including spongiosis and mineralization were not appreciable, however, there was some evidence of axonal swelling and deposition of cellular debris.

High-dose combination chemotherapy has been frequently used as a therapy for metastatic breast cancer as well as for adjuvant therapy for patients at high risk for development of metastatic disease. Various combinations of high-dose therapy have been used; the commonest regimens include cyclophosphamide plus thiotepa, with or without carboplatin; or BCNU, cisplatin and cyclophosphamide; or melphalan, etoposide and carboplatin. There are reports of development of depression, possible cognitive disturbances and various reports of retinopathy with/without optic neuropathy.[2,3]

Optic disorders following high-dose chemotherapy for breast cancer have usually presented 1–5 months following hematopoietic stem cell transplantation. In those who develop retinopathy alone, clinical features have usually resolved, whereas those with optic neuropathy tend to have permanent visual changes. It has been speculated that high doses of BCNU and/or carboplatin alter the permeability of the blood–brain barrier by damaging blood vessel walls, thereby permitting high levels of these drugs to enter the central nervous system where they induce injury to the various brain cells. The clinicopathologic findings in this case support this view. Another possible causative factor leading to the CNS changes in this case is the prior administration of taxotere, which alters vascular permeability.[10] This is responsible for the well-described fluid-retention syndrome seen with this drug. Furthermore, taxotere commonly causes peripheral neuritis, but central nervous system changes as seen in our patient are rare, but have been described with taxol, a drug that is similar to taxotere. Altered vascular permeability may allow inappropriate leakage of subsequently administered high-dose chemotherapy agents such as BCNU or cisplatin as administered to our patient. Both these agents can cause CNS complications. Cisplatin in particular has been associated with the development of retinopathy similar to that seen in our patient, sensorineural ototoxicity, cranial neuropathy, peripheral neuropathy, encephalopathy, confusional states and seizures.[11] At least in some of these manifestations, there is an association with the finding of high levels of tissue platinum in the brain.[12]

Chemotherapy-induced cerebral abnormalities occur in a wide variety of settings and present with a wide range of clinical findings. Neurologic complications have been described with antineoplastic drugs including alkylating agents, antimetabolites, periwinkle derivatives and other agents including cisplatin and L-asparaginase.[13] Although this process occurs in response to a variety of chemotherapeutic agents with a wide range of mechanisms of action, common pathologic features have been described. The process usually preferentially involves white matter and small vessel abnormalities are common. Treatment for this complication of chemotherapy has been largely ineffective to date.

References

1 Bernauer W, Gratwohl A, Keller A *et al*. Microvasculopathy in the ocular fundus after bone marrow transplantation. *Ann Intern Med* 1991; **115**: 925–930.
2 Khawly JA, Rubin P, Petros W *et al*. Retinopathy and optic neuropathy in bone marrow transplantation for breast cancer. *Ophthalmology* 1996; **103**: 87–95.
3 Rubin P, Hulette C, Khawly JA *et al*. Ocular toxicity following high dose chemotherapy and autologous transplant. *Bone Marrow Transplant* 1996; **18**: 253–256.
4 Bruner JM, Tien RD, Thorstad WL. Structural changes produced by intracranial tumors and by various forms of antineoplastic therapy. In: Bigner DD, McLendon RE, Bruner JM (eds). *Russell and Rubenstein's: Pathology of Tumors of the Central Nervous System*. Arnold: London, 1998, pp 451–491.
5 Price RA, Jamieson PA. The central nervous system in childhood leukemia. II. Subacute leukoencephalopathy. *Cancer* 1975; **35**: 306–318.
6 Lyass O, Lossos A, Hubert A *et al*. Cisplatin-induced non-convulsive encephalopathy. *Anticancer Drugs* 1998; **9**: 100–104.
7 Suzuki K, Takemura T, Okeda R *et al*. Vascular changes of methotrexate-related disseminated necrotizing leukoencephalopathy. *Acta Neuropathol* 1984; **65**: 145–149.
8 Scully RE, Mark EJ, McNeely WF *et al*. Weekly clinicopathological exercises, case 24-1999. *New Engl J Med* 1999; **341**: 512–519.
9 Fassas ABT, Gattani AM, Morgello S. Cerebral demyelination with 5-fluorouracil and levamisole. *Cancer Invest* 1994; **12**: 379–383.
10 Semb KA, Aamdal S, Oian P. Capillary protein leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment. *J Clin Oncol* 1998; **16**: 3426–3432.
11 Macdonald DR. Neurologic complications of chemotherapy. *Neurol Clin* 1991; **9**: 955–967.
12 Gregg RW, Molepo JM, Monpetit VJ *et al*. Cisplatin neurotoxicity: the relationship between dosage, time, and platinum concentration in neurologic tissues, and morphologic evidence of toxicity. *J Clin Oncol* 1997; **15**: 199–206.
13 Shapiro WR, Young DF. Neurological complications antineoplastic therapy. *Acta Neurol Scand* 1984; **70** (Suppl 100): 125–132.