Cognitive Impairment With Significant Brain Parenchymal Volume Loss Following Standard Adjuvant Chemotherapy in a Patient With Breast Cancer

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In the United States, breast cancer is the most common nonskin cancer and second leading cause of cancer-related death in women.[1] Adjuvant chemotherapy is commonly used in patients at high risk of relapse.[2] Overall, chemotherapy is well tolerated and most side effects do not last long. Studies have shown that approximately 25% of patients develop cognitive impairment.[3] Typically, parenchymal damage secondary to chemotherapy is reported in high-dose chemotherapy settings, not after standard-dose adjuvant chemotherapy.[4] Here we report a case of cognitive impairment associated with significant brain parenchymal volume loss after standard-dose adjuvant chemotherapy for breast cancer.

Case

A 56-year-old woman was diagnosed with moderately differentiated infiltrating ductal carcinoma. Estrogen and progesterone receptors were negative by immunohistochemistry. She was otherwise healthy, without any previous medical problems. Family history was positive for breast cancer only in her 64-year-old sister. After lumpectomy and sentinel-node biopsy, the patient was found to have T2N0M0 (stage IIA) breast cancer. She was enrolled on the Eastern Cooperative Oncology Group 1199 clinical trial, was randomized, and received doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks followed by weekly docetaxel (35 mg/m^2). There were no significant complaints during the first four cycles of therapy except for nausea and vomiting, which responded to 5-HT$_3$ antagonists. After starting weekly docetaxel, the patient complained of severe fatigue, diarrhea, nausea, and occasional shortness of breath. Her examination, including a neurologic examination, was normal. Because of persistent grade 3 toxicity, the patient and her family opted to stop chemotherapy.

Approximately 2 years after discontinuation of chemotherapy, the patient complained of progressive mild memory loss and occasional confusion. She had additional complaints of difficulty concentrating and finding words as well as slowed cognitive processing. She was seen by a neuropsychologist, who concluded that these changes were consistent with frontal-lobe dysfunction likely related to the toxic effects of chemotherapy. Neuropsychologic examination in follow-up visits revealed prominent difficulties with perseveration, response-inhibition, and decreased flexibility. She also showed attention- and retrieval-based memory problems as well as continued slowed cognitive processing.

The patient continued to exhibit symptoms of memory loss and confusion during interviews and needed support from her husband. She had significant difficulties navigating her room and other surroundings. She took donepezil for 2 months with no response. Repeated neuropsychologic examination was suggestive of global diffuse progressive cortical dementia, with magnetic resonance imaging (MRI) showing diffuse prominence of subarachnoid space and convexity of sulci compatible with volume loss, which was more prominent than would be expected

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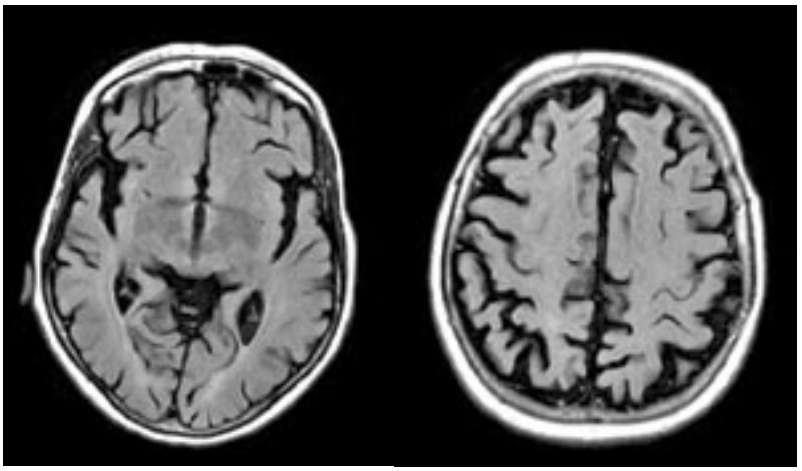

Figure 1. T2 flair axial section of brain magnetic resonance imaging showing parenchymal volume loss and prominent sulci.

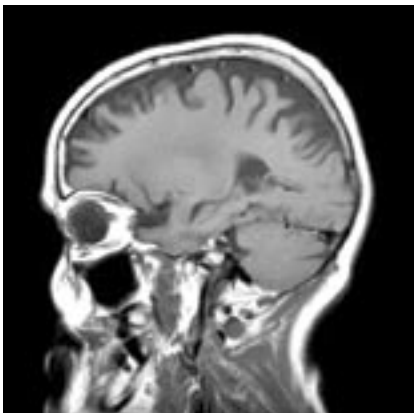

Figure 2. T1 sagittal section of brain magnetic resonance imaging showing diffuse parenchymal volume loss.

for the patient's age. These changes were found to be consistent and irreversible in a follow-up MRI taken 1.5 years later (Figures 1 and 2).

Discussion

Cognitive dysfunction is a rare side effect of chemotherapy.[5] Diagnosis is by neuropsychologic evaluation, which may include assessing verbal and spatial abilities, verbal and visual learning, memory, and psychomotor function.[6] Radiologic changes in the brain observed by clinical MRI are not very common. Previous studies indicate that chemotherapy can result in cerebral white matter changes. Occasional case reports in patients receiving high-dose chemotherapy have shown MRI changes in the water spaces of the white matter areas, and the lesions are usually periventricular. These studies tried to find whether the mechanism of disease is neuronal or extraneuronal.[4,7]

Cognitive impairment with standard-dose chemotherapy is relatively less common than with high-dose chemotherapy.[8] To our knowledge, in the last 10 years no cases were reported in which cognitive dysfunction and white-matter changes in MRI followed standard-dose adjuvant chemotherapy for breast cancer. The present case demonstrates cognitive impairment with standard-dose chemotherapy, with the MRI findings described above. Interestingly, these MRI findings are similar to those of Alzheimer disease.[9] Another finding of this case was iron accumulation in the basal ganglia bilaterally. Although iron accumulation is not uncommon for this patient's age group, it should be noted that neurodegenerative diseases like Alzheimer disease also show increased iron deposition.[10] The atypical MRI findings make this case notable.

The incidence, risk factors, and pathophysiology of cognitive impairment are not clear; hence, there is no definitive treatment for cognitive dysfunction following chemotherapy. Further research is needed to identify patients who exhibit cognitive dysfunction, and management strategies need to be developed.

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Review

Late Neuropsychologic Effects of Chemotherapy

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Swayampakula and colleagues reported delayed onset of cognitive impairment in a 56-year-old woman with breast cancer treated with standard-dose chemotherapy.[1] The patient developed progressive and diffuse cognitive impairment and cortical atrophy 2 years following treatment.

In recent years, neuropsychologic studies of breast cancer patients treated with standard-dose chemotherapy have documented cognitive problems in a significant proportion of cases,[2-6] although some studies reported no cognitive adverse effects.[7,8] The prevalence of cognitive dysfunction in this population ranged from 17% to 75% in cross-sectional studies; the variability may be in part related to methodologic issues. The cognitive changes associated with chemotherapy are often mild and involve processing speed, working memory, and acquisition and retrieval of new information, suggesting primarily frontal-subcortical dysfunction. Acute chemotherapy-related cognitive difficulties are relatively more common, but long-term posttreatment cognitive changes appear to persist in a subgroup of breast cancer survivors,[9] independently of mood or fatigue.[10] Recent prospective studies[11,12] documented pretreatment to posttreatment cognitive changes in a subgroup of patients; subsequent to chemotherapy there was evidence of a decline at short-term follow-up intervals but relatively stable or improved cognitive performance at longer follow-up intervals.

Neuroimaging studies have reported structural and functional changes in the brain associated with chemotherapy. Reduction in volume of brain structures important for executive functioning (eg, frontal cortex) and changes in the integrity of white matter tracks have been associated with cognitive changes in breast cancer patients treated with chemotherapy.[13,14] A recent prospective study evaluating breast cancer patients utilizing functional magnetic resonance imaging (MRI) prior to treatment and at 1 and 12 months posttreatment showed a pattern of reduced activation in the frontal cortex during a working memory task in patients treated with chemotherapy compared to untreated patients and healthy controls.[15] A functional positron emission tomography study found decreased metabolic activity in the prefrontal cortex during short- and long-term memory tasks in patients with breast cancer treated with chemotherapy compared to untreated patients and healthy controls.[16]

The development of delayed, progressive neurotoxicity after standard-dose chemotherapy is uncommon, and most studies assessing breast cancer survivors several years following treatment describe relatively stable, mild changes in cognitive function and brain structure.[11,12] The case reported by Swayampakula and colleagues is intriguing and raises the possibility that some patients may have increased vulnerability to the adverse effects of

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chemotherapy, and that these effects may manifest years after therapy. However, given the atypical presentation of this patient, it is important to consider that chemotherapy may have accelerated the progression of a preexisting condition, or factors other than chemotherapy may explain the pattern of findings.

Although the authors reported that the patient was healthy and without medical problems other than ductal carcinoma, the absence of pretreatment neuropsychologic and neuroimaging studies makes it difficult to exclude preexisting abnormalities. This difficulty is particularly relevant in light of recent prospective studies documenting lower-than-expected cognitive function (based on age and education) in a subgroup of patients prior to chemotherapy.[11,12,17] The patient reported onset of mild memory loss and occasional confusion 2 years after completion of chemotherapy, and the results of a neuropsychologic evaluation were consistent with frontal-lobe dysfunction. Follow-up neuropsychologic assessments showed a rapid decline, with diffuse cognitive impairment and significant generalized cortical atrophy on MRI. The time intervals for the subsequent follow-up were not specified but the relatively rapid decline is unusual and raises the possibility that an independent process may have occurred and/or the chemotherapy contributed to the progression of a preexisting condition, such as a neurodegenerative disorder. The patient's initial presentation with predominance of executive dysfunction and the rapid cognitive decline are atypical for Alzheimer disease, but other, less common neurodegenerative diseases could not be excluded. Interestingly, iron accumulation was detected in the patient's basal ganglia bilaterally. Increased iron levels in the basal ganglia are present in the early stages of multiple neurodegenerative diseases, and have been considered a risk factor for age of onset.[18] Also, it is unclear if comorbidities such as cerebrovascular disease, metabolic, infectious, or mood disorders, or a paraneoplastic process could have contributed to the patient's decline. Mild regional atrophy and white matter hyperintensities have been described in some breast cancer patients treated with standard chemotherapy,[13,14] but diffuse and prominent atrophy has not been documented in these patients, and this finding also raises the possibility of comorbidity.

The case study reported by Swayampakula and colleagues brings to attention the possibility that some breast cancer patients may be at increased risk for the development of delayed adverse cognitive effects of chemotherapy. Further, for some survivors, these changes may be more severe than have been previously reported in the literature. This case, and research finding lower-than-expected cognitive performance prior to beginning adjuvant treatment, raises the possibility that cancer treatments like adjuvant chemotherapy may accelerate the progression of preexisting conditions. Ongoing longitudinal studies of breast cancer patients receiving adjuvant treatments that utilize neuropsychologic evaluations and structural and functional imaging techniques should provide data relevant to these hypotheses. Understanding the incidence of this phenomenon and the underlying mechanisms may lead to improvements in treatment planning and implementation of interventions that could improve quality of life.

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