Toxic Leukoencephalopathy: A Review and Report of Two Chemotherapy-Related Cases

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Toxic leukoencephalopathy is a rare disorder that is characterized by edema of cerebral white matter (Filley & Kleinschmidt-DeMasters, 2001). Because this syndrome alters neurobehavioral function, patients may present in a confused state, which can progress quickly to irreversible dementia, coma, or death, depending on its severity (Cossaart, SantaCruz, Preston, Johnson, & Skikne, 2003; Filley, 1999; Filley & Kleinschmidt-DeMasters). Caused by toxins, such as chemotherapy agents, the prevalence of this disorder is unknown; however, it has been reported increasingly in the literature. Two cases of chemotherapy-related leukoencephalopathy are described in this article, along with a review of the current literature.

Case Reports

Ms. C, who is 66 years old, developed leukoencephalopathy following high-dose melphalan and stem cell rescue for multiple myeloma. Ms. W, a 50-year-old with acute myeloid leukemia, developed the syndrome following cytarabine and daunorubicin chemotherapy and methylprednisolone administration for an erythema multiforme rash. In both cases, complete resolution of symptoms occurred, although case reports have shown the course progresses rapidly, resulting in death (Cain, Burton & Holcombe, 1998; Cos- saart et al., 2003).

Leukoencephalopathy syndrome is a rare disorder that results from structural alterations of cerebral white matter, is characterized by cerebral edema, and can occur in patients of any age. Cranial irradiation and certain chemotherapy agents, especially those used in high-dose protocols, are causal agents. The prevalence of toxic leukoencephalopathy is unknown, however, this syndrome has been reported increasingly in the literature in patients who develop neurobehavioral changes following exposure to various toxins. Diagnosis must confirm exposure to a toxin and the presence of neurobehavioral deficits and neuroradiologic abnormalities. In most reported cases, clinical symptoms are reversible after the offending toxin is withdrawn. This article describes two cases of chemotherapy-related leukoencephalopathy and reviews the nursing care of patients experiencing this syndrome.

Key Words: leukoencephalopathy, toxins, neurologic manifestations

Case Study 1

Ms. C was admitted to an acute private hospital in Australia on June 10, 2002, for high-dose chemotherapy and an autologous stem cell transplant to treat her multiple myeloma. On the third day of admission in preparation for the transplant, she received melphalan 200 mg/m² (380 mg) as the conditioning regimen. Twenty-four hours after melphalan administration, Ms. C was re-infused with 7.08 x 10⁹ CD34 cells. She subsequently experienced nausea and vomiting, fluid retention with a weight gain greater than 1 kg that required 40 mg of furosemide via IV on days 5–7 of her admission, and moderate to severe mucositis and esophagitis that necessitated a morphine infusion on day 10 of her admission. Neutropenic fever occurred on day 7; as a result, ticarcillin and clavulanic acid, gentamicin, and vancomycin were initiated.

On day 13 of her admission, Ms. C became increasingly confused. Her blood pressure (BP) was 140/90 mm/Hg, and her electrolytes were within normal limits, except for an increased level of creatinine from 0.81 mmol/l to 1.34 mmol/l (normal range = 0.04–0.12 mmol/l). Her confusion persisted, and she became disoriented to time and place. No headaches were reported. A computed tomography (CT) scan of the head performed at this time was normal, and biochemical and hematologic parameters were within normal limits. On day 16, Ms. C remained disoriented to time and place, was agitated, and developed hypertension (BP 196/90 mm/Hg). Further neurologic deterioration occurred: The patient was unresponsive to verbal commands, her eyes deviated to the right, and she developed cortical blindness (i.e., loss of sight because of a lesion in the cortical representation of vision, yet the fundus and pupillary reflexes are normal). On day 17, a lumbar puncture yielded


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cerebrospinal fluid with a leukocyte count of four per microliter and a red cell count of 33 per microliter. Cerebrospinal fluid protein elevated to 1.49 g/l (normal range = 0.15–0.45 g/l), and her cultures and cytology were negative. A second CT scan of the brain showed no abnormalities, but a magnetic resonance imaging (MRI) scan of the brain on day 18 revealed changes consistent with bilateral edema of posterior occipital and parietal lobes (see Figure 1).

Neutrophil recovery of the peripheral blood had been achieved on day 14, and antibiotics were discontinued. Antibiotics were restarted on day 18 for ongoing fever and continued for seven days.

By day 19, Ms. C was alert, but her bilateral cortical blindness persisted. An electroencephalogram revealed bioccipital epileptic discharges. On day 25, her vision remained impaired with prominent diplopia; however, a repeat MRI showed significant improvement in the occipital area (see Figure 2). Ms. C was discharged on day 35 with ongoing visual disturbances of diplopia and depth perception. Subsequent MRIs revealed further improvement, and by day 75 post-transplant, she had recovered completely from the toxic leukoencephalopathy.

Case Study 2

On June 20, 2002, four days after completing induction chemotherapy for acute myeloid leukemia (cytarabine 100 mg/m² [150 mg] every 12 hours for seven days and daunorubicin 60 mg/m² [90 mg] for three days), Ms. W developed an itchy maculopapular rash and fever. After being admitted to the hospital, a skin biopsy was performed on day 2 that showed a lichenoid drug reaction. The patient started on methylprednisolone 40 mg twice daily. Serology for mycoplasma, rubella, parvovirus, and measles was negative at this time. The methylprednisolone was increased to 100 mg twice daily to control the rash on day 3.

On day 6, Ms. W was afebrile, the rash had resolved, and the dose of methylprednisolone was reduced to 80 mg twice daily; however, she began to experience a headache and reported hemianopia (i.e., loss of vision in half of the visual field). MRI of the brain revealed white matter changes in both occipital lobes, right posterior thalamus, and posterior frontal paraventricular regions, which is consistent with toxic leukoencephalopathy (see Figure 3). Cerebrospinal fluid analysis showed a leukocyte count of 19 per microliter and red cell count of 40 per microliter; her glucose was elevated at 5.8 mmol/l (normal range = 2.5–4.5 mmol/l). Cultures were negative for herpes simplex virus I and II and varicella zoster virus, and cytology was negative. Ms. W’s creatinine level was within normal limits, and her hepatic enzymes were elevated slightly.

The patient’s condition continued to deteriorate, and she experienced a tonic clonic seizure four hours after the onset of visual symptoms. Immediately postictal, Ms. W’s oxygen saturation level was 98% and her blood glucose level was 9 mmol/l (normal range = 3.6–7.7 mmol/l). Phenytoin 1 g was administered via IV. A second tonic clonic seizure occurred 45 minutes later, and clonazepam 0.25 mg IV was given. On day 9, consolidation chemotherapy was administered (cytarabine 1.5 g/m² [1.5 g] every 12 hours on days 1, 3, and 5 with daunorubicin 60 mg/m² [90 mg] on days 1 and 2). Ms. W continued to receive phenytoin throughout her hospital stay and did not experience any additional seizures. MRI on completion of her second cycle of chemotherapy revealed complete resolution of the toxic leukoencephalopathy (see Figure 4).

Leukoencephalopathy

Leukoencephalopathy syndrome has been associated with a variety of conditions, including hypertension, eclampsia, central nervous system infections, and hypertensive resulting from renal disease (Hinchee et al., 1996; Krupp, Lipton, Swerdlow, Leeds, & Llena, 1985; Richardson, 1961). This disorder also can present in patients with multiple sclerosis, cerebrovascular disease, or AIDS (Filley & Kleinschmidt-DeMasters, 2001; Langford et al., 2002). Toxic leukoencephalopathy results from exposure to a toxin and may occur following exposure to cranial irradiation, cytotoxic and other therapeutic drugs, drugs with abuse potential, and environmental toxins (Filley, 1999; Lee, Nauert, & Glass, 1986). Figure 5 outlines the possible causes of toxic leukoencephalopathy.

Chemotherapy agents, including methotrexate (administered by intrathecal, intraventricular, or high-dose IV routes), cytarabine, L-asparaginase, 5-fluorouracil, intrathecal and intraventricular thiourea, and IV and intracarotid cisplatin (with or without car-
mustine), can cause toxic leukoencephalopathy (Buckanovich et al., 2002; Cohen, Lossov, & Polliack, 2002; Henderson, Rajah, Nicol, & Read, 2003; Ki et al., 2002; Lee et al., 1986; Rathi et al., 2002; Sueblinvong et al., 2002). Fludarabine, cladribine, and pentostatin also have been identified as producing white matter changes in MRI scans associated with toxic leukoencephalopathy syndrome include the immunosuppressive agents cyclosporin and FK-506 and the biotherapy agents interferon-alfa (Filley, 1999) and interleukin-2 (Filley, 1999; Vecht et al., 1990).

Cranial irradiation and/or chemotherapy are responsible for the changes seen in cerebral white matter (Asato et al., 1992; Corn et al., 1994; Crossen, Garwood, Glatstein, & Neuwelt, 1994; Lee et al., 1986). Corn et al. determined that white matter changes correlate with cranial radiation doses and higher doses are more likely to cause encephalopathy than lower doses. In an analysis of 29 studies, Crossen et al. found cognitive impairment in 213 of 748 patients who received therapeutic cranial radiation and 100 of 368 patients who received prophylactic cranial radiation. Radiation encephalopathy appears to be more common than radiation necrosis, and long-term follow-up of these patients is needed to assess for any neurobehavioral change. Lee et al. also found that the interval to detect white matter changes was shortened when patients received whole-brain irradiation followed by various chemotherapeutic protocols.

**Pathophysiology**

The brain is protected by an autoregulation system that maintains perfusion against extremes in blood pressure. Changes in the blood-brain barrier can occur when the autoregulation system is exceeded. For example, severe acute hypertension impairs the autoregulation system and sympathetic stimulation results in vasoconstriction (Cain et al., 1998). Researchers accounted for the abnormalities of toxic leukoencephalopathy by suggesting that vasospasm occurs in the cerebral vasculature and produces edema (Trommer, Homer, & Mikhael, 1988). Alternatively, Schwartz et al. (1992) posited that a vasodilatory mechanism is responsible for edema and related abnormalities because radiologic findings suggesting ischemia or infarction are seen infrequently. The posterior circulation of the brain lacks the sympathetic innervations of the anterior circulation, which may account for the vasodilation of the posterior vessels and the abnormalities largely seen in the posterior region (Cain et al.). Hinchey et al. (1996) postulated that, in leukoencephalopathy syndrome, abnormalities occur as a result of a brain capillary leak syndrome related to hypertension, fluid retention, and the effects of chemotherapy agents or immunosuppressive agents on the vascular endothelium.

**Clinical Presentation**

Toxic leukoencephalopathy syndrome can occur in patients of any age. Clinical manifestations include headache, decreased alertness, confusion, memory loss, hallucinations, asterixis (e.g., flapping tremors primarily in the hands), hemiparesis, hypertension, seizures, and visual disturbances (e.g., blurred vision, hemianopia, flashing lights, cortical blindness) (Filley, 1999; Hinchey et al., 1996; Lee et al., 1986; Pavlakis, Frank, & Chusid, 1999; Schwartz et al., 1992). In severe cases, presentation can include dementia, abulia (i.e., the inability to perform voluntary actions), stupor, and coma (Filley & Kleimschmidt-DeMasters, 2001). Clinical manifestations usually correlate with the severity of the white matter changes demonstrated on imaging. In most reported cases, clinical symptoms are reversible by removing the underlying cause or withdrawing the offending drug.

Visual disturbances have been linked with the high frequency of bilateral occipital lobe involvement on MRI scans. In a review of 15 patients with encephalopathy, Hinchey et al. (1996) found that 10 had visual disturbances ranging from blurred vision to cortical blindness. Other reports also have documented significant white matter changes in two patients receiving amphotericin B (Walker & Rosenblum, 1992), a patient treated with CHOP chemotherapy and high-dose steroids (Cain et al., 1998), and three patients treated with 5-fluorouracil and levamisole (Hook et al., 1992).

Radiologic findings of leukoencephalopathy include white matter abnormalities in the posterior regions of the cerebral hemispheres (Hinchey et al., 1996; Schwartz et al., 1992). These abnormalities typically encompass both hemispheres; are seen commonly in the occipital, posterior parietal, and posterior temporal lobes; and have been reported in the thalamus, cerebellum, and frontal regions (Hinchey et al.; Schwartz et al.). Hypodense lesions of subcortical white matter may be apparent on CT or MRI scans (Schwartz et al.).
Diagnosis

Diagnosis relies on the clinician identifying the exposure to a toxin, presence of neurobehavioral deficits on patient examination, and neuroradiologic abnormalities (Filley & Kleinschmidt-DeMasters, 2001). Filley (1998) outlined the occurrence of white matter damage when deficits occur in attention, memory, visuospatial skills, executive function, and emotional status with preservation of language. Detection of these deficits may be difficult because language is spared and tests such as the Mini-Mental State Examination rely mainly on the assessment of verbal abilities (Filley, 1998). Therefore, assessment must focus on detection of inattention, memory deficits, and visuospatial dysfunction. In addition to neurobehavioral assessment and clinical observation, MRI scans are very sensitive in detecting changes in the white matter of the cerebrum (Reddick, Glass, Langston, & Helton, 2002).

Discussion

Ms. C’s leukoencephalopathy manifested initially by a sudden deterioration in mental state with increasing confusion. Neuroimaging findings from the first CT scan did not identify any abnormalities; however, with continuing deterioration in her condition, a subsequent MRI scan revealed abnormalities in the white matter (see Figure 1). This is similar to other published cases where CT scans were less sensitive than MRI scans to changes in the white matter of the brain (Asato et al., 1992; Corn et al., 1994). Clinical findings were similar to those reported in the literature (e.g., altered mental status, confusion, visual disturbances such as cortical blindness) (Filley, 1999; Hinchey et al., 1996). Fortunately, the symptoms experienced by Ms. C were slowly reversible. Melphalan appeared responsible for the toxic leukoencephalopathy.

Ms. W’s symptoms developed rapidly over a period of hours and began with a headache and visual disturbances. Her MRI scan documents white matter changes in the occipital lobes bilaterally (see Figure 3). The patient received a loading dose of phenytoin and remained on a daily dose of 300 mg throughout her second course of chemotherapy. Seizures have been documented following methyleneproline administration; however, they have not been associated with changes in imaging studies, such as CT scan abnormalities (Suchman, Condemi, & Leddy, 1983). Cain et al. (1998) reported a single case of fatal leukoencephalopathy in a patient with lymphoma treated with CHOP chemotherapy and high-dose steroids. Cytarabine also has caused toxic leukoencephalopathy (Lee et al., 1986), but weeks had passed since Ms. W received this drug. Additionally, two further courses of cytarabine have been given without complications since June 2002.

Management

Corticosteroids, anticoagulation, ventriculoperitoneal shunting for cranial irradiation-induced leukoencephalopathy, and leucovorin for methotrexate-induced toxicity may be useful in the management of toxic leukoencephalopathy (Filley & Kleinschmidt-DeMasters, 2001). Most importantly, once the toxin has been identified, it should be withdrawn or the dose reduced. For those who develop leukoencephalopathy, prompt treatment in controlling symptoms associated with elevated blood pressure and fluid retention is paramount. These measures usually result in the reversal of the cerebral edema and associated signs and symptoms.

Nursing Implications

Nursing assessment of risk factors and neurologic function must be initiated when treatment begins and continue regularly throughout the duration of treatment. A thorough assessment includes identifying neurologic risk factors, performing a neurologic examination, and assessing mental status, especially targeting memory recall. During treatment, signs and symptoms such as headache, visual disturbances, elevated blood pressure, increased creatinine levels, and fluid retention need to be detected promptly and monitored closely. Family members should be involved in the assessment process because they are usually the first to observe mental status changes in patients (Meriney & Grimm, 1997).

Patients with mental status impairment and visual disturbances require a safe environment to protect them from injury. They may require support with activities of daily living and use of assistive devices (Pearce, 1998). Patients also may need to be observed and supervised, particularly during the night. Additionally, reorientation to time, place, and person may be necessary.

Psychosocial support is essential. Patients and families need support to cope with this treatment complication. Healthcare providers must ensure that patients and families are informed that the condition usually is reversible if the toxin is identified and removed and symptoms are treated promptly. Although the syndrome typically is reversible, in conditions that are slow to resolve or progressive, nurses must prepare patients and families for a potentially fatal outcome and may be involved in arranging for or providing palliative care.

Conclusion

Toxic leukoencephalopathy syndrome is a rare disorder characterized by cerebral edema, and various factors lead to its development. Prompt recognition is vital so that the offending agent can be withdrawn and symptoms can be treated. Nurses play an important role in the detection and treatment of this disorder.

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References


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**Rapid Recap**

**Toxic Leuкоencephalopathy: A Review and Report of Two Chemotherapy-Related Cases**

- Toxic leuкоencephalopathy syndrome is a rare disorder that results from exposure to a toxin. Cranial irradiation, certain chemotherapy and biotherapy agents, immunosuppressive drugs, and drugs with abuse potential can cause this disorder.
- Clinical manifestations include headache, visual disturbances, altered mental status, and seizures. Toxic leuкоencephalopathy may be fatal.
- Diagnosis involves documentation of exposure to a toxin and presence of neurobehavioral deficits and neuroradiologic abnormalities.
- Prompt recognition of this disorder is vital so that the offending agent can be withdrawn and the symptoms caused by the cerebral edema can be treated.