

Cortical Blindness during Chemotherapy: Clinical, CT, and MR Correlations

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Abstract: Two patients treated by chemotherapy for a non-Hodgkin malignant lymphoma developed focal neurological symptoms including disorientation, hemiplegia, and cortical blindness 5 and 15 days after the end of a polychemotherapy course, including methotrexate and vindesine. In both patients ECG and blood pressure were normal. Case 1 had a slight increase of protein level without cells on CSF examination and presented with a paralytic ileus. Case 2 developed an inappropriate antidiuretic hormone secretion (IADHS) syndrome. In both cases, noncontrast CT scans showed bilateral, symmetrical low density areas within the temporooccipital regions. Postcontrast CT images stressed major cortical and subcortical enhancement predominantly over the gray matter. In Case 2 the lesions also affected the right parietal lobe. Magnetic resonance scans 2-3 weeks after the onset of neurological symptoms demonstrated low intensity signal lesions on T1-weighted images and bright signal on T2-weighted images. In Case 1 the visual deficit failed to regress and in Case 2 the patient died 2 months later because of the natural evolution of her lymphoma. The clinical and radiological data suggested that a vascular ischemic process was responsible for the cerebral lesions in these two patients. As Vinca alkaloids and not methotrexate have been implicated as a cause of cortical blindness, and as our two patients presented signs of overdose of vindesine (paralytic ileus and IADHS), we suggest that the neurological and radiological abnormalities in our patients may have been due to neurotoxicity of vindesine. **Index Terms:** Cortical blindness—Drugs, toxicity—Lymphoma—Computed tomography—Magnetic resonance imaging.

Cortical blindness refers to loss of vision induced by lesions affecting the geniculocalcarine visual pathways and is most frequently caused by vascular involvement (1). Recently, transient cortical blindness related to vincristine toxicity has been described (2). We report two cases of cortical blindness during intensive chemotherapy for non-Hodgkin lymphoma. Analysis of clinical and radiological data led us to suggest a toxic etiology and to propose vindesine administration as the causal agent.

CASE REPORTS

Case 1

A 58-year-old woman was hospitalized for a check-up and treatment of an abdominal B cell non-Hodgkin lymphoma. She had no previous cardiovascular, neurologic, or visual impairment. Fifteen years ago, she had undergone successful radiotherapy for breast cancer. The current treatment of the lymphoma lasted for 6 months and included several cytotoxic drugs according to the chemotherapeutic protocol detailed in Table 1. A total dose of 10 mg of vindesine was administered during a 3 month period. Five days after the end of the chemotherapy, a paralytic ileus occurred, and at the same time, cortical blindness, right hemiplegia, and left hemiparesia without facial involvement developed. Visual and motor deficits were associated with temporospatial disorientation and gross anterograde amnesia. Cardiovascular examination was normal, including the arterial blood pressure. Three days later, a CSF study showed mildly elevated proteins (0.7 g/L) with normal glucose and cell count. Blood plate-

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TABLE 1. Chemotherapeutic protocol of case 1

Phase A

D1 mitoxantrone (15 mg)
 D1-3 ifosfamide (1,500 mg)
 D1 teniposide (225 mg)
 D5 mitoguanzone (450 mg)
 D5 teniposide (225 mg)
 D15 methotrexate i.v. (2,100 mg)
 D3 and 15 intrathecal methotrexate (15 mg)
 D3 intrathecal cytosine arabinoside (60 mg)

Phase B (15 days after end of Phase A)

D1 and 2 Adriamycin (55 mg)
 D1 vindesine (3 mg)
 D1 and 2 cyclophosphamide (900 mg)
 D1 bleomycin (15 mg)
 D1 adriamycin (55 mg)
 D1-5 prednisone (60 mg)
 D5 intrathecal methotrexate (15 mg)

The same sequence was repeated 15 days after the end of Phase B. A complete remission was obtained without major side-effects and 6 wks later a new treatment regimen was started, which included

D1 mitoxantrone (15 mg), etoposide (225 mg), and ifosfamide (1,500 mg)
 D2 and D3 ifosfamide (1,500 mg)

4 wks later:

D1 Adriamycin (40 mg), cyclophosphamide (600 mg), and vindesine (2 mg)
 D2 Adriamycin (40 mg) and cyclophosphamide (600 mg)
 D7 vindesine (2 mg) and methotrexate (300 mg)

D, day.

let counts were high ($500 \times 10^9/L$). Noncontrast, emergency CT revealed bilateral, grossly symmetrical, and slightly heterogeneous low density areas within the temporooccipital regions. The hypodensities spared the inner part of the occipital lobes, had sharp boundaries, and exerted no mass effect upon the adjacent structures (Fig.

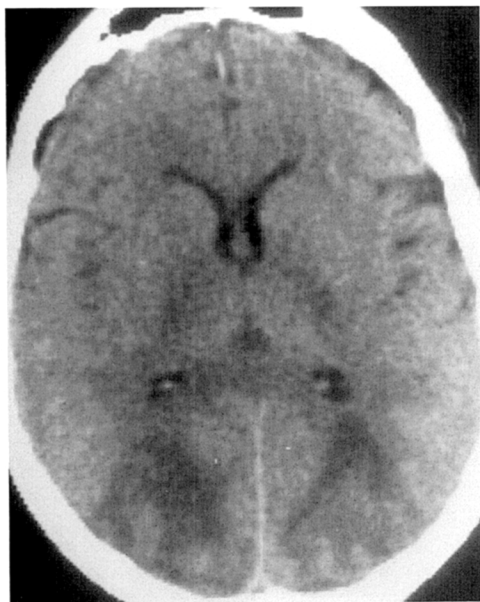


FIG. 1. Case 1. Axial noncontrast CT scan shows well delimited, symmetrical areas of hypodensity in the occipitotemporal areas. Both white and gray matter appear to be involved.

1). Postcontrast CT 10 days later showed enhancement of the same lesions predominantly over the gray matter (Fig. 2). Magnetic resonance (MR) imaging (Signa;GE) conducted 3 weeks after the advent of the clinical symptoms demonstrated temporooccipital lesions that were hypointense on T1 and hyperintense on T2 images (Fig. 3). Nine months later the left hemiparesia had resolved completely, but neurological examination disclosed moderate improvement of the other symptoms. Right hemiparesia was persistent and visual acuity was limited to color and form recognition with associated major optic ataxia. Anterograde amnesia completely resolved.

Case 2

A 62-year-old woman was hospitalized in February 1988 for the treatment of a lymphoproliferative syndrome with hypersplenism. She had been successfully treated 15 years previously for cancer of the uterus with surgery and radiotherapy. Currently, a splenectomy was performed to assess the histological type of the lymphoma. The diagnosis of splenic, low malignancy non-Hodgkin lymphoma was made and no treatment was prescribed. In June the patient exhibited a rapid onset of multiple adenopathies and infiltration of both kidneys disclosed by abdominal ultrasound. Histological analysis of the adenopathies revealed a great cell lymphoma (G international classification). Polychemotherapy was started according to a protocol described in Table 2. A total dose of 7.6 mg of vindesine during a 1 week course was administered. The CSF analysis showed no abnormality. One week after the end of chemotherapy, she presented with sudden bilateral deafness and tinnitus. Five days later hyponatremia (113 mmol/L) due to inappropriate antidiuretic hormone secretion (IADHS) was recognized. This hyponatremia brought about clinical symptoms of encephalopathy followed by the sudden onset of a left hemiplegia associated with cortical blindness. There was no history of head

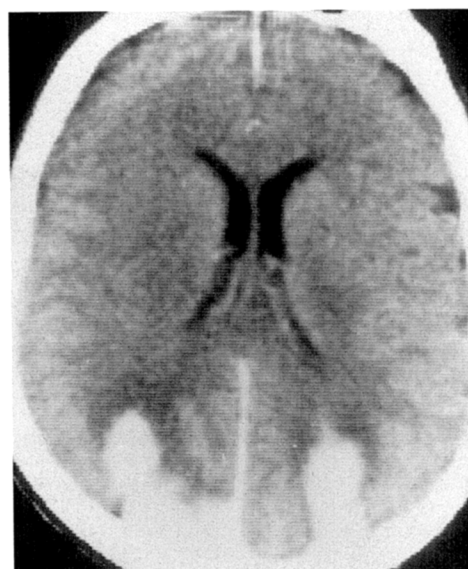


FIG. 2. Case 1. Axial postcontrast CT scan shows enhancement of the lesions described in Fig. 1.



FIG. 3. Case 1. Axial T2-weighted MR image (TR 2,000 ms, TE 90 ms) shows high signal intensity in the affected areas.

trauma or of lowering of blood pressure. The CSF analysis, heart echography, and ECG were normal. The platelet count was high (between 500 and $625 \times 10^9/L$) since the splenectomy and was not modified. Noncontrast CT showed bilateral low density areas at the temporooccipitoparietal junctions (Fig. 4). The MR scans showed corresponding hypointensity (T1) and hyperintensity (T2) areas (Fig. 5). Two months later CT showed a decrease in the size of the lesions (Fig. 6) accompanied by a slight improvement in the neurological disorders: The patient was conscious, but kept a serious left hemiplegia and a cortical blindness. During the following 2 months, the vision slightly improved and the IADHS was under control. Because of the huge volume of the remaining adenopathies, a new chemotherapy course was initiated. Later complications developed and the patient died of septic shock.

DISCUSSION

The onset of cortical blindness in our two patients was associated with CT and MR abnormalities. To us, the CT features seemed peculiar both in their topography and in their postcontrast enhancement. The lesions were well delimited, low density areas within the occipital lobes involving both white and gray matter. Their gyriform enhancement was sug-

TABLE 2. Chemotherapeutic protocol of Case 2

D1 Adriamycin (105 mg) and cyclophosphamide (1,700 mg)
D1 and 5 vindesine (3.8 mg)
D1 and 5 bleomycin (10 mg)
D1-5 prednisone (100 mg)
D5 intrathecal methotrexate (15 mg)

D, day.

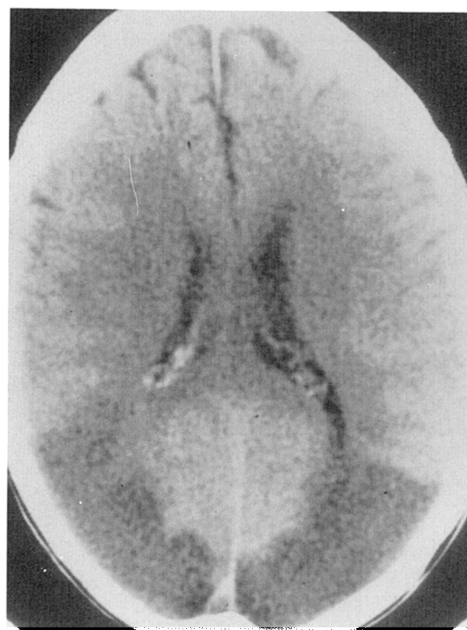


FIG. 4. Case 2. Axial noncontrast CT scan shows large bilateral and symmetrical occipitoparietotemporal areas of hypodensity.

gestive of brain ischemia and their topography was compatible with watershed distribution. In addition, the MR findings were consistent with the hypothesis of vascular occlusion-related necrotizing lesions (3). Arterial mediation seems more likely, since no evidence of venous thrombosis could be



FIG. 5. Case 2. Axial T2-weighted MR image (TR 2,000 ms, TE 90 ms) shows high signal intensity of the lesions described in Fig. 4.

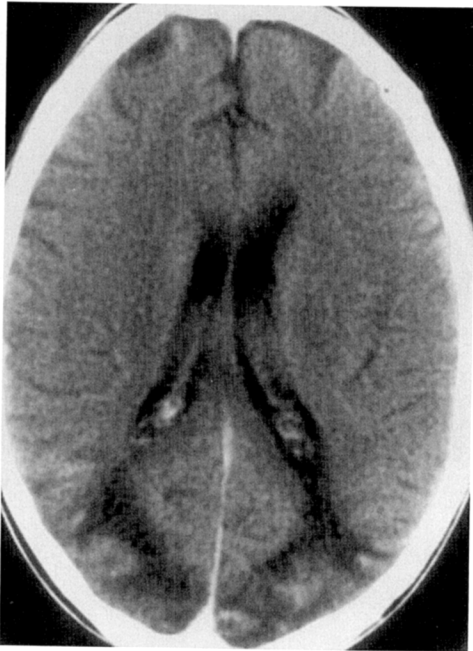


FIG. 6. Case 2. Postcontrast CT scan several months later shows that the lesions have somewhat diminished in size. They still show some enhancement.

elicited either by CT or by MR. Brain lymphoma and infection were ruled out by the imaging results and by the evolution. The most common cause of cortical blindness is vascular impairment of the posterior cerebral arteries and the basilar trunk (1). The variations in the cerebral vascular supply may explain other neurological derangements such as hemiparesia and memory deficits. Cortical blindness has been associated with spontaneous ischemic stroke, cardiac surgery, cerebral angiography, and especially selective vertebral arteriography (4,5). Some other rare causes have been reported, such as peritoneal dialysis, complex partial seizures, cardiac arrest, and head trauma (1).

Since no usual etiology of cortical blindness was discovered in our cases, drug toxicity has to be suspected. Few cases of cortical blindness complicating chemotherapy have been reported after administration of *cis*-platinum (6), vincristine (2), or association of *cis*-platinum and vinblastine (7). All these patients presented transient neurological symptoms that resolved within 48 h. In these cases CT scans were normal and no MR was available. Our two patients sustained permanent cortical blindness with very peculiar and similar abnormalities on CT and MR. They had received many other chemotherapeutic agents (but no *cis*-platinum, vincristine, or vinblastine), among which two products (methotrexate and vindesine) could be implicated in the cerebral toxicity, whereas the others had no known central neurotoxicity. Methotrexate has a wide range of side-effects upon the CNS, mainly leu-

koencephalopathy with extensive hypodensity of the white matter, without lesions of the gray matter. To our knowledge, no methotrexate-related cortical blindness has been reported yet. On the other hand, vindesine, a Vinca alkaloid, is more likely responsible, since cortical blindness due to vincristine has been already reported (2) and because the two patients simultaneously exhibited other signs of toxicity due to vindesine. Case 1 had paralytic ileus, which is a known sign of neurotoxicity of the Vinca alkaloids (8), and Case 2 had IADHS, which may also be related to a vindesine overdose. The onset of IADHS during Vinca alkaloid treatment is well documented: It develops 1–2 weeks after Vinca therapy, especially if the dosages have been high (9,10). In our two patients, the neurological impairment appeared suddenly 1 week after the last vindesine injection. Vinca alkaloids have well known neurotoxic side-effects (8,11,12). The earliest and most constant sign of Vinca alkaloid neurotoxicity is a peripheral neuropathy but cranial nerve impairment, optic neuropathy, and cortical blindness have also been described (2,8). In addition, Vinca neuropathy may be more frequent in patients with malignant lymphoma (13). Finally, our two patients had elevated platelet counts, a classic complication of vindesine therapy (14) that could favor vascular thrombosis. Direct endothelial toxicity could also be implied since some chemotherapeutic agents have demonstrated arterial toxicity during intraarterial administration (15). Recently, similar radiological findings have been reported after treatment with tiazofurim (16).

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