Cortical blindness and seizures possibly related to cisplatin, vinblastine, and bleomycin treatment of ovarian dysgerminoma

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Ovarian dysgerminoma is the most common ovarian malignancy in young women. Conservative treatment is indicated in the reproductive-age woman who wishes to preserve childbearing capacity. This case report describes a patient with ovarian dysgerminoma who underwent chemotherapy with a cisplatin-vinblastine-bleomycin regimen that resulted in serious toxic complications—including cortical blindness and seizures—that were transient in nature. Although current chemotherapy regimens have dramatically improved the overall survival of women with germ-cell tumors, there are toxic complications such as those demonstrated in this report, and toxicity must be balanced against presumed benefit.

(Key words: Chemotherapy, dysgerminoma, cortical blindness)

The challenge of treating germ-cell ovarian tumors in young women is to adequately treat the malignancy while at the same time, if possible, preserving reproductive capacity. Therapeutic options for dysgerminoma include conservative surgery and postoperative chemotherapy or radiation therapy. Similar survival rates have been obtained with both methods; therefore, when a patient wishes to retain her childbearing capacity, conservative management with surgery and chemotherapy may be indicated.[1,2] This case report concerns a patient who was seen for serious, but reversible, toxic complications of treatment with a cisplatin-vinblastine-bleomycin regimen.

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Report of case

A 21-year-old nulligravid woman was seen at the David Grant USAF Medical Center gynecology clinic on June 22, 1988, with a complaint of increasing abdominal girth of 1 month's duration and abdominal pain, nausea, and bloody diarrhea over the previous 24 hours. Her menses were regular, with a cycle length of 28 days, a flow of 7 days, and mild dysmenorrhea. There was no history of pelvic inflammatory disease, intrauterine device use, sexually transmitted disease, or a family history of gynecologic malignancy. She had been taking oral contraceptives for the previous 4 months.

Physical examination revealed the patient to be alert and oriented but pale and mildly dyspneic at rest. Abdominal examination revealed a suprapubic mass to the level of the umbilicus and to the flanks laterally. Guarding was present but rebound tenderness was not noted. Pelvic examination revealed a 10 × 20-cm fixed, solid mass in the midline extending to the umbilicus. The uterus was small and displaced posteriorly. Rectovaginal examination confirmed the mass and was Hemoccult-negative. Findings of the remainder of the physical examination were unremarkable.

Barium enema and intravenous pyelogram stud-

ies did not show significant abnormality except for the central mass effect. An ultrasound examination of the abdomen and pelvis identified a 20 × 20-cm mixed echogenic mass in the pelvis with presumed tumor studding on the anterior abdominal wall and ascites. Laboratory studies produced the following results: complete blood cell (CBC) count (white blood cell [WBC] count, 8400 cells/mm^3; hemoglobin [Hgb], 13.0 g/dL; hematocrit [Hct], 37.3%; and platelet count, 347,000/mm^3); urinalysis, negative; sodium, 140 mEq/L; potassium, 4.4 mEq/L; chloride, 102 mEq/L; CO_2, 27 mEq/L; glucose, 75 mg/dL; blood urea nitrogen (BUN), 15 mg/dL; creatinine, 0.7 mg/dL; human chorionic gonadotropin (HCG), negative; α-fetoprotein, < 2.0 ng/mL; CA-125, 15 U/L; and lactate dehydrogenase (LDH), 588 U/L.

Two days after admission, the patient underwent an exploratory laparotomy. The operative findings included bloody ascites (positive cytology), and a 10 × 20-cm left ovarian tumor. The uterus and right ovary were normal. A left salpingo-oophorectomy, an omentectomy, peritoneal biopsies, and lymph node sampling were performed.

Frozen section analysis produced a diagnosis of a germ-cell ovarian carcinoma of undetermined type. Final pathologic analysis determined the lesion to be an ovarian dysgerminoma. A single anterior wall excisional biopsy of a 1-cm nodule indicated metastatic tumor. However, all lymph node analyses produced negative results. The patient was therefore classified as International Federation of Gynecology and Obstetrics (FIGO) stage IIIb.

The patient did well postoperatively. A combination chemotherapy regimen consisting of cisplatin (100 mg/m^2 administered intravenously [IV] on day 1, vinblastine sulfate (18 mg/m^2 IV on days 1 and 2), and bleomycin (15 units/m^2 administered intramuscularly on days 1, 8, and 15) was initiated on postoperative day 7. No significant toxicities were noted, and the patient was discharged on July 2. The plan was to repeat the chemotherapy cycle every 21 days, if tolerated by the patient, for a total of four courses.

On July 9, the patient was readmitted with a diagnosis of pyelonephritis and neutropenia. She received transfusion of 2 units of packed red blood cells, and empiric antibiotic therapy (imipenemcilastin) was begun. Rapid resolution of the pyelonephritis permitted the patient to receive her third dose of bleomycin, thus completing the first cycle of cisplatin [Platinol]-vinblastine-bleomycin (PVB) therapy on July 14.

Despite the fact that pyelonephritis and neutropenia had developed, the patient was believed to have recovered completely and was therefore kept on the original chemotherapy schedule. The second cycle of PVB was given at 100% dose levels on July 21. However, the patient was again readmitted on July 27 with severe arthralgia, myalgia, anorexia, and nausea.

She was afebrile and denied having sweats, chills, diarrhea, or dysuria. Physical examination revealed a thin, anxious woman in moderate distress but entirely normal physically. Laboratory studies produced the following values: CBC count (WBC count, 0.6/mm^3; Hgb, 7.0 g/dL; Hct, 20.6%; platelets, 135,000/mm^3); sodium, 132 mEq/L; potassium, 3.8 mEq/L; chloride, 96 mEq/L; CO_2, 25 mEq/L; glucose, 131 mg/dL; BUN, 15 mg/dL; creatinine, 0.8 mg/dL; LDH, 598 U/L. Blood cultures were obtained. Results of urinalysis were negative. The patient received a transfusion of 2 units of packed red blood cells, and a posttransfusion CBC count showed a WBC count of 0.3/mm^3; Hgb, 14.0 g/dL; Hct, 39%; and platelets, 129,000/mm^3.

On July 28, the patient received her second dose of intramuscular bleomycin as a part of the second cycle. On July 29, a new complaint surfaced. An inability to focus and blurred vision had developed over the preceding 12 hours. Optokinetic examination was positive for bilateral vision loss. Intravenous dexamethasone therapy was initiated, and a computed tomography (CT) scan of the head was obtained. During the scan, the patient experienced two grand mal seizures. She was stabilized with diazepam, labetalol, and intravenous phenytoin.

A lumbar puncture to evaluate cytologic values, cultures, viral serology studies, immunocomplex assays, and cisplatin levels was performed. Other laboratory studies showed the following values: WBC count, 0.3/mm^3; Hgb, 13.8 g/dL; Hct, 39.5%; platelets, 157,000/mm^3; glucose, 156 mg/dL; BUN, 9.0 mg/dL; creatinine, 0.6 mg/dL; sodium, 132 mEq/L; potassium, 3.6 mEq/L; chloride, 95 mEq/L; and CO_2, 25 mEq/L. An electrocardiogram showed normal results.

The head CT scan showed an equivocal area of echogenicity in the left occipital region without evidence of a mass. Magnetic resonance imaging revealed bilateral occipital and frontal cortical abnormalities with high signal intensity consistent with a possible toxic cause. Results of a cerebral angiogram were normal.

The patient had two additional seizures on July 29. No subsequent seizure occurred. Clinically, the patient's visual symptoms improved and, on July

30, a neurologic examination revealed no evidence of optic neuritis. Optokinetic examination at that time revealed increased perception of light and motion bilaterally. The patient's vital signs were stable and her WBC count was 0.4/mm^3.

On July 31, the WBC count was 1.5/mm^3. Dexamethasone therapy was discontinued but oral phenytoin therapy was continued. On August 1, 4 days after the onset of blindness, visual acuity had returned and results of the neurologic examination were normal. Cerebrospinal fluid, cytology, cultures, viral serology, and immunocomplex assays were normal as were values for antinuclear antibody and rapid plasma reagin. An electroencephalogram showed a paroxysmal discharge from the occipital cortex.

On August 5, the patient was discharged with normal vision and no further seizures. Because the chemotherapy could not be definitively excluded as the cause of the seizure disorder and transient blindness, the patient chose to discontinue further chemotherapy and opted instead for close clinical follow-up. This follow-up consisted of physical examinations and serial CT examinations of the abdomen and pelvis as indicated. The patient declined radiation therapy because of fertility concerns.

The patient has been followed up with serial abdominopelvic CT scans and frequent physical examinations. There was no evidence of recurrent disease 10 months after chemotherapy was discontinued. Phenytoin therapy has been discontinued because of an allergic reaction. There has been no further seizure activity.

Discussion

Dysgerminoma is the most common ovarian malignancy in young adults but is rare overall, accounting for only 2% of all malignant ovarian tumors.[3] Although the classic treatment has been total abdominal hysterectomy and bilateral salpingo-oophorectomy with postoperative radiation, chemotherapy has been shown to be equal in effectiveness.[1,3,4] Conservative treatment is indicated in the reproductive-age female with stage I disease who wishes to preserve childbearing capacity.[1-4] This conservative management is permitted in light of the fact that the majority of recurrences appear in the first 2 years after initial therapy and can be eradicated by radiation therapy or chemotherapy.

The patient in this case had a tumor classified as FIGO Stage IIIb on the basis of a single 1-cm anterior wall biopsy specimen. The patient's tumor was considered to be a "minimal" stage III and this, coupled with her desire for future fertility, was the reason she was selected for conservative management.

The known toxic effects of cisplatin include renal, gastrointestinal, audiologic, hematologic, and neurologic dysfunction. Cortical blindness and seizures that occur up to 2 weeks after administration have also been reported.[5-8] Bleomycin has documented toxicity that includes damage to the gastrointestinal tract, pulmonary fibrosis, edema of the hands, alopecia, and temperature elevation, but no hematologic toxicity.[3,8] Side effects of vinblastine include alopecia and gastrointestinal, hematologic, and neurologic (loss of reflexes) complications.[3,8]

The onset of this patient's blindness and seizures was temporally related to the cisplatin administration in such a way that they could be attributed to the chemotherapy. In addition, the patient had had a recent febrile illness (pyelonephritis), which supports the theory of combined factors leading to the diagnosis of acute disseminated encephalomyelitis (ADEM).

Causes of this disease can be associated with postinfections (viral or mycoplasmal) or can be carcinoma-associated or idiopathic. Clinically, ADEM is characterized by an abrupt onset with symptoms and signs of brain or spinal cord white matter damage. Mortality is 20% and up to half of the survivors have residual deficits.[9]

Comment

Current chemotherapy regimens have dramatically improved the overall survival rate of women with germ-cell tumors. However, this progress has not been without a certain price in toxicity. Acceptable toxicity must always be balanced against presumed benefit. Physicians need to remain alert and flexible in their response to drug effects. This case report demonstrates one such uncommon possible toxicity.

References

1. Gallion HH, Van Nagel JR: Ovarian dysgerminoma: Report

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of seven cases and review of the literature. *Am J Obstet Gynecol* 1988;158:591-595.

2. Vriesendorp R, Aalders JG, Sleijfer DT, et al: Treatment of malignant germ cell tumors of the ovary with cisplatin, vinblastine, and bleomycin (PVB). *Cancer Treat Rep* 1984;68:779-781.

3. DiSaia PJ, Creasman WT: *Clinical Gynecologic Oncology*, ed 3. St Louis, Mo, CV Mosby Co, 1989.

4. Bianchi VA, Sartor E, Favalli G: New trends in treatment of ovarian dysgerminoma. *Gynecol Oncol* 1986;23:246-251.

5. Pippitt CH, Muss HB, Homesley HD, et al: Cisplatin-associated cortical blindness. *Gynecol Oncol* 1981;12:253-255.

6. Berman IJ, Mann MP: Seizures and transient cortical blindness associated with cisplatin (II) diamminedichloride (PDD) therapy in a thirty-year-old man. *Cancer* 1980;45:764-766.

7. Walsh TJ, Clark AW, Parhad IM, et al: Neurotoxic effects of cisplatin therapy. *Arch Neurol* 1982;39:719-720.

8. Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, NY, McGraw-Hill Book Co, 1985, p 1279, pp 1285-1287, pp 1290-1291.

9. Braunwald E, Isselbacher KJ, Petersdorf RG, et al (eds): *Harrison's Principles of Internal Medicine*, ed 11. New York, NY, McGraw-Hill Book Co, 1987, pp 1999-2000.