Acute encephalopathy associated with continuous vincristine sulfate combination therapy: case report

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Summary

Neurotoxicity is a well-recognized and commonly observed side effect associated with the use of vincristine sulfate in cancer chemotherapy. The clinical manifestations of vincristine neuropathy cover a wide spectrum of peripheral neurologic dysfunctions that have been described to be reversible and cumulative in most instances (1, 2). Paresthesias, loss of tendon reflexes, and progressive weakness are the most common clinical features (3, 4). Sensory impairment, cranial nerve palsies, gastrointestinal disturbances, and autonomic dysfunctions including atonic bladder, impotence, and orthostatic hypotension may occur (5). Acute CNS complications, usually presenting as generalized seizures, are extremely rare and only a few cases have been reported which were without underlying biochemical or structural abnormalities (1, 5–9). We describe the case of a woman with multiple myeloma, who developed fulminant encephalopathy following 4 days of continuous vincristine, adriamycin, and day 1–4 pulse dexamethasone (VAD) combination therapy.

Case report

A 54 year old woman with multiple myeloma, diagnosed in 1981 was referred to the Department of Internal Medicine II of the University Medical School in Vienna in July 1984. Previous treatment had included palliative irradiation of the sternum and the lumbosacral vertebral region, and 3 courses of combination chemotherapy consisting of melphalan (15 mg/m² i.v. day 1), cyclophosphamide (450 mg/m² i.v. day 1), vincristine (1.4 mg/m² i.v. day 1) and prednisone (40 mg p.o., day 1–7 and 20 mg day 8–14). This had been followed by an intermittent schedule with vincristine sulfate at weekly intervals (2 mg intravenously/course × 5), based on the results of an in vitro chemosensitivity profile of the tumor (10). After a cumulative dose of 16 mg, transient peripheral neuropathy had been noted. A partial response was then achieved and maintained for a duration of approximately 14 months. Because of inadequate therapeutic results after reintroduction of combination chemotherapy at relapse, the patient had subsequently been treated with a low-dose total body irradiation (200 rads) which resulted in pain relief. The last of the two radiation courses had been terminated 3 months before readmission to the hospital. At this time the patient was complaining of increasing diffuse bone pain and weight loss, due to disease progression.

Physical examination revealed a pale, afebrile patient in a remarkably reduced general condition and suffering from pain-related decreased mobility. Cardiopulmonal findings and abdominal examination presented no abnormalities. There was no lymphadenopathy nor any evidence of an extra-
medullary manifestation of the basic disease. Importantly, neurologic deficits were not noted at that time.

Laboratory investigations disclosed a hemoglobin level of 9.6 g/dl and a hematocrit reading of 29.5%. Erythrocyte sedimentation rate (Westergren) was 69 mm/hr. Total leukocyte count was 3,800/mm³, differentiated as 64% polymorphs, 34% lymphocytes, 1% eosinophiles, and 1% monocytes. The platelet count was within the normal range.

Serum protein electrophoresis revealed a narrow peak in the gamma region. The protein content was 11.2 g/dl, of which 3.4 g was albumin. The amount of the M-protein, which was classified as IgG-k by immunoelectrophoresis, was 5.9 g/dl. Quantitation of immunoglobulin by radial immunodiffusion showed an IgG of 7014 mg/dl (normal 800–1700), and a decrease in IgA to 48 mg/dl (normal 190–400) and in IgM to 59 mg/dl (normal 60–280). No Bence Jones protein was detected in the urine. Serum glutamic oxaloacetic transaminase (SGOT) was 23 U/l (normal 0–20), lactic dehydrogenase (LDH) 177 U/l (normal 80–240), and serum alkaline phosphatase 290 U/l (normal 60–170). The serum level of sodium was 135 mEq/l, of chloride 97 mEq/l, and of potassium 3.5 mEq/l. Serum calcium was remarkably elevated with 15.3 mg/dl, although clinical symptoms were not present. The phosphorus concentration was 3.2 mg/dl. Serum viscosity was 1.91 (normal 1.18–1.60). A complete skeleton X-ray revealed the presence of multiple lytic bone lesions in the ribs, the pelvic and vertebral region with compressions of the lower thoracic and lumbar vertebral segments. Bone marrow biopsy showed focal prominence of immature plasma cells (marrow plasmocytosis of 25%) with a decrease in the erythroid and myeloid series.

In an attempt to normalize serum electrolytes, the patient was initially treated with hydration, saline, furosemide and 60 mg prednisone per day; the hypercalcemia responded promptly with a decrease of serum calcium to 12.0 mg/dl. The anemia was also corrected with blood transfusions.

On the fifth day of hospitalization antineoplastic therapy was initiated, consisting of a 4-day continuous infusion of vincristine (0.4 mg per day) and adriamycin (15 mg per day); in addition, the patient received dexamethasone in a dose of 40 mg for 4 consecutive days, which was to be repeated on days 9 and 17 of each cycle (11).

On the last of the four days of cytostatic drug administration, the patient was complaining of difficulties in speaking. This symptom gradually worsened and was accompanied by disorientation for time and place. Neurologic examination at that time revealed clinical symptoms correlating to an organic brain syndrome; in addition, left facial palsy, anisocoria, and reduced strength of both left extremities were noted. Deep tendon reflexes were left-accentuated with positive pyramidal signs. Peripheral neurologic symptoms included bilateral diminished Achilles tendon reflex excitability and mild stocking glove hypesthesia. Pain, temperature, position, and vibratory sensitivity were intact. A frontotemporoparietal lesion of the right hemisphere was suspected, in which the presence of motor aphasia was considered to be compatible with the patients left-handedness. A CT-scan revealed no pathologic findings. Thirty minutes thereafter, the patient experienced a focal seizure with tonic eye deviation to the right and left-unilateral clonic jerks, which was controlled by intravenous diazepam. Subsequently, a left-sided transient paroxysmal flaccid type hemiplegia occurred. Within the next hours the psycho-organic syndrome progressed to severe mental confusion with intermittent hyperactivity and pronounced affect-irritability. This was accompanied by global aphasia.

No specific abnormalities were detected on physical examination or laboratory investigation to account for the severe neuropsychiatric symptoms. The residual slight increase of serum calcium and viscosity were not considered causative. No signs of increased intracranial pressure were apparent which might have suggested cerebral edema, an underlying tumor lesion or possibly an acute cerebrovascular event. Skull X-rays and subsequent computerized tomographic brain scans, with and without contrast, were normal. A subarachnoid hemorrhage and an acute CNS infection were excluded by lumbar puncture. The cerebrospinal fluid showed a normal cell count but an elevated total protein of 52.5 mg/dl (normal 18–42). Radial im-