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CASE REPORT

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Fatal Accidental Intrathecal Injection of Vindesine

ABSTRACT: A 25-year-old woman being treated for non-Hodgkin's lymphoma was accidentally given vindesine intrathecally. The error was recognized immediately and a spinal cord washing was performed through syringing with isotonic saline. However, the patient died 6 weeks later with increasing paralysis, which was followed by neurologic failure. The deceased was autopsied and the central nervous system was removed for a microscopic examination. The results showed microscopic lesions extending from the lumbar to the thoracic portion of the spinal cord, which included pseudocystic transformation of the cells, degeneration of myelin, and microhemorrhages. The brain was edematous and, in the cerebellum, the vermis showed a loss of granule and Purkinje cells. The authors compare this report on vindesine toxicity with cases in the literature involving vincristine. The treating physician admitted responsibility and was sentenced to both a fine and imprisonment.

KEYWORDS: forensic science, death, vindesine, vincristine, intrathecal, degeneration of myelin and axons, pseudocystic transformation, loss of Purkinje cells

Treatments for Hodgkin's lymphoma and other neoplasmia include the Vinca alakaloids, such as vinblastine (Vielban™, Velsat™), vincristine (Oncovin™, Vincasar PES™, Vincrex™), or vindesine (Eldisine™). These are administered either intravenously or as a bolus. Use occasionally leads to side effects such as peripheral neuropathy. Vindesine, a widely used antitumor alkaloid agent, binds tighly to the microtubules including the mitotic spindle cell tubules and the neurotubules. Its oncolytic action consists in aggregating tubulins, causing a metaphase arrest in the mitotic cycle. Because of its action on the neurotubules and the microtubules, the neural tissue is particularly sensitive to the effects of the drug. Some published cases describe inadvertent intrathecal administration of vincristine and described severe and irreversible lesions of the central nervous system (CNS) (1–4). We report here on the first published case of death due to an intrathecal injection of vindesine.

Case Report

A 25-year-old woman, diagnosed with stage III non-Hodgkin's lymphoma, presented for treatment. Lymphomatous cells were present in the cerebrospinal fluid (CSF) but neurologic function was satisfactory. The therapy included systemic adriblastine, cyclophosphamid, bleomycine and vindesine, and an intrathecal administration of methotrexate, and methylprednisolone. During her fourth chemotherapy treatment, vindesine, which should have been injected intravenously, was accidentally injected intrathecally by the physician. The error was immediately recognized and, before removing the needle, 40 mL of CSF were withdrawn and an initial washing was performed. The same day, a new lumbar puncture was performed in order to rewash the spinal cord with Ringer's lactate solution. According to medical data, the patient was transferred to a neurosurgical unit, a spinal catheter was inserted, and a continuous perfusion with Ringer's lactate solution was administered for 24 h. The woman was then admitted to a medical intensive care unit. During the first week, she suffered from leg pain with a decrease in the motor activity, a distal paresthesia, and sensory loss. Over the second week, there was a lower extremity paralysis and this was followed by an upper extremity paralysis. Ascending sensory and motor dysfunction were then observed. Her consciousness level declined and the confusion progressed to lethargy. Respiratory dysfunction was noted and a tracheotomy was performed to help the breathing. By the fourth week, she was comatose and after 6 weeks, she suffered respiratory arrest and died. An autopsy, performed 2 days after the death, showed that the terminal event was pulmonary edema. Two fibrotic masses, filling the upper mediastinum and infiltrated by lymphocytes, were thought to represent the residual tumor. The brain weighed 1250 g and was edematous. The spinal cord was macroscopically normal. The cord was examined microscopically and histological and immunohistochemical investigations revealed only early signs of a pseudocystic transformation with resorption and inflammation (Fig. 1). A degeneration of the myelin and the axons, numerous CD68-positive macrophages, and focal microhemorrhages were also found (Fig. 2). In the brain, histopathological changes showed an edema. In the cerebellum, the vermis showed a loss of granule and Purkinje cells as well as a cystic degeneration of the molecular layer (Fig. 3). Death was attributed to the consequences of neurologic dysfunctions linked to the accidental intrathecal administration of vindesine.

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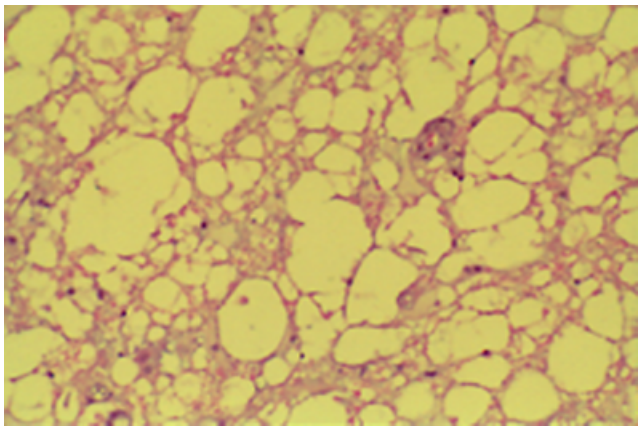

FIG. 1—*The arrow shows the degeneration of myelin and axons with pseudocystic transformation (HES, 200).*

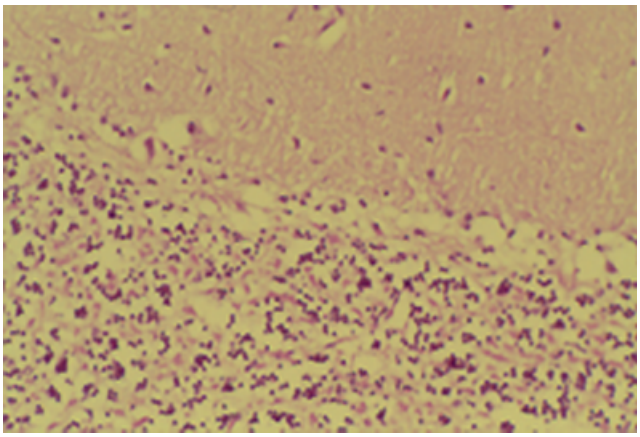

FIG. 3—*The arrow shows the cerebellum with extensive loss of Purkinje cells (HES, 200).*

The treating physician admitted accidentally injecting vinblastine intrathecally. He explained that there were two syringes, one containing corticoids and the other vinblastine, and that he was confused between them. He was sentenced to 3 months' imprisonment and to pay a fine of 1000 euros to the patient's family.

Discussion

The intravenous administration of vindesine may lead to side effects, such as peripheral neurologic effects, for example paresthesias, a loss of deep tendon reflexes, or paralytic ileus (1–8). However, vindesine is considered to be less toxic than the other chemotherapeutic agents, especially vincristine. Vincristine is considered to be the most neurotoxic of chemotherapy drugs, causing axonal sensorimotor neuropathy as well as autonomic neuropathy. Although the other Vinca alkaloids may also cause neurotoxicity, they are in order of decreasing: vincristine> vinorelbine>vindesine>vinblastine (9). The vinca plant alkaloids (vincristine, vinblastine, vindesine) exert their antineoplasic effect by an inhibition of the mitosis. Apparently, the microtubules of the axon transport system are inhibited, resulting in an axonal degeneration (10). Initial symptoms are sequential: myalgias, painful paresthesias of the hands and feet, sensitivity to light touch and temperature, and a decrease in the ankle reflexes. Continued drug administration often leads to motor weakness in the wrist (extensors) and foot (dorsiflexors) (11). Damage to the autonomic fibers can occur (12). The factors that increase the risk of neuropathy when using vincristine are: the route of administration, frequent drug administration (weekly), a dose greater than 2 mg, and age greater than 60 years (13). Experimental intrathecal administration of vincristine or vinblastine produces striking neuronal changes, creating vast aggregates of neurofilaments and crystalline masses, which may be composed of neurotubules. The crystals appear about 30 min after a direct exposure but disappear after 8 days. Vindesine has the same physiopathology (14,15). Some cases of accidental injection of vincristine have been reported (1,16–18). These cases demonstrate that an inadvertent intrathecal administration of vincristine resulted in a central neurological failure and an ascending paralysis. Death occurred between several weeks to 1 year after the administration (1).

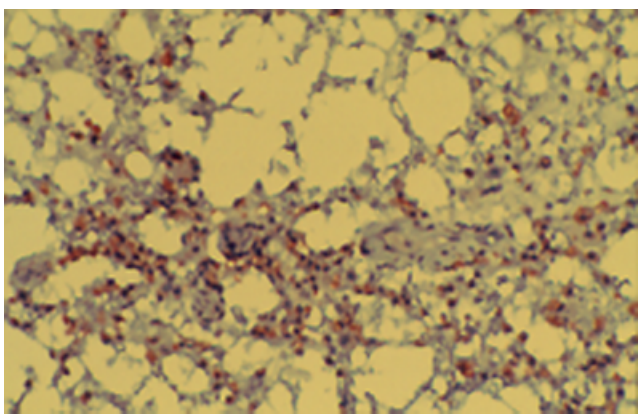

FIG. 2—*The arrow indicates immunohistochemical demonstration of numerous CD68-positive macrophages (CD68, 200).*

No fatalities involving vindesine have been reported previously. This case shows the clinical features of an accidental intrathecal administration of the drug. The first sign included a leg pain and a motor weakness, followed by a progressive sensory loss, paresthesias, ascending paralysis, and an alteration of the conscious state. A respiratory dysfunction appeared during the third week. Coma developed and respiratory arrest resulted in death. This suggests that the physiopathologic mechanisms are similar between vincristine and vindesine, although the time frame may differ. In this case, death occurred 6 weeks after the administration, compared with the reported 2 weeks after vincristine administration intrathecally (2,4).

After intrathecal administration of vincrisitine neuroanatomopathology, examination of the spinal cord showed a formation of neurofilaments aggregates, the destruction of the dynamic cytoskeleton, a pseudocystic transformation with resorption, and inflammation signs. In the brain, there was a degeneration of the myelin and the axons, numerous CD68-positive macrophages with focal microhemorrhages, edema, a loss of granule and Purkinje cells, and a cystic degeneration of the molecular layer in the cerebellum (1–4,7). This report describes the same lesions in this case of vindesine intrathecal administration.

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