Case Report

Inadvertent Intrathecal Vincristine Administration: Report of a Fatal Case Despite Cerebrospinal Fluid Lavage and a Review of the Literature

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Accidental intrathecal vincristine administration results in progressive ascending radiculomyeloencephalopathy usually leading to fatal outcome. No specific therapy for intrathecal vincristine toxicity has been reported. We report a 63-year-old man with diffuse large B-cell lymphoma at the right testis who inadvertently received intrathecal vincristine. Direct CSF aspiration and irrigation was done 30 minutes after the incident. Ventriculostomy and lumbar drain was placed. Intrathecal irrigation was started at 6.5 hours using FFP-containing lactate solution and continued for 11 days. In addition, antineurotoxic and neuroprotective agents were given. His neurological symptom deteriorated slowly and he died on day 12. Among 16 reported cases undergoing lumbar drainage and/or irrigation, 56.3% can survive 30 days or more and 37.5% had survive more than 6 months. Immediate CSF drainage and early irrigation is related to good outcome (prolonged survival with no encephalopathy). In our case, his poor outcome might be due to the delayed starting of irrigation. In conclusion, the appropriate and effective management of this complication is unknown. However, emergency cerebrospinal fluid drainage and irrigation remains the principal of management.

Keywords: *Intrathecal Vincristine*

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Vincristine sulfate is an alkaloid that is widely used in both children and adults to treat a variety of hematologic malignancies and solid tumors including acute lymphoblastic leukemia, Hodgkin lymphoma and non-Hodgkin lymphoma. It is administered intravenously, usually in combination with other chemotherapeutic agent.

Vincristine is a microtubule-depolymerizing drug that exerts its cytostatic effects on mitotic spindle fibers causing cell cycle arrest during metaphase. It also attacks neurotubules, which explain why peripheral motor and sensory neuropathy are common side effects. Some studies found that pyridoxine, glutamic acid and folinic acid given in combination may alleviate the neuropathy, but the supporting data are inconsistent[1-8].

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Inadvertent intrathecal administration of vincristine causes ascending, progressive myeloencephalopathy. Almost all patients have died despite cerebrospinal fluid (CSF) aspiration and lavage[9-14].

Case Report

A 63-year-old male patient came to hospital with enlargement of right testis. Physical examination revealed a mass at right testis sized of 6 x 10 cm and a mass at mid abdomen sized of 6 x 6 cm. After right orchidectomy, the tissue biopsy showed diffuse large B cell lymphoma (positive CD20, negative CD3). Staging workup showed normal chest x-ray, normal bone marrow study and abnormal findings on abdominal ultrasonography which showed a well defined hyperechoic mass sized of 1.88 x 2.07 x 2.36 cm at left hepatic lobe and a heterogenous echoic mass sized of 4.91 x 5.77 x 6.22 cm at mid upper abdomen. His lymphoma stage was in stage IV and his performance status (ECOG) was 0. The plan of systemic chemotherapy included cyclophosphamide, doxoru-

bicin, vincristine, prednisolone (CHOP) for 8 cycles with intrathecal chemotherapy (methotrexate, cytosine arabinoside, and hydrocortisone) as primary CNS prophylaxis.

During the third chemotherapy session, vincristine was inadvertently administered intrathecally instead of hydrocortisone. Thirty minutes later the mistake was noticed, thus direct 50-ml CSF aspiration with 50-ml normal saline replacement was done. The patient was in good consciousness without focal neurological deficit. The patient was sent to operative room for ventriculostomy and lumbar drain placement. Afterwards he was monitored closely in intensive care unit. The intrathecal compartment was irrigated (started at 6.5 hours after the incident) using FFP-containing lactate solution with the rate of 100 ml per hour for one day and reduced to 60 ml per hour for 5 days and 40 ml per hour for 5 days (totally 11 days). The level of external ventricular and lumbar drainage bag was adjusted to achieve an effective irrigation.

During the period of CSF irrigation, daily 150-mg folinic acid, 2-gm glutamic acid every 12 hours and 4-mg dexamethasone every 6 hours were given intravenously. Vitamin B6 (100 mg/day), vitamin E (400 mg/day) and vitamin C (3 gm/day) were also given via nasogastric tube.

Clinical course

Eight hours after inadvertent event, his consciousness deteriorated (Glasglow Coma Scale, GCS = 3/15, E1V1M1) with generalized tonic-clonic seizure lasting for 30 seconds. He was intubated. Vital signs were as follow: BP 110/65 mmHg, HR 120/min, RR 18/min; with pupil size of 3 mm both reactive to light (BRTL). On day 2, his consciousness was recovered. He could open his eyes and respond to verbal command. On day 3, he developed muscle weakness at both lower extremities (motor power grade 3) and progressive drowsiness. On day 5, paraparesis was worsened.

During the following six days, his clinical symptom and sign was steady with GCS 5t/15 (E4VtM1), pupil size of 2 mm BRTL. The patient could move his eyes following sound. On day 12, physical signs were GCS 2t/15, HR of 68/min, BP of 94/60 mmHg, pupil size of 5 mm slightly reactive to light. His daughter and son decided to take him home and the patient died at 16.00 on that day.

Discussion

Vincristine is effective in cancer treatment due to its ability to bind to the tubulin, causing mitotic arrest and cell death. Intravenous vincristine overdose causes neurotoxicity, usually peripheral neuropathy. Other manifestations have also been described such as ocular palsies and autonomic bowel dysfunction[1,14]. Administration of vincristine intrathecally causes a predictable clinical sequence. Data from autopsy showed microscopic lesion of pseudocystic transformation of cell, degeneration of myelin and micro hemorrhage[13,15]. As reported from previous case series, urinary retention and loss of anal sphincter function are the early signs followed by progressive ascending paralysis causing paraparesis[9,16]. Almost all patients die, though few patients survived with paraparesis[16,17-20]. Until now, there is no antidote for vincristine. Many previous case reports mentioned about the efficacy of removing the chemical and diluting the concentration of vincristine in CSF by CSF irrigation via ventriculostomy and lumbar drain[10,16-20]. As shown in the tables, we reviewed the reported cases that received CSF drainage and/or CSF irrigation, including our case. We founded that 9/16 (56.3%) of the cases had survived 30 days or more and 6/16 (37.5%) had survived more than 6 months or still survived at last follow-up. Among five cases who got only CSF drainage without CSF irrigation, there is only one case who had survived more than 6 months but he had survived with prolonged coma (dense encephalopathy from electroencephalogram). Among 10 cases who got both CSF drainage and CSF irrigation, there are 5 cases who survived more than 6 months without encephalopathy. Despite CSF irrigation, two cases who got vincristine injection via Ommaya had poor outcome. Immediate CSF drainage and early CSF irrigation is related to good outcome (prolonged survival with no encephalopathy). The fluid commonly used in irrigation is FFP-containing Ringer lactate solution and the infusion rate varies from 55-83 ml/hr. Some case got initial lavage at rate of 150 cc/hr (data from National Association for the Central Texas 2005).

One animal research reported a potential role of hypochlorous acid (HOCl) in the treatment of accidental vincristine overdose[8]. Other authors additionally administered neuroprotective and antineurotoxic medication (corticosteroids, folinic acid, glutamic acid and pyridoxine)[1-7, 21]. However, scientific support for the clinical use of these drugs is weak.

In our case, simple lumbar puncture for CSF irrigation was initiated 30 minutes after the incident. Ventriculostomy and lumbar drainage were done and FFP-containing lactate solution irrigation was started 6.5 hours after the accident. He died at day 12. The

Table 1. Cases that received drainage and/or irrigation and survived 30 days or more

Author	Age (yr) /Sex	Vincristine	Symptoms	Intervention	Outcome
Alcaraz A[22]	12/F	2 mg	Asymptomatic for 48 hours, then ascending paralysis, hiccups, cranial neuropathy, comas	35 ml CSF drained at 30 minutes then additional drainageof 15 ml CSF replaced with lactated ringers. Ventriculo-lumbar perfusion at 3 hours using lactated ringers with 15 ml FFP/L for total drainage of 615 ml CSF over 10 hours. 0.785 mg removed	Fatal day 83
Al Ferayan A[16]	7/F	0.5 mg	Ascending weakness, pain, paraplegia	Upright position. Immediate drainage 75 ml CSF within 15 minutes and replacement with lactate ringers. Ventriculo-lumbar perfusion started within 2 hours using 150 ml/hour lactated ringers for 10 hour then FFP 15 ml in 1 L lactated ringers as irrigant at 55 ml /hr for 24 hours. Other adjuncts.	Paraplegia, neurogenic bladder, Survived
Bleck TP[19]	23/M	2 mg	Headache day 1, leg weakness day 2-3 followed by ascending myeloencephalopathy with coma at day 10, seizures	Drainage of 110 ml CSF at 10 minutes, " large volume lumbar punctures" day2 and 3, adjunctive intravenous therapy –Dexamethasone, folinic acid, vitamin B12, thiamine and pyridoxine IV	Prolonged coma (denseencephalo-pathy) Fatal at 12 mo. Recurrence of primary disease 1 yr
Dyke RW[17]	Adult	2 mg	Ascending paralysis	Immediate CSF drainage of unreported quantity and replacement with lactated ringers.Ventriculo-lumbar perfusion 150 ml/ hour for 24 hours then 25 ml FFP in 1L isotonic solution at 75 ml/hour for undefined time. 95% recovery of vincristine10% glutamic acid IV over 24 hour then 500 mg hourly	Lower extremity neuropathy
Meggs WJ[23]	59/F	Ommaya reservoir 2 mg	Nausea, vomiting day 1, altered mental status, tremor, chills, hiccups, nystagmus, coma over 1 week	50 ml CSF drainage at 10 minutes followed by 75 ml CSF drainage at 30 minutes. Ventriculo-lumbar perfusion with lactated ringers and FFP over 24 hours.	Fatal day 40
Michelag-noli MP[18]	10/F	?	Asymptomatic for 6 days. Then ascending paraparesis with incontinence	Immediate drainage of CSF for 15 minutesPlacement of epidural catheter above the lumbar drainage site with lumbo-lumbar irrigation using 500 ml lactated ringers with 12.5 ml FFP	Survived with normal cognitive
Zaragoza MR[20]	6/M	?	Peripheral neuropathy, chorea , urinary retention day 2, ascending paralysis, Quadriplegia week 2	Immediate drainage 50 ml CSF Ventriculo-lumbar drain with drainage of CSF and exchange with Ringer Lactated containing 15 ml FFP/L for 18 hoursGlutamic acid 10 g over 24 hour IV then 250 mg q 8 hr Folinic acid rescue 25 mg 6-hourly and pyridoxine 50 mg 8-hourly IV	Alive at 24 mo with upper extremity weakness and paralysis of lower extremities
Qweider M[9]	32/M	1 mg	D2 urinary retention, loss sphincter tone D8 proximal lower extremities paraparesis Following days: the deficit ascended and progressive intensity D19 paraparesis were exacerbated, dysesthesia, hyperesthesia below T-9 level	Immediate 6 ml of CSF was aspirated. Sitting position. Bolus 300 mg folic acid IV. External ventricular and lumbar drains were placed. Irrigate using FFP-containing RL solution rate 50-80 ml/hr on day 1-5 and day 7-10. Glutamic acid and pyridoxine IV.	Day 60 stable in complete sensorimotor deficit below T-9 level.
Bain PG et al[24]	56/M	0.3 mg		Immediately recognition, ? ml of CSF aspiration	30 days

? = not stated, mo = month, yr = year

Table 2. Cases that received drainage and/or irrigation and survived less than 30 days

Author	Age (yr) /Sex	Vincristine	Symptoms	Intervention	Outcome
Fernandez CV [25]	4/F	1.5 mg	Nystagmus, encephalopathy, ascending paralysis, transient improvement	Immediate drainage 18 ml CSF in 3-ml aliquots. NS. An additional 30-40 ml drained over 30 minutes, starting Replacement at 10 minutes. Ventriculo-lumbar perfusion using Plasmalyte to replace 200 ml CSF over unknown rate. Then 6 ml FFP in 250 ml. Plasmalyte at 50 ml/hour for 4 hours	Fatal day 13
Gaidys WG [10]	23mo/F	0.68 mg in 6.8 ml	Coma by day 3	Ventriculo-lumbar perfusion began at 4.5 hour with initial drainage 500 ml CSF and replacement with normal saline over 90 minutes. Subsequent drainage and replacement of 145 ml	Fatal day 6
Schochet SS [26]	2.5/F	3 mg	Opisthotonos day 2	200 ml CSF drainage in 10 ml aliquots. Replacement with NS.	Fatal day 3
Lau G [27]	27/F	Ommaya reservoir ? mg	Ascending paralysis	Detail limited-CNS 'washout" FFP and "lactate solution" in undefined quantities. Timing not described (recognition after 24 hours).	Fatal day 10
Shepherd DA [28]	5.5/?	1.2 mg	Headache, vomiting and backache at 3 hours; nystagmus, extremity weakness at 72 hours, autonomic instability, encephalopathy	Drainage of 20 ml CSF at 30 minutes repeated on day 2. Intrathecal corticosteroids	Fatal day 12
Slyter H [29]	29/F	2 mg	Headache, ascending paraplegia, cranial neuropathy, coma	Immediate intrathecal infusion 5 ml normal saline with drainage of 10 ml CSF. Positioned upright; additional 60 ml CSF drain at 3 hours	Fatal day 14 (pulmonary embolism on autopsy)
Present case	63/M	2 mg	Seizure day 1 (30 seconds) Muscle weakness day 3 Paraparesis day 5 Ascending paralysis with coma on day 12	50 ml CSF drain at 30 minutes. Ventriculostomy and lumbar drain replacement (start 6.5 hours after the injection) with FFP-containing lactate ringer rate 100 ml/hour for 1 day and 60 ml/hour, 40 ml/hour for 5 and 5 days. (Total 11 days)	Fatal day 12

poor outcome could be a result of the delayed starting of CSF irrigation after vincristine injection.

The effective management after this fatal accident is not yet established. The best fluid which should be used and the appropriate rate for CSF lavage and the golden period to start irrigation are yet unknown exactly.

Conclusion

Inadvertent intrathecal vincristine is not a common event. However, the consequence is predictable in which almost all patients have paraparesis and death. The appropriate and effective management is unknown. Prevention is the best strategy for this problem. However, if this event occurs, emergency cerebrospinal fluid lavage remains the principal of management.

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Potential conflicts of interest

None.

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การฉีดยาเคมีบำบัดวินคริสตินเข้าช่องน้ำไขสันหลัง: รายงานผู้ป่วยหนึ่งรายและทบทวนวารสาร

ศรัญญา พงษ์อุดม, ยิ่งยง ชินธรรมมิตร์

การฉีดยาวินคริสติน (vincristine) เข้าช่องน้ำไขสันหลังโดยความพลั้งเผลอทำให้เกิดภาวะ ascending radiculomyeloencephalopathy และทำให้ผู้ป่วยเสียชีวิตในที่สุด ขณะนี้ยังไม่มีรายงานการรักษาจำเพาะ คณะผู้นิพนธ์ได้รายงานผู้ป่วยชายอายุ 65 ปี มาพบแพทย์ด้วยถุงอัณฑะข้างขวาโต และได้รับการวินิจฉัยว่าเป็นมะเร็งต่อมน้ำเหลืองชนิด diffuse large B cell ผู้ป่วยได้รับการฉีดยาวินคริสตินเข้าช่องน้ำไขสันหลัง ในระหว่างการรักษาหลังจากฉีดยา 30 นาที ผู้ป่วยได้รับการเจาะระบายน้ำไขสันหลังและล้างช่องน้ำไขสันหลัง จากนั้นจึงได้รับการทำ ventriculostomy และ lumbar drain เพื่อล้างช่องน้ำไขสันหลังที่ 6.5 ชั่วโมงหลังเกิดเหตุการณ์โดยใช้พลาสมาสดผสมในสารน้ำ Ringer lactate และล้างอย่างต่อเนื่องเป็นเวลา 11 วัน รวมทั้งได้ให้สารต้านการทำลายเส้นประสาท (antineurotoxic and neuroprotective) แก่ผู้ป่วย อาการทางระบบประสาทค่อยๆ แย่ลง และผู้ป่วยเสียชีวิต 12 วันต่อมา จากการทบทวนรายงานผู้ป่วย 16 ราย พบว่าในผู้ป่วยที่ได้รับการเจาะระบายยา ทางไขสันหลังและหรือ การล้างช่องน้ำไขสันหลังมีผู้ป่วย 56.3% สามารถมีชีวิตรอดได้มากกว่า 3 เดือน และ 37.5% รอดชีวิตนานมากกว่า 6 เดือน การเจาะระบายน้ำไขสันหลังทันที และล้างช่องน้ำไขสันหลังอย่างรวดเร็วสัมพันธ์กับผลลัพธ์ที่ดี คือมีชีวิตรอด ได้นานขึ้น และสมองทำงานปกติ ในผู้ป่วยรายนี้ผลการรักษาที่ไม่ดีน่าจะเกิดจากความล่าช้า ในการเริ่มล้าง ช่องน้ำไขสันหลัง การรักษาและการจัดการที่เหมาะสมยังไม่เป็นที่ทราบแน่ชัด การป้องกันยังคงเป็นกลยุทธ์ที่ดีที่สุด แต่อย่างไรก็ตามในกรณีที่เกิดเหตุการณ์นี้ขึ้นการเจาะระบายและล้างช่องน้ำไขสันหลังอย่างรวดเร็วยังเป็น หลักการสำคัญในการดูแลผู้ป่วย