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Case report

Inadvertent intrathecal administration of daunomycin resulting in fatality: Case report and therapeutic considerations

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ABSTRACT

Background: Daunomycin is a chemotherapeutic agent of the anthracycline family that is administered intravenously, most commonly in combination therapy. The authors report the first known adult case of inadvertently administered daunomycin directly into the human central nervous system and the neurologic manifestations and therapeutic interventions that followed.

Clinical description: A 53-year-old male presenting to the hospital for his second cycle of consolidation therapy for acute promyelocytic leukemia t(15;17) was accidentally administered 93 mg of intrathecal (IT) daunomycin. Within several hours of injection, the patient subsequently developed bilateral lower extremity pain, ascending paresthesias, headache, and left cranial nerve (CN) III palsy. Immediately following these neurologic sequalae, a subarachnoid lumbar drain was placed at the L4-5 interspace for the initial irrigation and drainage of cerebrospinal fluid (CSF). By hospital day 2, the patient's mental status significantly declined requiring an external ventricular drain (EVD) for hydrocephalus. Despite therapeutic interventions, the patient developed an ascending radiculomyeloencephalopathy with deterioration in clinical status. Eighteen days after the inadvertent injection of IT daunomycin, the patient became comatose and lost all cranial nerve function.

Conclusions: Accidental IT injection of daunomycin is a neurosurgical emergency and warrants prompt intervention. Symptoms can mimic other medical conditions, making it imperative an accurate diagnosis is made so that appropriate therapies are implemented. At this time, therapies include rapid removal of the chemotherapeutic agent from the IT compartment by aspiration and irrigation; however, it is unclear if neuroprotective agents may provide added benefit.

1. Background and importance

Daunomycin (or daunorubicin) is a cytotoxic anthracycline antibiotic that is often used in combination therapy for treatment of acute myelocytic leukemia (AML), acute lymphoblastic leukemia (ALL), neuroblastoma, and rhabdomyosarcoma [1]. Discovered over 50 years ago, daunomycin is an produced naturally by *Streptomyces peucetius*, a species of actinobacteria [2]. Daunomycin imparts its effects by DNA intercalation through a thermodynamically favorable process. Daunomycin binds DNA with a preference for a triplet sequence containing an AT base-pair flanked by adjacent GC base-pairs, as this provides an arrangement of hydrogen bonds with an ideal stereochemical fit [3]. A potent inhibitor of topoisomerase II, daunomycin facilitates the formation of double strand breakages [3].

Daunomycin and other anthracycline derivatives such as doxorubicin are commonly associated with cardiotoxicity [4]. While the association with adverse cardiac events have been extensively documented, relatively little is known about the potential adverse effects of daunomycin on the central nervous system (CNS). Dose-dependent neurotoxic effects of doxorubicin have been demonstrated, however, and is thought to occur by impairment of long-term potentiation, induction of apoptosis, and increased superoxide production and lipid peroxidation [5,6]. While anthracycline administration is typically performed intravenously, doxorubicin is thought to accumulate within the CNS in

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cancer patients due to reduced blood-brain barrier integrity given an upregulation in pro-inflammatory cytokines [2,5].

Not uncommonly, inadvertent intrathecal (IT) injection is another means by which neurotoxic agents may be introduced to the CNS. For example, 35 cases of accidental IT administration of vincristine have been reported, with 28 case fatalities [7]. Direct aspiration and continuous irrigation of CSF has been proposed as a means of reducing the concentration of an inadvertently intrathecally administered toxic agent and preventing diffuse nervous system damage [8]. With respect to daunomycin, only a single case has been reported in a pediatric patient that led to progressive diffuse cerebral atrophy with fatal outcome despite aggressive measures [9]. Here, the authors report the first case of accidental IT administration of daunomycin in an adult patient and describe the clinical course, neurologic manifestations, and therapeutic interventions that followed.

2. Clinical presentation

2.1. History

A 53-year-old man with a past medical history of obstructive sleep apnea (OSA), Helicobacter gastritis, and prior myocardial infarction was admitted to Georgetown University Hospital for treatment of acute promyelocytic leukemia in September 2010. At the time of his acute myocardial infarction in June 2010, the patient was diagnosed with acute promyelocytic leukemia, t(15;17). He was transferred to Georgetown University Hospital and underwent induction therapy with All-Trans Retinoic Acid (ATRA), daunomycin, and cytarabine. His hospital course at that time was complicated by neutropenic fever and typhilitis. After induction treatment, a bone marrow biopsy in July 2010 revealed normocellular activity without residual blasts consistent with a complete morphologic remission.

The patient was subsequently admitted in August 2010 for the first cycle of consolidation therapy with ATRA, idarubicin, and cytarabine. The patient also received his first dose of prophylactic intrathecal chemotherapy with methotrexate, cytarabine, and hydrocortisone. A bone marrow biopsy at that time showed no morphologic evidence of leukemia. The patient was admitted in September 2010 for his second cycle of consolidation therapy with daunomycin (128 mg) and high-dose cytarabine (4140 mg). He received his first dose of intravenous daunomycin and cytarabine without incident. The following day, the patient was brought down to the radiology suite for a fluoroscopic guided lumbar puncture with administration of intrathecal chemotherapy. Lumbar puncture (LP) was performed, revealing clear CSF, 2 RBCs, 1 WBCs, protein 58, and glucose 60. Over the next few hours, the patient began to complain of bilateral leg pain and paresthesias, increasing back pain, and headache. At that time, it was discovered that he had inadvertently received 93 mg of daunomycin intrathecally instead of triple therapy with methotrexate, cytarabine, and hydrocortisone. The neurosurgical service was consulted several hours after intrathecal administration, and the patient was transferred to the neurosurgical intensive care unit for further management.

2.2. Presentation and treatment

On admission to the neurosurgical intensive care unit, the patient complained of bilateral lower extremity pain, paresthesias, and headache. Immediately after assessing the patient, a subarachnoid lumbar drain (LD) was placed at the L4-5 interspace. Red-tinged CSF was noted to drain at the time of lumbar puncture. Prior to placement of lumbar drain, a CSF lavage was performed followed by continuous CSF drainage at a rate of 15 mL per hour. Laboratory analysis after LD placement revealed pink CSF, 100 RBCs, 40 WBCs, 2135 protein, and 118 glucose.

On hospital day 2, a right external ventricular drain (EVD) was placed after endotracheal intubation due to a decline in mental status and concern for hydrocephalus on radiological studies, including increased size of the third ventricle and temporal horns of the lateral ventricles. The intracranial pressure was 40 cm H_2O at the time of insertion, and the EVD was opened to drain at 10 cm H_2O. Elevated intracranial pressure and cerebral edema seen on serial computed tomography (CT) scans were managed using CSF drainage, hypertonic saline, and hyperventilation. An attempt to wean the EVD in the ensuing days was unsuccessful due to elevated intracranial pressures. On hospital day 14, the patient was taken to the operating room for the insertion of a ventriculo-peritoneal (VP) shunt. Postoperative head CT showed moderate improvement in the size of the lateral ventricles, however, a subsequent head CT on postoperative day 2 revealed dilated lateral ventricles and raised concern for proximal shunt failure. The patient was therefore taken emergently to the operating room for revision of the proximal shunt catheter.

2.3. Clinical course

Several hours after the incident, the patient was examined and noted to have a left CN III palsy. The patient experienced a decline in mental status requiring intubation and placement of an EVD on hospital day 2. During the subsequent days, the patient developed bilateral lower extremity paraparesis, which progressed in an ascending manner. An MRI of the patient's lumbosacral spine demonstrated thickening and perimedullar enhancement of the conus medullaris and cauda equina (Fig. 1). By hospital day 5, the patient was unable to move his lower extremities. He was areflexic in his lower extremities and hyperreflexic in his upper extremities. The patient intermittently followed commands in his upper extremities but was only able to move his thumbs. On hospital day 8, the EVD was raised to 15 cm H_2O, but the patient was unable to tolerate as ICPs were sustained above 20 cm H_2O. Therefore, a VP shunt was placed on hospital day 14. An MRI scan of the brain showed diffuse leptomeningeal enhancement of the skull base and anterior interhemispheric fissure (Fig. 2).

Eighteen days after the incident, the patient's neurological state severely deteriorated. The patient was unable to follow commands and lost all cranial nerve function on examination. Cold caloric testing was performed on hospital day 19 and demonstrated an absent vestibulo-ocular reflex. Due to the patient's poor neurological examination, the family chose to withdraw care and allow natural death.

3. Discussion

Inadvertent injection of IT daunomycin been documented only once previously in the literature in a pediatric patient [9]. To our knowledge, this is the first reported case of inadvertent IT daunomycin injection in an adult patient, as well as the first in the neurosurgical literature. The

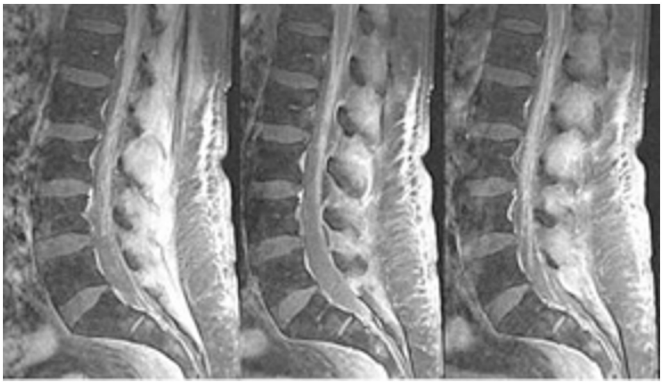

Fig. 1. Parasagittal Gd-enhanced T1-weighted magnetic resonance images of the lumbosacral spinal cord obtained 13 days after inadvertent intrathecal daunomycin administration, showing thickening and abnormal enhancement of the conus medullaris and cauda equina.

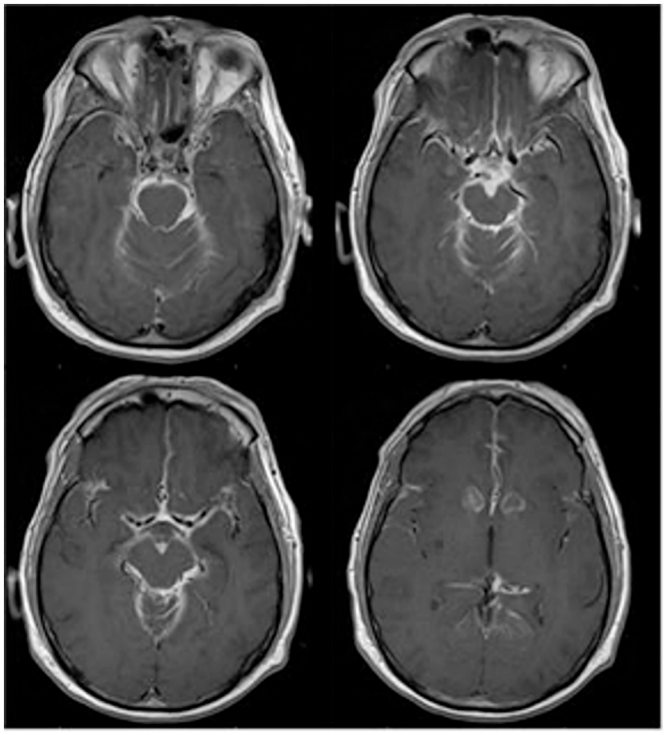

Fig. 2. Axial Gd-enhanced T1-weighted magnetic resonance images of the brain 10 days after inadvertent intrathecal daunomycin administration, demonstrating diffuse abnormal leptomeningeal enhancement at the base of the skull, Sylvian fissures, and anterior interhemispheric fissure. There is also signal abnormality at the nuclei accumbens in the basal ganglia regions.

prior case involved a 3½-year-old girl with pneumonia and otitis media who was diagnosed with ALL. A mislabeling error led to the inappropriate IT injection of daunorubicin as opposed to cytosine arabinoside, which was recognized one hour after injection. At this time, hydrocortisone was injected into the IT space, a 2-day course of intravenous methylprednisolone was started, and a LD was placed for continuous CSF drainage. CT head, neurological examination, and nerve conduction studies were all normal at this time, and the LD was removed on day 4.

Unlike our patient, it took nearly 1 week for symptom onset, with a presentation of meningeal signs being evident on day 6. CSF studies at this time demonstrated elevated protein (3200 mg/dL), glucose (109 mg/dl), and RBCs (208 cells/mm^3), similar to the CSF profile of our patient. On day 10, CT head demonstrated cerebral atrophy, and profound neurologic deterioration occurred by day 17. Another difference from our case was that this patient remained relatively stable in this condition for at least another 7 weeks until electroencephalography at 9 weeks demonstrated no brain activity; ventilator support was discontinued at this time. A side-by-side comparison of these two cases is presented in Table 1.

The antitumor effects of anthracycline agents such as daunomycin are distinct from their intrinsic cytotoxic mechanisms. In neoplastic tissue, daunomycin induces double strand DNA breaks by the inhibition of topoisomerase II, a process that leads to tumor cell death [1]. In contrast, healthy tissues, including the heart, brain, and kidney, may be affected by a variety of dose-dependent mechanisms. Daunomycin is not traditionally considered neurotoxic such as vincristine; however, a number of different mechanisms may be at play including formation of reaction oxygen species, enhanced brain nictric oxid synthase formation, and persistent activation of microglia and increased acute phase reactents [10–13].

Intrathecal injection of daunomycin acts by a dose-dependent mechanism to cause neuronal cytotoxicity in the CNS [9]. As the current case demonstrates, most damage is initially present near the site of injection (L4-L5 interspace), and progresses cranially to cause ascending paraparesis and other neurologic deficits. This phenomenon and transverse myelopathy has been reported in similar cases resulting from the inadvertent IT administration of other chemotherapeutic compounds. This includes methotrexate, cytarabine, and most commonly vincristine [7,14–17]. Since the first reported IT injection of vincristine in 1968, 35 cases have been published; this is thought to be an underestimate, with many more cases going unreported and anecdotal accounts suggesting more than 100 cases [7,18]. Over the last two decades, discussion over the best preventative practices have taken place including dilution of vincristine concentrations or replacing syringes altogether with minibags [7,19]. Despite this, fatal cases of inadvertent IT injections continue to be reported, with one group mistakenly attributing symptoms to Guillain-Barre Syndrome [20,21].

Table 1
A comparison of two cases of inadvertent intrathecal daunomycin injection.

	Patient 1	Patient 2[3]
Age, sex	53, Male	3½, Female
Diagnosis	APL	ALL
Time to symptom onset	3–4 h	6 days
Initial presentation	Headache, back pain, bilateral leg pain, paresthesias	Headache, neck stiffness
Initial imaging studies	Hydrocephalus, conus medullaris enhancement	Normal
CSF profile at symptom Onset	Red-tinged, 100 RBCs, 40 WBCs, 2135 protein, 118 glucose	Red-tinged, 208 RBCs, 3200 protein, 109 glucose
Time to intervention	3–4 h	1 h
Interventions implemented	CSF lavage, continuous CSF drainage, EVD (Day 2), VP shunt (Day 14)	IT hydrocortisone injection, 2-days IV methylprednisolone, continuous CSF drainage.
Time of brain death	Day 19	Day 63

Methods of limiting neurotoxicity after inadvertent injection include reducing drug availability within the CSF and preventing excessive caudo-cranial transport of the compound. Since drug cytotoxicity is dose-dependent, removal of drug by immediate CSF aspiration can theoretically limit diffusion and direct cytotoxic effects. However, studies have shown that CSF aspiration alone fails to retrieve substantial quantities of drug; in cases of intrathecal vincristine injection, no patient survived in which only aspiration of CSF was performed [14]. When irrigation of the intrathecal compartment was combined with aspiration, survival improved and damage was limited to sensorimotor deficits in the upper and lower extremities, but only when irrigation lasted more than 24 h and continuous drainage was maintained by lumbar drain and EVD [8,14]. Irrigation and drainage serves not only to remove substantial quantities of drug, but also to limit caudo-cranial diffusion, a process that may be further limited by maintaining the patient at a minimum 45° angle throughout treatment.

In cases of inadvertent IT vincristine injection, several compounds have been used as empiric antineurotoxic therapy, although the evidence for the use of these agents is weak [8,14]. Glutamic acid, folic acid, pyridoxine, and corticosteroids have traditionally been used, based on evidence acquired from animal studies [22–24]. Only glutamic acid has been proven to limit neurotoxicity in clinical trials but only when chemotherapy had been given at therapeutic, intravenous doses [25]. However, no patient survived in which antineurotoxic therapy had been used exclusively [8,14]. Only when paired with aspiration and irrigation may these compounds benefit the patient, although survival remains poor. As previously mentioned, similar studies have highlighted the use of compounds like dexrazoxane and epicatechin to limit cytotoxicity of daunomycin when the drug is given at conventional, intravenous doses [12,13]. Thus, in cases of inadvertent IT administration of daunomycin,

these drugs may have similar benefit when paired with aggressive neurosurgical therapy.

4. Conclusion

To date, this is the second documented case of inadvertent intrathecal administration of daunomycin, and the first reported case in an adult patient. Our report describes the time course, neurologic manifestations, and radiographic findings associated with direct daunomycin neurotoxicity despite neurosurgical intervention. A few hours after receiving an accidental intrathecal injection of daunomycin, the patient experienced bilateral lower extremity pain and paresthesias, which progressed within days to bilateral lower extremity paralysis and the eventual loss of all cranial nerve function by hospital day 18. MRI of the patient's lumbosacral spine revealed progressive thickening and enhancement of the conus medullaris and cauda equina. MRI of the brain was characterized by diffuse, abnormal leptomeningeal enhancement of the skull base, Sylvian fissures, and anterior interhemispheric fissure.

Like many chemotherapeutic agents, daunomycin causes a dose-dependent cytotoxicity. As with previously reported cases, care was taken to rapidly remove the chemotherapeutic agent from the IT compartment by aspiration and irrigation and followed by continuous drainage by LD and EVD. However, even aggressive neurosurgical therapy did not prevent progressive neurological decline in our patient. In this case, the patient became symptomatic hours after accidental injection. It is therefore unknown whether earlier recognition, leading to more prompt initiation of therapy, would have improved the patient's outcome. In addition, it remains unclear whether administration of neuroprotective agents would have been effective in this case, although this remains something to explore in future instances.

Patient consent

Consent was not obtained as the patient expired and this report has been completely anonymized and does not include identifiable personal health information.

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Declaration of Competing Interest
The authors deny any conflict of interest.

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