Case Reports/Case Series

Encephalopathy and rhabdomyolysis induced by iotrolan during epiduroscopy

[Encéphalopathie et rhabdomyolyse provoquées par l'iotrolan durant l'épiduroscopie]

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Purpose: We describe a complication of epiduroscopy with encephalopathy and rhabdomyolysis associated with the contrast medium iotrolan.

Clinical features: A 76-yr-old man with failed back surgery syndrome underwent epiduroscopy. Sufficient lysis could not be achieved in the epidural space above the level of L₄ due to dense adhesions and scar tissue. After epidural injections of iotrolan and mepivacaine, he developed motor weakness and hypoesthesia in both legs, which lasted for three hours. He also became confused, agitated, disoriented, and developed neck stiffness and tremors involving the head and legs. Computed tomography revealed diffuse contrast enhancement within the intracranial cerebrospinal fluid (CSF) spaces, indicating an intraoperative dural tear. Marked increases in serum creatinine phosphokinase and myoglobin indicated subsequent acute rhabdomyolysis. Crystalloid infusion and semi-recumbent positioning facilitated iotrolan absorption from the CSF, and the patient recovered uneventfully.

Conclusions: Dural tear during epiduroscopy may allow access of contrast media into the CSF. Neurotoxicity secondary to iotrolan within the CSF was a likely contributing factor to the encephalopathy and subsequent rhabdomyolysis. This is an instructive example of the importance of diagnosing inadvertent dural tear during epiduroscopy under iotrolan, for avoidance of adverse events such as encephalopathy and rhabdomyolysis.

Objectif: Nous décrivons une complication survenue lors d'une épiduroscopie avec le produit de contraste iotrolan consistant en une encéphalopathie et une rhabdomyolyse.

Éléments cliniques: Un homme de 76 ans présentant des séquelles d'un échec d'une chirurgie aux rachis a subi une épiduroscopie. Une lyse suffisante n'a pas pu être obtenue dans l'espace péri-dural au-dessus de L₄ à cause d'adhésions denses et de tissus cicatriciels. Suite à des injections péri-durales d'iotrolan et de mépivacaïne, il a développé une parésie ainsi qu'une hypoesthésie au niveau des membres inférieurs qui durèrent trois heures. Il est également devenu confus, agité, désorienté, et a développé une raideur du cou et des tremblements de la tête et des jambes. La tomodensitométrie a révélé un rehaussement diffus du produit de contraste dans les espaces intracrâniens du liquide céphalo-rachidien (LCR), indiquant une déchirure péroperatoire de la dure-mère. Des augmentations significatives de la créatinine-phosphokinase sérique et de la myoglobine signalant une rhabdomyolyse aiguë ultérieure ont été observées. Une perfusion de cristalloïde ainsi qu'un positionnement semi-allongé ont facilité l'absorption de l'iotrolan du LCR, et le patient s'est rétabli sans problème.

Conclusions: La déchirure de la dure-mère durant l'épiduroscopie peuvent permettre l'injection de produit de contraste dans le LCR. Une neurotoxicité due à l'iotrolan dans le LCR est un facteur qui a possiblement contribué à l'encéphalopathie et à la rhabdomyolyse subséquente. Ceci est un exemple instructif de l'importance du diagnostic de la déchirure de la dure-mère commises par inadvertance durant l'épiduroscopie sous iotrolan, afin d'éviter des complications telles que l'encéphalopathie et la rhabdomyolyse.

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LUMBAR epidural adhesions involving nerve roots can be responsible for persistent low back and leg pain. Epiduroscopy enables direct visualization of structures within the epidural space, appropriate adhesiolysis, and administration of local anesthetic agents and steroids to target specifically affected nerve roots.^{1,2} Epiduroscopy can provide substantial and prolonged pain relief to patients with chronic low back and leg pain due to lumbar disc herniation, spinal canal stenosis, and failed back surgery syndrome (FBSS).^{1,2} Although epiduroscopy has been considered to be a safe procedure in experienced hands, severe complications such as retinal bleeding with visual impairment³ and epidural abscess⁴ have been occasionally reported. Iotrolan, a non-ionic water-soluble radiographic contrast medium, has often been used for epidurography.⁵ We report a case of encephalopathy and rhabdomyolysis, probably induced by iotrolan following an accidental dural tear during epiduroscopy. Consent for publication was obtained according to guidelines of the University of Tokyo Hospital.

Case report

A 76-yr-old man with chronic low back pain and sciatica due to FBSS presented for epiduroscopy. His medical history included hypertension and diabetic mellitus, but no alcoholism, psychosis, or epilepsy. He underwent laminoplasty at L₄ and L₅ ten years previously, posterior lumbar fusion with instrumentation at L₄ and L₅, as well as subsequent removal of infected implants six years previously, and autogenous bone grafting at L₅ five years prior to the current presentation. On examination, straight leg raising test

was positive for nerve root tension, without evidence of sensory, motor, or reflex abnormality. Magnetic resonance imaging revealed epidural adhesions with postoperative changes, spinal canal stenosis with bulging discs at L₂₋₃, L₃₋₄, L₄₋₅, and L₅-S₁, and anterior spondylolisthesis of L₅. A variety of pain therapies, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, and nerve blocks were ineffective. Preoperative laboratory tests were normal except for mild renal insufficiency (Table).

In the operation room and following application of routine monitors, he was placed in the prone position and lightly sedated with midazolam 2.5 mg *iv* and fentanyl 100 µg *iv*. Cefazolin 1 g was infused prophylactically at the time of incision. Under aseptic conditions, and with local anesthesia, an 18.5-G Tuohy needle was introduced by an epiduroscopist into the epidural space through the sacral hiatus. Correct needle placement was confirmed by injection of iotrolan 10 mL (Isovist 240®, 240 mg I·mL⁻¹, Schering, Berlin, Germany) under fluoroscopy. The epidurography showed complete block of contrast flow at the level of L₄₋₅. An introducer sheath was advanced into the sacral epidural space using the Seldinger technique. A 0.9-mm flexible endoscope (3000E, Myelotec, Roswell, GA, USA), covered with a 2.9-mm steering catheter (2000, Myelotec, Roswell, GA, USA), was introduced through the sheath and advanced cephalad into the epidural space, under frequent fluoroscopic monitoring. Adhesions in the epidural space were mobilized with the tip of the instrument under careful direct vision. However, sufficient lysis could not be achieved in the epidural space above the level of L₄ due to dense adhesions and scar tissue. A further

TABLE Hematology and blood chemistry

	Normal range	PRE	OD (5 hr)	POD 1 (18 hr)	POD 1 (24 hr)	POD 2	POD 3	POD 4	POD 5
WBC ($\times 10^3 \cdot \mu\text{L}^{-1}$)	3.5-9.2	6.30	11.00	10.20	11.30	8.20	7.30	6.20	-
RBC ($\times 10^6 \cdot \mu\text{L}^{-1}$)	4.20-5.54	3.86	3.31	2.99	3.22	2.96	2.71	2.90	-
Hb (g·dL ⁻¹)	13.8-16.6	14.9	13.0	11.5	12.4	11.6	10.5	11.3	-
PLT ($\times 10^3 \cdot \mu\text{L}^{-1}$)	155-365	207	188	175	199	149	134	169	-
GOT (IU·L ⁻¹)	9-38	28	27	102	181	186	147	124	82
GPT (IU·L ⁻¹)	4-36	20	15	27	45	49	44	53	49
LDH (IU·L ⁻¹)	125-237	268	275	358	579	536	515	542	619
AMY (IU·L ⁻¹)	39-156	-	-	583	734	367	161	124	90
CK (mg·dL ⁻¹)	55-210	358	-	6794	11371	10005	6618	4820	2286
Mb (ng·mL ⁻¹)	0-70	-	-	-	6853	2396	806	363	208
BUN (mg·dL ⁻¹)	9.0-21.0	22.2	16.4	24.0	29.1	18.3	12.1	11.5	13.3
Cr (mg·dL ⁻¹)	0.6-1.2	1.26	1.13	1.41	1.46	1.23	1.15	1.08	1.10
CRP (mg·dL ⁻¹)	0.0-0.3	0.27	-	3.49	7.69	15.33	11.64	7.82	3.76

PRE = preoperative day; OD = operative day; 5 hr = postoperative 5 hr; POD1 = first postoperative day; WBC = white blood cell; RBC = red blood cell; Hb = hemoglobin; PLT = platelet; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; LDH = lactate dehydrokinase; AMY = amylase; CK = creatine kinase; Mb = myoglobin; BUN = blood urine nitrogen; Cr = creatinine; CRP = C reactive protein.

FIGURE 1 Epidurography with iodrolan following epiduroscopy. There is complete contrast filling of the epidural space at L₅-S₁, but incomplete filling at the L₂-L₄ spinal levels.

attempt of adhesiolysis was abandoned and the operation was terminated after 38 min, due to his frequent complaints of low back pain and movement during the procedure, despite one additional dose of midazolam 1 mg *iv* and fentanyl 100 µg *iv*. The epidurography with iodrolan 10 mL demonstrated complete contrast filling of the epidural space at L₅-S₁, but incomplete, narrow filling at L₂-L₄ (Figure 1). At the end of epiduroscopy, 0.25% mepivacaine 30 mL were injected into the epidural space for analgesia. The total volume of saline used for epidural irrigation was 300 mL.

No sooner had the epiduroscopy been completed than he developed muscle weakness and hypoesthesia of both legs, which persisted for three hours. Ninety minutes postoperatively, he became confused, disoriented, and agitated, moving vigorously, calling out while remaining unresponsive to command. He developed urinary incontinence and occasional tremors involving the head and legs, which deteriorated to a state of extreme agitation, requiring bed restraint. To manage the delirium chlorpromazine 50 mg *iv* and haloperidol 5 mg *iv* were administered. A computed tomography (CT) scan of the head obtained 4.5 hr postoperatively revealed diffuse contrast enhancement throughout the intracranial cerebrospinal fluid (CSF) spaces (Figure 2). After being returned to the ward, he was febrile, with his

FIGURE 2 Non-contrast head computed tomography 4.5 hr postoperatively

There is diffuse contrast enhancement throughout the intracranial cerebrospinal fluid spaces, including cortical sulci, basal cisterns, and cerebral ventricles.

temperature peaking at 39.1°C eight hours postoperatively, despite treatment with cooling and administration of NSAIDs and cefazolin 1 g *iv* every eight hours. He was maintained in a 30° head-up position to minimize cephalad migration of iodrolan. Crystalloid was administered in an attempt to facilitate iodrolan absorption from the CSF and excretion into urine. The psychomotor agitation slowly resolved over several hours and he regained nearly full consciousness and orientation by the 13th hour postoperatively. All symptoms and signs but the tremors and neck stiffness resolved.

Blood counts and serum chemistries at 18 hr and 24 hr postoperatively showed marked elevations in serum creatinine phosphokinase (CK) and myoglobin (Mb), indicating occurrence of rhabdomyolysis (Table). He had mild renal insufficiency, moderate leukocytosis, and elevated serum C-reactive protein. Serum CK and Mb levels peaked at 24 hr, and decreased thereafter. Vigorous hydration and antibiotics were continued, and analgesics, including NSAIDs and pentazocine, were administered repeatedly to relieve generalized myalgia-like pain. The remaining tremors and neck stiffness disappeared completely by the 20th hour postoperatively, and he was able to resume walking 24 hr postoperatively. A repeat CT scan of the head on the fourth postoperative day revealed no residual contrast. His recovery proceeded uneventfully and he was discharged home seven days postoperatively.

Discussion

This case presents a rather dramatic constellation of signs of acute psychomotor disturbance occurring with-

in a few hours following epiduroscopy. The clinical signs resolved over the next several hours while supportive therapy was administered, to be followed by biochemical evidence of acute rhabdomyolysis. A dural tear, not detected during epiduroscopy, was suspected from the appearance of regional motor and sensory blocks. Evidence for the dural tear was confirmed subsequently with a CT scan revealing diffuse contrast enhancement within the intracerebral CSF. We assume migration of iotrolan into the CSF via a dural tear, resulted in the encephalopathy and secondary rhabdomyolysis.

As a contrast medium, iotrolan is considered to be associated with a lower risk of seizures and adverse events for intrathecal use, because it does not interfere with glucose metabolism and normal metabolic pathways.^{6,7} However, mild side effects such as headache, neck pain, neck stiffness, tinnitus, nausea, vomiting, dizziness, and allergic reactions may occur up to two to four days following iotrolan following myelography in as many as 24–36% of procedures.^{6–9} The frequency of side effects for cervical myelography may approach 56%.⁸ Subarachnoid injection of iotrolan actually induced agitation and seizures in a rabbit model.¹⁰ Myelography with iotrolan has also been shown to result in symptomatic aseptic chemical meningitis.^{11,12} Further, hydrocephalus after myelography with iotrolan has been reported, possibly due to arachnoiditis, hypersensitivity reaction, or dural sinus thrombosis.¹³ Rhabdomyolysis secondary to anticonvulsant-resistant seizures following myelography with iohexol, a non-ionic contrast medium, has also been reported.¹⁴ Such adverse responses may be dose-dependent.¹⁵ As iotrolan is a dimer, and thus a larger molecule compared to iohexol, it has a longer half-life in the CSF, and a decreased rate of resorption.¹⁶ The plasma concentration following subarachnoid injection of iotrolan peaks after two to six hours.¹⁷ As there are no reported side effects of epidurally-administered iotrolan, it seems very plausible that the encephalopathic signs and rhabdomyolysis observed in this patient resulted from direct neurotoxicity of iotrolan penetrating into the central nervous system via the CSF following a dural tear during epiduroscopy. This case warns of inadvertent dural tear, resulting in known neurotoxicity of iotrolan or other contrast agents.

In this patient, we opted for conservative management with *iv* hydration and elevation of the head and trunk¹⁸ in an effort to minimize the cephalad migration of iotrolan. While use of a lumbar intrathecal catheter has been described for the purpose of performing drainage and lavage of the intrathecal space,^{11,13,18} we would warrant caution for the introduction of another invasive procedure without clear indications.

There are three different ways to detect a dural tear, which include direct visualization with an epiduroscope, aspiration of CSF from the epidural space, and contrast injection under fluoroscopy. In this patient, as adhesions and scar tissue were dense and an accidental dural tear might have been difficult to observe, we failed to demonstrate^{4,19} a dural tear initially by any of the above methods. Further, as a moderate saline infusion was used during the procedure, it was difficult to aspirate any CSF.

Marked elevations in serum CK and Mb concentrations indicated development of rhabdomyolysis. Tremors persisted for hours in this patient, and such vigorous involuntary movement might have contributed to the development of rhabdomyolysis. Further, unusual skeletal muscle hyperactivity due to vigorous struggling against physical restraint most likely contributed to exertional rhabdomyolysis²⁰ in this patient. A malignant neuroleptic syndrome secondary to neuroleptics²¹ was considered unlikely, as symptoms developed before administration of chlorpromazine and haloperidol. It has been recommended that neuroleptics e.g., phenothiazine derivatives, should be discontinued 48 hr before myelography and avoided 24–48 hr after myelography with iotrolan, because they reduce the seizure threshold.²² In the case of our patient, it is difficult to ascertain how the use of these neuroleptics affected the course of the psychomotor disturbance and subsequent rhabdomyolysis.

Electroencephalographic (EEG) studies have shown that radiocontrast materials can alter seizure thresholds, in the form of non-convulsive status epilepticus, including absence status epilepticus and complex partial status epilepticus.²² The symptoms are often indistinguishable from delirium.²³ The psychological disorders accompanying EEG alterations are not rare in humans after cervical myelography with iotrolan.²⁴

In conclusion, we describe a patient who experienced an acute encephalopathy and subsequent rhabdomyolysis following an accidental dural tear associated with epiduroscopy, most probably secondary to neurotoxicity of iotrolan migrating into the CSF. This case highlights a potential and serious complication of epiduroscopy where a dural tear may be difficult to diagnose. Clearly, all precautions should be taken to avoid an intrathecal injection of iotrolan, if the dura is inadvertently injured.

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