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Case Report

CASE REPORT

Successful epidural fibrin glue patch to treat intracranial hypotension in a patient with bacteraemia and malignancy

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Abstract

Cerebrospinal fluid leaks after diagnostic lumbar puncture are often treated using an epidural blood patch; however, there are situations in which this may not be a desirable or safe option. We describe a case of a 55-yr-old male who developed a cerebrospinal fluid leak with intracranial hypotension and subdural haematoma after multiple diagnostic lumbar punctures who also had *Klebsiella* bacteraemia, malignancy, and low platelets. Given concern about bacterial and malignant seeding of the epidural space, we considered several options including a patch with banked blood or neurosurgical intervention. To treat impending brain herniation, we opted to perform an epidural patch using fibrin glue. The fibrin patch is an absorbable surgical sealing patch that is placed on wound tissue. In this case, it was used to close the assumed dural tear, which resulted in a good outcome for the patient without need for neurosurgical intervention.

Keywords: Cerebrospinal fluid leak; Fibrin glue; Post-dural puncture headache; Subdural hematoma

Cerebrospinal fluid (CSF) leakage is caused by a rupture or tear in the membranes (usually dura) protecting the brain or spinal cord. CSF leaks can happen spontaneously, or in some cases, be triggered by trauma such as head injuries, brain or spinal surgery, or lumbar punctures.[1] Lumbar punctures are often used in clinical neurology for diagnostic purposes and are becoming increasingly important in clinical research for evaluating different CSF biomarkers. Post-dural puncture headache (PDPH) is the most common adverse event associated with lumbar puncture, and it can be debilitating and cause severe morbidity. The diagnostic criteria put forward by the current International Criteria for Headache Disorders guidelines[2] suggest PDPH should be diagnosed when a low-pressure headache occurs within 5 days of a dural puncture, and is not better accounted for by an alternative diagnosis. PDPH, as with other low pressure headaches, often but not invariably has a notable postural component – worsening when upright, and improved with lying down.[3] For patients with acute PDPH, conservative management includes medications such as oral caffeine, lying flat for a period of time, antiemetics, and intravenous hydration or even systemic steroids.[4] After conservative approaches have been exhausted, or if a CSF leak has resulted in mental status changes signifying intracranial hypotension and imminent herniation, the most frequent treatment for spinal CSF leaks is an epidural blood patch.[5] However, this option is not always feasible depending on patient-specific factors, as described in our case.

Case report

A 55-yr-old male presented to the emergency department for progressively worsening shortness of breath, dyspnoea on exertion, and non-productive cough for 1 month. Further investigation revealed metastatic mantle cell lymphoma in the pleural fluid and bone marrow, and a lumbar puncture demonstrated central nervous system involvement. During his admission, the patient was incidentally found to have a left brachiocephalic deep vein thrombosis and was started on a therapeutic heparin infusion. The plan was to transition him

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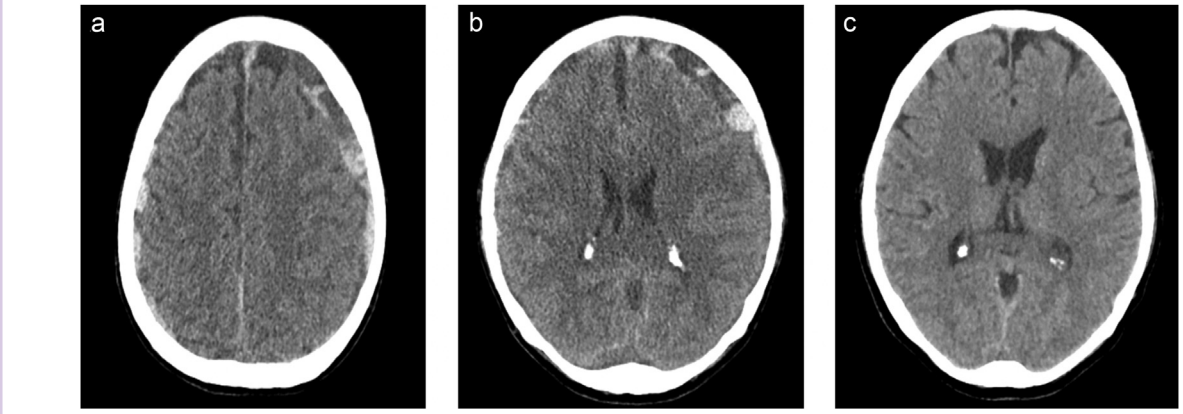

Fig 1. (a) Pre-epidural fibrin glue patch CT head scan. Bilateral subdural haematomas (left greater than right) with brain sagging. (b) One-day post-epidural fibrin glue patch CT head scan. Stable size of bilateral subdural haematomas. (c) Three-months post-epidural fibrin glue patch CT head scan. Interval resolution of bilateral subdural haematomas.

to a direct oral anticoagulant, such as apixaban, once his condition was stable but pancytopaenia precluded this immediate transition. The patient was also found to have a neutropaenic fever, and *Klebsiella pneumoniae* was grown in two out of two blood cultures shortly thereafter. Throughout the patient's admission, he remained thrombocytopaenic ($49–65\times10^9$ L^{-1}), presumably secondary to bone marrow involvement of his newly diagnosed malignancy.

Of note, three lumbar punctures were performed without image guidance through his hospital stay, two of which were performed with the heparin infusion stopped for 4 h before the procedure, including a therapeutic lumbar puncture for intrathecal administration of cytarabine 100 mg at the L4–L5 interspace using a 22G Sprotte needle. The other two lumbar punctures were documented at the L3–L4 interspace; however, the size and gauge of the needle were not documented. Seven days after the therapeutic lumbar puncture for chemotherapy instillation, the patient acutely developed a new onset, severe headache. Immediate head CT scan showed bilateral acute on chronic subdural haematomas (left-sided 12 mm, right-sided 7 mm) and brain sagging with crowding of the midbrain and effacement of the pre-pontine cistern (Fig. 1a), consistent with intracranial hypotension.[6] This was recognised as a life-threatening emergency at this time. The heparin was stopped and reversed with protamine despite the presence of the brachiocephalic deep vein thrombosis for two reasons: (1) further expansion of the subdural haematoma – already showing acute on chronic haemorrhage facilitated by anticoagulation – presented an immediate risk of death or irreversible brain injury through herniation or kinking of cerebral veins; and (2) the apparent imminent necessity of performing an epidural patch. These considerations were determined to outweigh the real but lesser risks of deep vein thrombosis expansion and embolism associated with temporarily holding the anticoagulation. However, the patient remained bacteraemic with *Klebsiella*. He was transferred to the ICU for close monitoring, laid completely flat, and the Anesthesiology Department's Acute Pain Service, made up of anaesthesiologists and 'advanced practice providers', was consulted for an urgent epidural blood patch.

Immediately upon consultation, we recommended that the patient be laid completely flat, and placed on hourly neurological checks with repeat CT scans if any changes were observed. His neurological symptoms and signs remained unchanged, and this provided the time for heparin to be stopped, then reversed with protamine, and discussions between treating teams to occur given the medical complexity. The Neurosurgery, Infectious Disease, and Blood Bank teams were consulted by the Acute Pain Service, and ultimately it was decided not to use an epidural blood patch given the potential for contamination of the patients' blood with either *Klebsiella* or malignant cells. After discussion between pain physicians (IRC and VLT), the decision was made to proceed with fibrin glue patch at the lumbar region despite the patient's thrombocytopaenia (platelets were 102×10^9 L^{-1} and stable/increasing at the time of the procedure).

The patient was taken to the operating room for a fluoroscopy-guided epidural fibrin glue patch approximately 12 h after the CT scan of the head revealed brain sagging from the acute subdural haemorrhage. A 20G Tuohy needle was used to inject a total of 5 mL of VISTASEAL™ fibrin glue in the L3–L4 epidural space with two needle placements, one each using the right and left paramedian approach with a loss of resistance technique. There were no complications during the procedure, and the patient was then placed in slight Trendelenburg position for the next 24 h. A repeat CT scan of the head showed no increase in haematoma size or herniation (Fig. 1b). The patient's headache progressively improved after the procedure. He was discharged a week later in a stable condition with a plan for follow-up with the oncology service and he had no further sequelae related to the CSF leak. Now, at 6 months post-patch, he remains headache-free, without any complications of the dural punctures, and has resolution of his subdural haematomas (Fig. 1c).

Discussion

It is well appreciated that the non-iatrogenic, spontaneous forms of spinal CSF leak and resulting spontaneous intracra-

nial hypotension can result in brain injury, coma, and death.[5] The life-threatening compromise of CSF leak is understood to arise from (1) the development of subdural haematomas with mass effect, (2) caudad brain displacement ('brain sag') that can compromise cerebral venous outflow leading to ischaemia or haemorrhage, and (3) caudal displacement of the brain that can culminate in lethal herniation.[6] PDPH is an iatrogenic form of spinal CSF leak that also results in intracranial hypotension, and these same complications can arise in the setting of a previously uncomplicated PDPH.[7] In this case, the occurrence of a new onset severe headache 7 days after the third dural puncture, likely reflected not the initial onset of CSF leak and intracranial hypotension, but rather the onset of the life-threatening acute on chronic subdural haematoma and brain sag seen on the CT scan. The preceding PDPH was hardly noted, which may not be surprising in light of two circumstances: (1) the patient was a critically ill inpatient spending most of his time in bed – a circumstance delaying recognition of a new postural headache; and (2) the patient had known malignant CNS involvement to which head discomfort might otherwise be attributed without further investigation or alarm. As in this case, the new onset of a more severe headache occurring in a delayed fashion after a dural puncture should prompt an expansion of the differential diagnosis and imaging to look for unusual but dangerous complications of intracranial hypotension including subdural haematoma, bacterial meningitis, and venous sinus thrombosis.[8,9]

Current clinical management of PDPH includes conservative measures such as bed rest, oral hydration, and simple analgesics including acetaminophen (paracetamol) and NSAIDs. If conservative treatment fails, an epidural blood patch can be performed by injecting the patient's freshly drawn blood through an epidural needle into the epidural space. This manoeuvre is thought to compress the thecal sac and increase the intrathecal CSF pressure, which can relieve symptoms and in extreme cases prevent herniation. Injected blood is also thought to 'patch' the CSF leak site through initiation of a clotting and inflammatory cascade. If, despite numerous attempts, epidural blood patches fail to resolve symptoms of CSF leak, percutaneous epidural fibrin sealant or surgical placement of fat or muscle patches may be used. If these procedures fail, alternative surgical options for repairing the leak involve open dural repair with sutures or aneurysm clips.[10]

Subdural haematomas are a known consequence of intracranial hypotension. In this case the use of anticoagulation in the setting of intracranial hypotension from the dural punctures might have contributed to the development of subdural haematoma. We considered this patient was not a candidate for conservative treatment for several reasons: (1) the patient's clinical status was worsening with acute haemorrhage despite the passage of 7 days since the last puncture; (2) ongoing intracranial hypotension could reasonably be expected to increase the risk of further subdural bleeding even in the absence of anticoagulation; (3) published reports of severe intracranial hypotension complicated by subdural haematoma emphasise that sealing the spinal leak is the most important lifesaving intervention; and (4) in the presence of a deep venous thrombosis the patient had a need for further anticoagulation, which would pose less risk of further acute subdural bleeding in the absence of ongoing intracranial hypotension.

To our knowledge, no substantive data quantify (1) a potential increased rate of subdural haematoma in patients with PDPH when given anticoagulation compared with a PDPH in patients without anticoagulation; or (2) the risks and benefits of prophylactically patching a patient with a known dural puncture before initiating anticoagulation. The potential benefits of a prophylactic epidural blood patch in a patient who has received a dural puncture before initiating anticoagulation are partially illustrated by this case: (1) an epidural patch might prevent the conversion of an uncomfortable PDPH without subdural haematoma to an iatrogenic life-threatening situation arising from the accumulated intracranial blood; and (2) it may prevent the subsequent need to stop therapeutic anticoagulation during the period of concern for venous thrombosis, and the associated risks of withholding anticoagulation. Although prophylactic epidural patches are not routinely offered after uncomplicated dural punctures, this case illustrates that patients who will subsequently receive therapeutic anticoagulation (and without other contraindications) may benefit from a prophylactic epidural patch before initiation of that anticoagulation.

Epidural blood patch is very effective in managing PDPH; however, there are times when patients do not respond or have contraindications to epidural blood patches. In our case report, the patient had *K. pneumoniae* bacteraemia and metastatic malignancy; therefore, injecting the patient's blood into the epidural space could have resulted in CNS infection or malignant seeding. Accessing the epidural space introduces a risk for infection, which can lead to meningitis, epidural abscess, and subdural empyema. The risk of infection after epidural procedures, including for epidural anaesthesia and epidural blood patch, is low; however, several case reports have demonstrated meningeal irritation and CNS infection as a result of autologous epidural blood patches in patients with systemic infection, including fungaemia and bacteraemia.[11,12] One case report by Trentman and colleagues[12] describes a patient with disseminated coccidioidomycosis who was evaluated for epidural blood patch for PDPH. However, an autologous epidural blood patch would have introduced fungal elements into the CNS, potentially leading to meningitis. Therefore, an allogeneic donor blood patch was used instead. Although we did consider this option, given the time pressure, and the complexity of patient care in the context of the ongoing COVID-19 pandemic, we had no clear path for identifying a live, immediately available donor for the blood.[8] The literature on the use of fibrin sealants to treat PDPH remains small and limited to case reports. The majority of these reports describe the use of fibrin as a rescue sealant for those patients in whom epidural patching with blood had been tried but failed.[13,14] Our case report highlights a different dimension of the utility of a fibrin patch: as an alternative to blood not as a rescue sealant, but as a primary option, when avoidance of blood is desired because of (1) the potential for epidural or unintended intrathecal contamination with malignant cells or bacteria, and (2) the potential impaired ability for the injected blood to clot owing to thrombocytopaenia and incomplete heparin reversal. Few reports deal with this issue, but we are aware of a case in which fibrin was used to treat an HIV and hepatitis C infected patient for parallel reasons.[15]

Our case report illustrates the potential use of fibrin patches, especially when autologous epidural blood patches could lead to central nervous system infection or malignant seeding. Fibrin glue has been used and described by neurosurgeons and orthopaedic surgeons to repair iatrogenic dural tears during spine surgery.[16,17] It has also been shown to be

effective in treating spontaneous intracranial hypotension and refractory headache in those with CSF leak because of dural puncture.[14,18,19] Fibrin patches were first described in the literature in 1997 by Gerritse and colleagues[20] as an injection of a fibrin sealant into the epidural space to repair a dural defect. VISTASEAL™ consists of one preloaded syringe containing concentrated human fibrinogen and a second preloaded syringe containing human thrombin derived from pooled human plasma that is treated in a process designed to reduce the risk of viral transmission inherent in pooled human blood products. Mixing of the solutions triggers the last step of the coagulation cascade, the enzymatic conversion of fibrinogen into fibrin by thrombin. VISTASEAL™ carries a formal indication in the USA as 'an adjunct to haemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical'. It is not formally approved for percutaneous epidural patching. Risks of fibrin sealants, including VISTASEAL™, arise from the potential for accidental intravascular injection, anaphylaxis, and transmission of undetected viruses or prions to the patient.[21] Intravascular injection such as into an epidural vein could precipitate a venous clot or embolism, whereas injection into the artery of Adamkiewicz with consequent spinal cord ischaemia is a risk when taking a transforaminal approach to the epidural space. As fibrin sealants are derived from pooled clotting factors from human donors, they expose patients to foreign proteins, which can cause allergic reactions. In this context, repeated exposure may elevate the risk. Aproptinin may increase the risk and is commonly found with fibrin sealants such as Tisseel. In our case we used VISTASEAL™ which has no aprotinin, to reduce the risk of anaphylaxis that is attributable to aprotinin. Furthermore, injection of such products requires extensive user knowledge and time to allow for reconstitution. It can also be significantly more expensive than traditional epidural blood patches. Fibrin glue patches offer several advantages over traditional epidural blood patch: smaller volume necessary to achieve clotting[22] and avoidance of introducing potential pathogens into the epidural space (or with an unrecognised inadvertent unrecognised dural puncture, introducing pathogens into the intrathecal space). In this case we wished to avoid the potential to inject infected blood, or even haematogenous cancer cells, into either the epidural or intrathecal space. Fibrin sealants can also be useful in the patient with difficult venous or arterial access for the blood draw – a situation not uncommon in cancer patients who have received repeated i.v. chemotherapy.

In our case report, the fibrin glue patch was effective in treating intracranial hypotension and impending tonsillar herniation from iatrogenic dural tear from multiple diagnostic lumbar punctures and avoided the risk of central nervous system infection and malignant seeding from the injection of autologous blood. Future studies are warranted to evaluate the potential use of fibrin glue products in patients in whom epidural blood patch is unsafe or contraindicated.

Authors' contributions

Writing of the case study, Discussion: AG
Figures: AG
Editing of the manuscript: AG, VM, IC, VLT
Writing of Abstract, Introduction: VM
Participation in clinical care: VLT

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Declarations of interest

The authors declare they have no conflict of interest.

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