REVIEW AND CASE PRESENTATION

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Hematomyelia after epidural anesthesia: a rare complication with putative multifactorial and occult etiology

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Abstract

Subarachnoid hemorrhage (SAH) and spinal hematomas are considered serious but rare complications of spinal pathology. They occur after spinal anesthesia, especially in patients with risk factors such as autoimmune diseases, blood coagulation pathology, anticoagulant treatment, vascular malformations, intramedullary or spinal cord tumors, or can be multifactorial. Usually, anticoagulant therapy represents an additional factor regarding spinal SAH (SSAH) or spinal hematomas. None of the direct oral anticoagulants has a higher chance of producing a spinal hemorrhage. The diagnosis can be established based on the clinical picture of SSAH or myelopathy syndrome, completed with magnetic resonance imaging (MRI). In this study, we present the latest data from the literature regarding SSAH and hematomas and compare them with the data of a 77-year-old man with a history of atrial fibrillation, on oral anticoagulant treatment, who developed a SSAH and spinal hematoma after elective surgery for an inguinal hernia.

Keywords: regional anesthesia, hematomyelia, subdural hematoma.

Introduction

Subdural anesthesia and spinal subdural hematoma are rare complications associated with the combined spinal-epidural anesthesia technique [1]. Subarachnoid hematoma is formed when the needle causes rupture of the radicular vessels that enter the subarachnoid space (SAS) along with segmental nerve roots [2]. Needle puncture or insertion of the catheter through the vertebral space can cause injury to the epidural veins, which can lead to bleeding [3]. According to a peer-reviewed article, more than half of hematomas occur within the first 24 hours after catheter removal [3].

Hemorrhages affecting the spinal cord are rare and can be differentiated according to the area in which the bleeding occurs, including (intramedullary) hematomyelia, subarachnoid, subdural and epidural hemorrhage [4]. Of all types of spinal bleeding, intramedullary hemorrhage (hematomyelia) is the rarest encountered [5]. Intramedullary hemorrhage associated with anticoagulant therapy has been reported exclusively in association with Warfarin administration [6].

Spinal epidural hematoma, post-neuraxial anesthesia, is a rare complication, generally manifested by sudden onset of acute neurological symptoms [7]. Although direct injury to the Batson's venous plexus is considered the main pathogenetic mechanism, factors such as preoperative coagulation status and anticoagulant treatment also influence the occurrence of this condition [7].

Heparins, including unfractionated heparin and various forms of low-molecular-weight heparin (LMWH), are widely used as anticoagulants [8]. LMWH is commonly used in various medical institutions due to its efficacy in preventing deep vein thrombosis, with a favorable safety profile. However, its use has been associated with an increased risk of spinal hematomas after neuraxial anesthesia procedures. Studies indicate that patients treated with LMWH have an incidence of spinal hematomas of 33 per 100 000 for epidural anesthesia and one per 100 000 after spinal anesthesia compared with an incidence of one in 150 000 after epidural block and one in 220 000 after spinal block [9].

To promptly diagnose hematomyelia, early detection of a specific pattern of spinal cord injury is essential, which may involve various forms of myelopathy, such as transverse, central, anterior, posterior or unilateral [10].

Symptoms of spinal hematomas include somatosensory deficits such as localized or radiating back pain, paresthesia, sphincter dysfunction, motor deficits, both paresis and plegia [11].

Aim

The aim of this study was to provide the latest literature data on rare complications of spinal anesthesia such as subarachnoid hemorrhage (SAH) or subdural spinal hematoma, and particularly the association between their occurrence and anticoagulant treatment. We have also compared these data with those of a case of a 77-year-old man known to have atrial fibrillation for which he was receiving anticoagulant treatment, who suffered such a complication following inguinal hernia surgery.

Clinical manifestations

Spinal cord hemorrhages or SAHs are much less common than cerebral hemorrhage or cerebral SAH [2, 3] and represent pathologies with different etiologies [4]. The most common etiologies are the use of anticoagulants, spontaneous hemorrhage, trauma, vascular malformations or aneurysms, neoplasms, coagulopathies, autoimmune disease [5].

The clinical features of spinal cord hemorrhage and hematomyelia have a sudden onset of symptoms with intense local or radicular back pain, motor deficit, sensory disturbance, and urinary retention [10]. At the same time, meningitis symptoms or epileptic seizures may also appear. The most common location is at the level of the thoracolumbar spine [11] and can extend along the entire SAS [7].

Clinical manifestations depend on the location of the hemorrhage in the spinal cord [3]. Lesions above the 5th cervical vertebra clinically present quadriplegic-type motor deficit with all the signs of central motor neuron palsy with sensory disorders affecting all types of sensitivity from the level of the lesion downwards and sphincter disorders. Lesions of the first cervical segments can be associated with sensory disorders in the trigeminal area and lesions at the C3–C4 level lead to serious respiratory disorders [6]. Lesions at the C5–T2 level can cause peripheral motor neuron symptoms in the upper limbs by damaging the anterior spinal horn, while below the involved level the deficit has a pyramidal lesion feature.

Lesions below T2 can cause paraplegia with all pyramidal signs, with sensory disturbances from the arm and subclavian level down. From this point down until the lumbar region, the lesion produces the same spastic paraplegia, the upper limit of sensory disturbances depending in relation to the site of spinal cord lesion and the abdominal cutaneous reflexes are affected [8, 9]. Lesions at the L1–L4 level cause paraplegia, abolition of the cremasteric reflex, atrophy of the quadriceps muscle with exaggerated or abolished patellar reflexes, presence of Achilles and Babinski reflexes, as well as sensitivity disorders. Flaccid paraplegia, muscle atrophy and abolished Achilles and plantar reflexes occur in lesions at the level of L5–S2. Sensory disorders cause anesthesia in addition to sphincter and sexual dysfunction [10].

Imaging findings

Compared to computed tomography (CT), magnetic resonance imaging (MRI) images have superior contrast of soft tissues, nerve roots, blood vessels, or intervertebral discs. In addition, MRI can differentiate a new fracture from an old one [12]. Thus, MRI is the method of choice for the diagnosis of hematomyelia and spinal SAH (SSAH), especially for this etiology [13].

Although CT can show a filling defect in the case of SSAH called “capping”, it does not offer a precision in terms of diagnosis, such as MRI does, considering the possibility of this technique to highlight blood products but also the causes that can determine this type of hemorrhage. In case of suspicion of a vascular malformation, CT angiography or spinal angiography can complete the imaging picture in order to elucidate the etiology [14].

MRI represents the “gold standard” investigation regarding the accurate diagnosis of SSAH or spinal hematomas. The appearance of the hematoma differs depending on the time that has passed since the initial or triggering event. Thus, as soon as the hematoma is formed, it appears isointense on T1 and hyperintense on T2 sequences, and over 80% of cases present a hyperintense ring around hematoma. In the subacute phase, extravasated methemoglobin catabolized from the red blood cells (RBCs) appears on T1 and T2 sequences as hyperintense, while in the chronic phase it appears hypointense on T1 and T2. A better overall view of the lesion will be obtained by imaging in at least two anatomical planes.

In hematomyelia, the central gray matter necrosis will appear as a hypointensity in T2 sequence. Also, the edema that accompanies intramedullary hemorrhage has the appearance of hyperintensity on T2 with the loss of the differentiation between white and gray matter.

Treatment

Treatment of spinal cord hemorrhage or SAH represents an emergency and is adapted to the etiology and correction of the triggering factors. Thus, in the case of trauma, administration of large doses of corticosteroids, surgical decompression, stopping anticoagulation where appropriate, and last but not least, careful monitoring of vital functions will decrease complications.

Regarding spinal vascular malformations, the treatment of choice is also surgical, either by microsurgery or by an endovascular approach aimed at restoring normal perfusion of the spinal cord [15].

In the case of bleeding spinal tumors, embolization through various techniques is a therapeutic solution [16].

In patients undergoing anticoagulant treatment, close monitoring can prevent the development of hematomyelia or SSAH. If bleeding occurs, it should be stopped, and an emergency laminectomy and decompression of the spinal cord is mandatory in order to minimize neurological sequelae [17].

Vital signs should be monitored to avoid complications such as hypotension [18], cardiovascular complications (bradycardia may occur in severe, high cervical injuries) [19], respiratory complications (respiratory failure, pulmonary edema, pneumonia or pulmonary embolism), [20], venous and pulmonary thromboembolism [21].

Among other complications that may occur and need further treatment, are pain control, urinary catheterization, gastrointestinal stress ulceration, paralytic ileus, temperature control [22, 23].

There are no clinical trials or guidelines to guide the treatment of hematomyelia and therefore the underlying cause must be managed. An initial imaging evaluation of the spine and neurosurgical consultation is necessary because most patients progress to irreversible neurological deficit unless urgent surgical decompression is performed [24, 25]. Conservative treatment should also be considered in patients with incomplete spinal cord dysfunction and evidence of neurological recovery within 24 hours of onset [24].

Histopathology and immunohistochemistry

Published data describing pathological changes in hematomyelia are very scarce, since the cases of hematomyelia reported in the literature are also very rare. On macroscopic evaluation, intramedullary hemorrhage is observed mostly in the gray matter and the neighboring white matter, and it shows a tendency to expand vertically over several spinal segments rather than transversely [26–28]. The size of the hemorrhage varies from patient to patient, but as a general observation, they do not usually expand into the neighboring SAS. On microscopy, organized hematomas or diffuse RBCs extravasate associated with hemosiderin deposits, and structured and unstructured necrosis which preferentially involves the neuronal elements and leads to the vacuolization of the neuropil but sometimes preserves the overall morphology of existing blood vessels although endothelium is clearly lost on most instances. Remaining neurons show extensive degeneration features like ballooning and chromatolysis or Nissl bodies, hypoxic-eosinophilic shrunken perikarya with pyknotic nuclei, and these changes can also be found above and below hemorrhagic areas due to the degenerating axonal pathways. Small previously undiagnosed millimeter-sized vascular malformations seem to be the usual cause of bleedings [29]. In the remaining cases, blood coagulability disorders are usually the cause, such as hemophilia, von Willebrand's disease, liver disease-associated bleedings, vitamin K deficiency-associated bleedings, and anticoagulant therapy [30, 31]. Cardiovascular pathology such as atherosclerosis and hypertension can also explain some of the casuistry, as well as a plethora of other disorders, such as meningomyelitis, myelitis, syphilitic arteritis, compressive tumors, trauma among others [32, 33].

Immunohistochemistry (IHC) studies add on the data obtained by classical histopathology by helping in identifying the remnant cellular structures and tissular morphological changes such as gliosis and inflammatory infiltrate around the hemorrhagic and necrotic foci. Neuronal nuclei (NeuN) and perikarya can be identified by anti-NeuN and anti-neuron-specific enolase (NSE) antibodies, which can be used to identify the changes undergone by neurons, and loss/fragmentation of normal staining in necrotic/hemorrhage areas and surrounding hypoxic tissue. Neuritic loss, dystrophic changes and neuronal cytoskeleton integrity can be assessed by antibodies recognizing neurofilaments and ubiquitin. All classes of glial cells can be explored by antibodies targeting astrocytes (glial fibrillary acidic protein – GFAP), microglia [cluster of differentiation (CD) 68 and ionized calcium-binding adapter molecule 1 (Iba1)], and oligodendrocytes (Olig-2 transcription factor or myelin basic protein – MBP). Furthermore, the gross morphological appearance of the blood–brain barrier (BBB) can be explored by utilizing antibodies targeting the endothelial cells (CD34) and basement membranes (collagen IV and laminin), and inflammatory infiltrate can be assessed by identifying T- and B-lymphocytes (CD3 and CD20), as well as monocytes/microglia (CD68) [34, 35].

Etiological differential diagnosis

Spinal hemorrhages are a rare pathology and can be classified depending on the anatomical space occupied by the bleeding: SSAH, epidural spinal hematoma, subdural spinal hematoma and hematomyelia [36]. SAH in the spinal cord occurs in 6/100 000 people annually and is the most common spinal hemorrhage [37]. The next most common spinal hemorrhage is epidural spinal hematoma which has an incidence of approximately 0.1 per 100 000. Subdural spinal hematoma is less common than the hemorrhages listed above. The rarest type of spinal hemorrhage is intramedullary hematomyelia or intramedullary hematoma which was first described in 1938 and since then several cases have been reported in the literature. Anticoagulant treatment has been the most commonly described cause of hematomyelia [38]. Causes for all types of spinal hemorrhage include spinal arteriovenous malformations, trauma, infection, spinal arteriovenous fistula, anticoagulant treatment. All spinal hemorrhages must be differentiated from spinal cord infections, ischemic vascular lesions, neoplasms, demyelinating diseases, abscesses [39]. In order to make a correct and complete differential diagnosis we need clinical manifestations accompanied by laboratory investigations [lumbar puncture and cerebrospinal fluid (CSF) analysis], together with imaging (CT and MRI) and in very rare cases, biopsies. The differential imaging diagnosis of spinal hemorrhage depends on the type of hemorrhage. In the case of hematomyelia, an increased T1 signal accompanied or not by T2 hypointensity is observed on MRI images of the spinal cord, depending on the stage of hemoglobin degradation products, which also leads to surrounding parenchymal edema [40, 41]. Tumors are generally described as masses of tissue more or less well or poorly circumscribed in T1 hyposignal, T2 hypersignal [42].

The positive diagnosis of hematomyelia is suspected primarily of the clinical manifestations represented by motor neurological deficit with or without sensory deficit, local or radicular spinal pain, urinary retention, level of sensitivity, all with sudden onset, occurring either in a patient who was on chronic anticoagulant therapy or after a local trauma [43]. Imaging investigations (CT spine and MRI spine) are performed to confirm the diagnosis. On spine CT scan one will observe hyperdense content both in the spinal cord and around it, and on spinal MRI in T2/short *tau* inversion recovery (STIR) sequences a reduced signal at the level of the spinal cord examined will be observed. At lumbar puncture, xanthochromatic or blood-tinged CSF is evident. Clinical manifestations accompanied by the explorations detailed above support the diagnosis of hematomyelia.

Case report

We are also reporting here one such rare case, that of a 77-year-old man with known history of atrial fibrillation,

on treatment with direct oral anticoagulants. The patient was scheduled for elective inguinal hernia repair. Five days prior to the procedure, oral anticoagulant was stopped, and Enoxaparin 0.6 mL twice daily was initiated.

A written informed consent was obtained from the patient regarding the presentation of his anonymized data.

After 12 hours postoperatively, the patient developed motor deficit in the lower limbs 0/5 Medical Research Council (MRC) and complete loss of tactile, thermal and pain sensitivity below T10 level accompanied by significant pain in the lumbar spine. Spinal MRI is performed, which raises the suspicion of thoracolumbar arachnoiditis.

The patient was transferred to the Department of Neurology, Emergency County Hospital, Craiova, Romania. A native MRI of the spine (cervical, thoracic and lumbosacral) was performed (contrast medium was not done because of the decreased renal clearance) which reveals spinal cord with heterogeneous signal in the cervicothoracic segment adjacent to the C6–T3 vertebral body, increased T2/STIR isosignal T1 isosignal over a distance of approximately 71 mm, with appearance suggestive of intramedullary bleeding. From the lower T10 level, T2/STIR signal was reduced in the longitudinal and anterior aspects of the spinal cord, and T10 medullary cone showed suggestive hemoglobin degradation compounds without hernial radicular compression, without paravertebral collection (Figure 1, A–D).

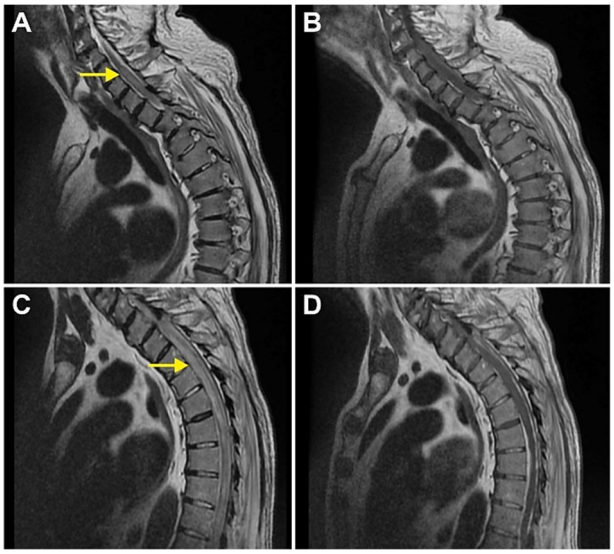

Figure 1 – ***(A) Sagittal section, increased T2 signal in the lower cervical spine; MRI of the cervicothoracic spine; (B) Sagittal section, T1 isosignal in the lower cervical medulla; cervicothoracic spine MRI; (A and B) Appear suggestive of intramedullary bleeding; (C) Sagittal section, increased T2 signal in the thoracic medulla; MRI cervicothoracic spine (appears suggestive of myelitis); (D) Sagittal section, T1 isosignal on thoracic medulla; cervicothoracic spinal MRI (appear suggestive of intramedullary bleeding). MRI: Magnetic resonance imaging.***

A native vertebral spinal CT scan was performed showing hyperdense, possibly hematic content, which surrounded the spinal cord from T10 to the sacral portion. The case was discussed in a multidisciplinary team (MDT) made up of neurosurgeon, neurologist, anesthesiologist and cardiologist and it was decided to continue conservative treatment due to the fact that neurosurgical intervention would not have brought additional benefits.

After seven days post-surgery, the patient developed cutaneous anesthesia with bilateral T4 level and brachial diparesis 2/5 MRC. After nine days post-surgery, patient presented increased pharyngeal secretions in increased quantity, impossibility to perform an effective expectoration, reason for which he is transferred to the intensive care unit for monitoring and specific treatment. After 10 days post-surgery, a native brain CT scan was performed and revealed bilateral parietal and occipital SAH (Figure 2); minimal hemorrhagic accumulation at the level of the posterior horns of both lateral ventricles (LVs); cerebral and cerebellar atrophy with dilatation of the pericerebral spaces. The patient was treated and carefully monitored by the MDT, but the evolution was unfavorable with persistent motor and sensory deficits, but under mechanical ventilation and vasopressor support with maximal doses the patient suffered a fatal cardiorespiratory arrest.

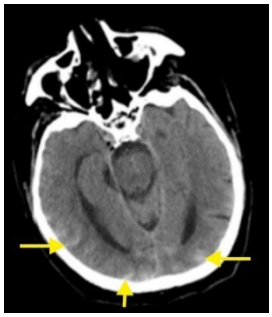

Figure 2 – ***Native brain CT showing bilateral parieto-occipital subarachnoid hemorrhage. CT: Computed tomography.***

Necropsy revealed an extensive SAH, both in the brain and in the medullary canal, with meningeal hyperemia, both at the level of the telencephalon and the cerebellum. After sectioning, there were multiple petechial hemorrhage areas in the cerebral hemispheres and cerebellum. On opening of the medullary canal, an extensive intramedullary hemorrhage at the T5–L2 levels was found, with macroscopic appearance suggestive of hematomyelia. Non-central nervous system gross pathological changes included steatosis and chronic stasis in the liver, hemorrhagic gastritis, and intensely hyperemic mucosa with hemorrhagic foci in the small intestine. We have also identified a right inguino-scrotal hemorrhage that compressed the parietal peritoneum, subcutaneous fat tissue and the right spermatic cord, and with the presence of a retroperitoneal hematoma of approximatively 6 cm in diameter.

Macroscopic and microscopic histopathological assessments have been performed in the Department of Pathology, Emergency County Hospital, Craiova, then the evaluation was completed with IHC in the Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova. Tissues were fixed in formalin and embedded in paraffin blocks, then sectioned as 5 μm-thick sections, then subsequently processed for IHC according to a standard protocol. Briefly, after an antigen retrieval step performed by microwaving the slides at 650 W in a pH 6 0.1 M citrate buffer solution, the endogenous peroxidase has been blocked by incubation in 1% hydrogen peroxide, and the unspecific binding sites were blocked with a 3% skim milk saline solution. The slides were next incubated with the primary antibodies for 18 hours at 4°C (Table 1), the next day the sections were incubated with

species-specific horseradish peroxidase (HRP)-labeled secondary antibodies, then the signal was detected using 3,3'-Diaminobenzidine (DAB, Nichirei-Bioscience), after which the sections were counterstained with Mayer's Hematoxylin, dehydrated, clarified in xylene and coversliped with a xylene-based mounting medium.

Table 1 – ***Antibodies utilized for immunohistochemistry evaluation of the case***

Antibody	Producer	Clone	Antigen retrieval	Dilution	Target
Anti-CD68	Dako	Mouse, clone KP1	Citrate, pH 6	1:100	Macrophages
Anti-CD3	Dako	Rabbit, polyclonal	Citrate, pH 6	1:50	T-lymphocytes
Anti-CD20	Dako	Mouse, clone L26	Citrate, pH 6	1:50	B-lymphocytes
Anti-NeuN	Abcam	Rabbit, polyclonal	Citrate, pH 6	1:1000	Neurons
Anti-GFAP	Dako	Rabbit, polyclonal	Citrate, pH 6	1:5000	Astrocytes
Anti-CD34	Dako	Mouse, clone QBEnd 10	Citrate, pH 6	1:50	Vascular endothelium

CD: Cluster of differentiation; GFAP: Glial fibrillary acidic protein; NeuN: Neuronal nuclei.

Histopathological assessment of the spine revealed massive subdural hemorrhage with widespread hemorrhagic necrosis in the whole parenchyma of the spinal cord and somatic ganglia, and with diffuse and intense axonal ballooning and degeneration of nerves roots (Figure 3A). The most resilient elements of the neuropil were blood vessels, some of them retaining an apparent intact endothelial reactivity for CD34 (Figure 3B), but other than this there were no other intact specific morphofunctional elements that could be further identified.

NeuN IHC could not identify any intact motor, sensory or association neurons in the necrotic debris, but only rare, ballooned neurons with chromatolysis of Nissl bodies and with faint reactivity towards the neuronal marker (Figure 3C). All the remaining non-liquefied tissue contained, however, a significant chronic inflammatory infiltrate composed mainly of macrophages (Figure 3D) and patchy T-lymphocytes (Figure 3E), but with no B-cells being identified (image not shown).

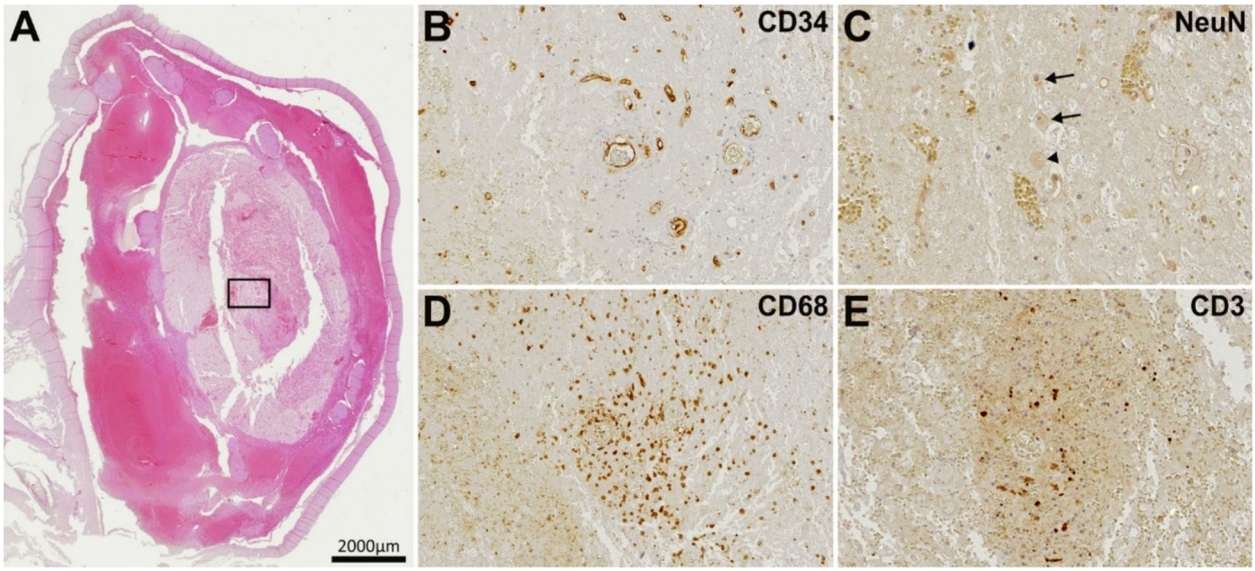

Figure 3 – ***Spinal cord pathology: (A) Overall transversal image of the thoracal spinal cord revels massive hemorrhage in the subdural space as well as necrosis and diffuse hemorrhagic infiltrate in the parenchyma (HE staining); On a detailed area from the central core of the spinal cord (rectangle in A, enlarged in B–E), blood vessels still show intact endothelial cells as revealed by IHC for CD34 (B), while only faint silhouettes of ballooned neurons are left based on IHC for NeuN, with (arrows) or without (arrowhead) remnant nuclei (C); A rich mononuclear inflammatory infiltrate is present, composed mostly of macrophages (CD68) (D) and T-lymphocytes (CD3) (E). (A) Slide scan; (B–E) ×100. CD: Cluster of differentiation; HE: Hematoxylin–Eosin; IHC: Immunohistochemistry; NeuN: Neuronal nuclei.***

In the isocortex, a hemorrhagic exudate was present in the leptomeninges (Figure 4A), with perivascular and peri-neuronal edema, vessels with stasis and microthrombosis (Figure 4B), and with moderate glial reactivity around vessels with stasis and microthrombosis (Figure 4C).

In the cerebellum, a fibrino-hemorrhagic reaction could be identified in the leptomeninges (Figure 4D), with moderate monocytary reaction (Figure 4E) and fragmented subpial astrocytic elements (Figure 4F), and with numerous thrombosed vessels in the parenchyma, petechial micro-hemorrhages, with decreased density of granular cells. Associated systemic pathology was represented by widespread hemorrhagic necrosis of the mucosa, stasis and thromboses in the gastric and intestinal walls, pancreas with areas of cyto- and steatonecrosis and hemorrhages in the surrounding fat, and lungs with massive stasis in both large and septal blood vessels, intra-alveolar RBCs and mononuclear cells extravasation.

All the changes found at necropsy, together with the chronic anticoagulant treatment and the liver function impairment that occurred on the seventh day after admission to the surgical ward, demonstrated that we were dealing with a patient with coagulation disorders that may justify the post spinal anesthesia complications.

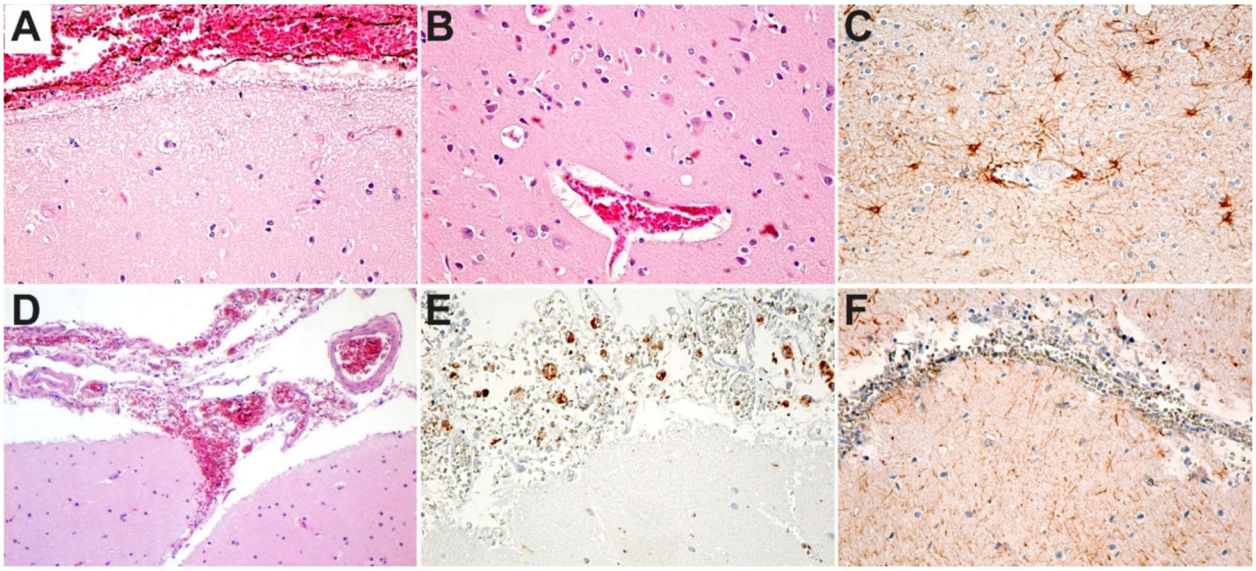

Figure 4 – ***Microscopy of the cerebral and cerebellar cortices: (A) Cerebral cortex showed hemorrhagic exudate in the leptomeninges; (B) Blood vessels with stasis and perivascular and pericellular edema; (C) Moderate perivascular gliosis as revealed by anti-GFAP antibody IHC, ×200; (D) Cerebellar cortex presented with stasis, hemorrhage and fibrin accumulation in the leptomeninges; (E) Numerous macrophages identified by anti-CD68 antibody IHC in the leptomeningeal exudative and cellular reaction, ×200; (F) Fragmented GFAP-positive extensions but without remnant cell bodies surrounding the hemorrhage areas. HE staining: (A, B and D) ×200. CD68: Cluster of differentiation 68 (marker of macrophages); GFAP: Glial fibrillary acidic protein (marker of astrocytes); HE: Hematoxylin–Eosin; IHC: Immunohistochemistry.***

Discussions

Uncommon but serious side effects of spinal anesthesia include spinal hematomas and SAH, especially in individuals receiving anticoagulant medication [44, 45]. The frequency of serious side effects from central neuraxial anesthesia in non-obstetric patients has been estimated to be between one in 6000 and one in 1000 for epidural procedures [25, 46, 47].

Numerous circumstances, such as challenges during dural puncture, coagulation issues, and elevated intra-abdominal pressure, might result in spinal subdural hematoma [1]. Elderly patients are more susceptible to developing spinal hemorrhages during epidural anesthesia [48, 49], and symptoms typically start to show up after the catheter is removed. Persistent neurological impairment seems to be most likely to occur in patients with a “bloody tap” during puncture, and sensory deficit prior to treatment [50]. The most common spinal hemorrhages include SAHs, epidural hematomas, and subdural hematomas [3, 7]. However, hematomyelia, or intramedullary hemorrhage, is one of the rarest and most severe forms of spinal bleeding [10, 38], often resulting from anticoagulation therapy overlayed on small cryptical vascular malformations or coagulation pathology, as most probably was the case of our patient.

This study emphasizes the serious repercussions of this diagnosis, as well as the intricate interactions between spinal anesthesia, anticoagulation, and the development of both subarachnoid and spinal hematomas. Our 77-year-old male patient with a history of atrial fibrillation who was on anticoagulant therapy and who experienced both hematomyelia and SAH following elective inguinal hernia surgery serves as an example of these risks and emphasizes the significance of prompt detection and treatment.

The risk of bleeding associated with long term use of an antithrombotic medicine is dictated by the dose administered and specific patient factors, which may impact the degree of anticoagulation [51, 52]. These include features such as obesity, age, kidney and hepatic function, and the concurrent use of other medications [53]. The patient was transitioned from direct oral anticoagulant to LMWH in order to prepare the patient for surgery, but despite this change, he developed significant neurological deterioration, ultimately resulting in cardiorespiratory arrest. This outcome raises several important considerations for the management of patients undergoing spinal anesthesia receiving anti-coagulation therapy.

Conservative therapy was more frequently associated with favorable neurological outcomes than surgical decompression in patients with moderate neurological symptoms. Those with less severe symptoms are more likely to receive conservative treatment and to recover completely [50, 54, 55]. Following surgery, patients with challenging punctures should be closely watched for changes in vital signs, and the occurrence of new symptoms, such as headaches or back pain [1]. An MRI should be done in order to diagnose any suspected intraspinal lesions [7]. The whole length of the SAS may be affected by subarachnoid hematomas [7].

In our case, the decision to continue with conservative management was made after careful evaluation by the MDT. This is consistent with the literature, which suggests that in cases of stable hemorrhage but with non-improving patient neurological function, conservative management may be the best option. However, the patient’s progressive decline, complicated by the development of both intra-cranial and intramedullary hemorrhages, led to a poor outcome, highlighting the severe risks associated with anticoagulation therapy in high-risk patients.

Overall, this case appears to have exhibited a complex pathology, with the hemorrhagic complications most likely due to an overlap of anticoagulant treatment with a coagulation disorder associated with liver dysfunction, or an unknown small vascular malformation.

Conclusions

Spinal hemorrhages are rare pathologies with a single or multifactorial substrate. If spinal trauma or vascular malformations can represent single conditions for hemorrhages, coagulation disorders, anticoagulant treatments or autoimmune diseases may be additional risk factors that one must have in mind as possible occult pathologies that can cause bleedings.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Gabriela-Camelia Roşu and Andrei Osman equally contributed to the manuscript.

References

[1] Bi Y, Zhou J. Spinal subdural hematoma and subdural anesthesia following combined spinal-epidural anesthesia: a case report. BMC Anesthesiol, 2021, 21(1):130. https://doi.org/10.1186/s12871-021-01352-3 PMID: 33902465 PMCID: PMC8074484

[2] Maiti TK, Bir SC, Nanda A. Spinal subarachnoid hemorrhage and aneurysms. Handb Clin Neurol, 2017, 143:215–223. https://doi.org/10.1016/B978-0-444-63640-9.00020-5 PMID: 28552143

[3] Shaban A, Moritani T, Al Kasab S, Sheharyar A, Limaye KS, Adams HP Jr. Spinal cord hemorrhage. J Stroke Cerebrovasc Dis, 2018, 27(6):1435–1446. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.02.014 PMID: 29555403

[4] Sankarappan K, Doucet D, Daly SR, Nguyen AV, Garrett D Jr, Lesley WS, Feng D, Vance AZ, Huang JH. Exploring spinal subarachnoid hemorrhage: a neurosurgical case series. Cureus, 2023, 15(9):e45627. https://doi.org/10.7759/cureus.45627 PMID: 37868412 PMCID: PMC10588961

[5] Kim JS, Lee SH. Spontaneous spinal subarachnoid hemorrhage with spontaneous resolution. J Korean Neurosurg Soc, 2009, 45(4):253–255. https://doi.org/10.3340/jkns.2009.45.4.253 PMID: 19444355 PMCID: PMC2682125

[6] Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, Johansen M, Jones L, Krassioukov A, Mulcahey MJ, Schmidt-Read M, Waring W. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med, 2011, 34(6):535–546. https://doi.org/10.1179/204577211X13207446293695 PMID: 22330108 PMCID: PMC3232636

[7] Kreppel D, Antoniadis G, Seeling W. Spinal hematoma: a literature survey with meta-analysis of 613 patients. Neurosurg Rev, 2003, 26(1):1–49. https://doi.org/10.1007/s10143-002-0224-y PMID: 12520314

[8] Fugate JE, Lanzino G, Rabinstein AA. Clinical presentation and prognostic factors of spinal dural arteriovenous fistulas: an overview. Neurosurg Focus, 2012, 32(5):E17. https://doi.org/10.3171/2012.1.FOCUS11376 PMID: 22537126

[9] Hasegawa C, Saladin M, Rehli MJ, Burkhart CS. Subdural spinal haematoma after epidural anaesthesia. BMJ Case Rep, 2023, 16(12):e255104. https://doi.org/10.1136/bcr-2023-255104 PMID: 38160037 PMCID: PMC10759102

[10] Leep Hunderfund ANL, Wijdicks EFM. Intramedullary spinal cord hemorrhage (hematomyelia). Rev Neurol Dis, 2009, 6(2):E54–E61. PMID: 19587631

[11] Domenicucci M, Ramieri A, Paolini S, Russo N, Occhiogrosso G, Di Biasi C, Delfini R. Spinal subarachnoid hematomas: our experience and literature review. Acta Neurochir (Wien), 2005, 147(7):741–750; discussion 750. https://doi.org/10.1007/s00701-004-0458-2 PMID: 15711890

[12] Kumar Y, Hayashi D. Role of magnetic resonance imaging in acute spinal trauma: a pictorial review. BMC Musculoskelet Disord, 2016, 17:310. https://doi.org/10.1186/s12891-016-1169-6 PMID: 27448661 PMCID: PMC4957861

[13] Schoenfeld AJ, Bono CM, McGuire KJ, Warholic N, Harris MB. Computed tomography alone *versus* computed tomography and magnetic resonance imaging in the identification of occult injuries to the cervical spine: a meta-analysis. J Trauma, 2010, 68(1):109–113; discussion 113–114. https://doi.org/10.1097/TA.0b013e3181c0b67a PMID: 20065765

[14] Zorilă AL, Zorilă MV, Marinaş MC, Ţolescu RŞ, Zorilă GL, Florou C, Neamţu MC, Knieling A, Busuioc CJ. Evaluation of brain injuries in children deceased due to head trauma. Rom J Morphol Embryol, 2017, 58(4):1417–1428. PMID: 29556636

[15] Chatterjee RN, Roy RN. Spinal vascular malformations and their treatment. Proc Aust Assoc Neurol, 1968, 5(3):607–610. PMID: 5709991

[16] Ladner TR, He L, Lakomkin N, Davis BJ, Cheng JS, Devin CJ, Mocco J. Minimizing bleeding complications in spinal tumor surgery with preoperative Onyx embolization *via* dual-lumen balloon catheter. J Neurointerv Surg, 2016, 8(2):210–215. https://doi.org/10.1136/neurintsurg-2014-011505 PMID: 25516532

[17] Constantini S, Ashkenazi E, Shoshan Y, Israel Z, Umansky F. Thoracic hematomyelia secondary to coumadin anticoagulant therapy: a case report. Eur Neurol, 1992, 32(2):109–111. https://doi.org/10.1159/000116804 PMID: 1563460

[18] Hadley MN, Walters BC, Grabb PA, Oyesiku NM, Przybylski GJ, Resnick DK, Ryken TC. Blood pressure management after acute spinal cord injury. Neurosurgery, 2002, 50(3 Suppl):S58–S62. https://doi.org/10.1097/00006123-200203001-00012 PMID: 12431288

[19] Lehmann KG, Lane JG, Piepmeier JM, Batsford WP. Cardiovascular abnormalities accompanying acute spinal cord injury in humans: incidence, time course and severity. J Am Coll Cardiol, 1987, 10(1):46–52. https://doi.org/10.1016/s0735-1097(87)80158-4 PMID: 3597994

[20] Jia X, Kowalski RG, Sciubba DM, Geocadin RG. Critical care of traumatic spinal cord injury. J Intensive Care Med, 2013, 28(1):12–23. https://doi.org/10.1177/0885066611403270 PMID: 21482574

[21] Velmahos GC, Kern J, Chan LS, Oder D, Murray JA, Shekelle P. Prevention of venous thromboembolism after injury: an evidence-based report – part II: analysis of risk factors and evaluation of the role of vena caval filters. J Trauma, 2000, 49(1):140–144. https://doi.org/10.1097/00005373-200007000-00021 PMID: 10912870

[22] Wuermser LA, Ho CH, Chiodo AE, Priebe MM, Kirshblum SC, Scelza WM. Spinal cord injury medicine. 2. Acute care management of traumatic and nontraumatic injury. Arch Phys Med Rehabil, 2007, 88(3 Suppl 1):S55–S61. https://doi.org/10.1016/j.apmr.2006.12.002 PMID: 17321850

[23] Karlsson AK. Autonomic dysfunction in spinal cord injury: clinical presentation of symptoms and signs. Prog Brain Res, 2006, 152:1–8. https://doi.org/10.1016/S0079-6123(05)52034-X PMID: 16198689

[24] Furlan JC, Hawryluk GW, Austin J, Fehlings MG. Spinal haemorrhage during anticoagulant regimen for thromboprophylaxis: a unique form of central nervous system haemorrhage. J Neurol Neurosurg Psychiatry, 2012, 83(7):746–752. https://doi.org/10.1136/jnnp-2011-301366 PMID: 22566595

[25] Bos EME, Haumann J, de Quelerij M, Vandertop WP, Kalkman CJ, Hollmann MW, Lirk P. Haematoma and abscess after neuraxial anaesthesia: a review of 647 cases. Br J Anaesth, 2018, 120(4):693–704. https://doi.org/10.1016/j.bja.2017.11.105 PMID: 29576110

[26] Karavelis A, Foroglou G, Petsanas A, Zarampoukas T. Spinal cord dysfunction caused by non-traumatic hematomyelia. Spinal Cord, 1996, 34(5):268–271. https://doi.org/10.1038/sc.1996.48 PMID: 8963973

[27] Milhorat TH, Adler DE, Heger IM, Miller JI, Hollenberg-Sher JR. Histopathology of experimental hematomyelia. J Neurosurg, 1991, 75(6):911–915. https://doi.org/10.3171/jns.1991.75.6.0911 PMID: 1941120

[28] Leech RW, Pitha JV, Brumback RA. Spontaneous haematomyelia: a necropsy study. J Neurol Neurosurg Psychiatry, 1991, 54(2):172–174. https://doi.org/10.1136/jnnp.54.2.172 PMID: 2019846 PMCID: PMC1014357

[29] Barnwell SL, Dowd CF, Davis RL, Edwards MS, Gutin PH, Wilson CB. Cryptic vascular malformations of the spinal cord: diagnosis by magnetic resonance imaging and outcome of

surgery. J Neurosurg, 1990, 72(3):403–407. https://doi.org/10.3171/jns.1990.72.3.0403 PMID: 2303875
[30] Zeidman SM, Olivi A. Cervical intramedullary hemorrhage as a result of anticoagulant therapy. J Spinal Disord, 1993, 6(5): 456–457; discussion 457–458. PMID: 8274814
[31] Pisani R, Carta F, Guiducci G, Silvestro C, Davini MD. Hematomyelia during anticoagulant therapy. Surg Neurol, 1985, 24(5):578–580. https://doi.org/10.1016/0090-3019(85)90277-0 PMID: 4049235
[32] Yu JS, Short MP, Schumacher J, Chapman PH, Harsh GR 4th. Intramedullary hemorrhage in spinal cord hemangioblastoma. Report of two cases. J Neurosurg, 1994, 81(6):937–940. https://doi.org/10.3171/jns.1994.81.6.0937 PMID: 7965128
[33] Rubin MN, Rabinstein AA. Vascular diseases of the spinal cord. Neurol Clin, 2013, 31(1):153–181. https://doi.org/10.1016/j.ncl.2012.09.004 PMID: 23186899
[34] Păun O, Cercel RA, Radu RI, Raicea VC, Pîrşcoveanu DFV, Honţaru SO, Zorilă MV, Mogoantă L. Histopathological lesions induced by stroke in the encephalon. Rom J Morphol Embryol, 2023, 64(3):389–398. https://doi.org/10.47162/RJME.64.3.10 PMID: 37867356 PMCID: PMC10720933
[35] Roşu GC, Pirici I, Istrate-Ofiţeru AM, Iovan L, Tudorică V, Mogoantă L, Gîlceavă IC, Pirici D. Expression patterns of aquaporins 1 and 4 in stroke. Rom J Morphol Embryol, 2019, 60(3):823–830. PMID: 31912092
[36] Novy J, Carruzzo A, Maeder P, Bogousslavsky J. Spinal cord ischemia: clinical and imaging patterns, pathogenesis, and outcomes in 27 patients. Arch Neurol, 2006, 63(8):1113–1120. https://doi.org/10.1001/archneur.63.8.1113 PMID: 16908737
[37] Madhugiri VS, Ambekar S, Roopesh Kumar VR, Sasidharan GM, Nanda A. Spinal aneurysms: clinicoradiological features and management paradigms. J Neurosurg Spine, 2013, 19(1): 34–48. https://doi.org/10.3171/2013.3.SPINE121026 PMID: 23621642
[38] Agarwal A, Kanekar S, Thamburaj K, Vijay K. Radiation-induced spinal cord hemorrhage (hematomyelia). Neurol Int, 2014, 6(4): 5553. https://doi.org/10.4081/ni.2014.5553 PMID: 25568739 PMCID: PMC4274409
[39] Dutra BG, da Rocha AJ, Nunes RH, Maia Júnior ACM. *Neuromyelitis optica* spectrum disorders: spectrum of MR imaging findings and their differential diagnosis. Radiographics, 2018, 38(1):169–193. https://doi.org/10.1148/rg.2018170141 PMID: 29320331
[40] Suzuki T, Kawaguchi S, Takebayashi T, Yokogushi K, Takada J, Yamashita T. Vertebral body ischemia in the posterior spinal artery syndrome: case report and review of the literature. Spine (Phila Pa 1976), 2003, 28(13):E260–E264. https://doi.org/10.1097/01.BRS.0000067285.39466.FB PMID: 12838116
[41] Jellema K, Tijssen CC, van Gijn J. Spinal dural arteriovenous fistulas: a congestive myelopathy that initially mimics a peripheral nerve disorder. Brain, 2006, 129(Pt 12):3150–3164. https://doi.org/10.1093/brain/awl220 PMID: 16921175
[42] Erdi F, Keskin F, Kalkan H, Karatas Y, Koc O. Ruptured spinal artery aneurysm associated with coarctation of the aorta. Spine J, 2016, 16(2):e23–e25. https://doi.org/10.1016/j.spinee.2015.09.015 PMID: 26370306
[43] Cakirer S, Basak M, Galip GM. Cervical hematomyelia secondary to oral anticoagulant therapy: case report. Neuroradiology, 2001, 43(12):1087–1088. https://doi.org/10.1007/s002340100626 PMID: 11792051
[44] Maddali P, Walker B, Fisahn C, Page J, Diaz V, Zwillman ME, Oskouian RJ, Tubbs RS, Moisi M. Subdural thoracolumbar spine hematoma after spinal anesthesia: a rare occurrence and literature review of spinal hematomas after spinal anesthesia. Cureus, 2017, 9(2):e1032. https://doi.org/10.7759/cureus.1032 PMID: 28357164 PMCID: PMC5354393
[45] Jeon SB, Ham TI, Kang MS, Shim HY, Park SL. Spinal subarachnoid hematoma after spinal anesthesia. Korean J Anesthesiol, 2013, 64(4):388–389. https://doi.org/10.4097/kjae.2013.64.4.388 PMID: 23646256 PMCID: PMC3640179
[46] Phillips JMG, Stedeford JC, Hartsilver E, Roberts C. Epidural abscess complicating insertion of epidural catheters. Br J Anaesth, 2002, 89(5):778–782. PMID: 12393782
[47] Brull R, McCartney CJL, Chan VWS, El-Beheiry H. Neurological complications after regional anesthesia: contemporary estimates of risk. Anesth Analg, 2007, 104(4):965–974. https://doi.org/10.1213/01.ane.0000258740.17193.ec PMID: 17377115
[48] Mahapatra S, Chandrasekhara NS, Upadhyay SP. Spinal epidural haematoma following removal of epidural catheter after an elective intra-abdominal surgery. Indian J Anaesth, 2016, 60(5):355–357. https://doi.org/10.4103/0019-5049.181610 PMID: 27212725 PMCID: PMC4870951
[49] Oliveira F, Fonseca D, Fernandes M, Teles AR, Fonseca S. Infected spinal hematoma after accidental exteriorization of an epidural catheter: a case report. Cureus, 2023, 15(10): e47722. https://doi.org/10.7759/cureus.47722 PMID: 38021824 PMCID: PMC10676040
[50] Raasck K, Habis AA, Aoude A, Simões L, Barros F, Reindl R, Jarzem P. Spontaneous spinal epidural hematoma management: a case series and literature review. Spinal Cord Ser Cases, 2017, 3:16043. https://doi.org/10.1038/scsandc.2016.43 PMID: 28382214 PMCID: PMC5289268
[51] Fitzmaurice DA, Blann AD, Lip GYH. Bleeding risks of antithrombotic therapy. BMJ, 2002, 325(7368):828–831. https://doi.org/10.1136/bmj.325.7368.828 PMID: 12376447 PMCID: PMC1124331
[52] Gunasekaran K, Rajasurya V, Devasahayam J, Singh Rahi M, Chandran A, Elango K, Talari G. A review of the incidence diagnosis and treatment of spontaneous hemorrhage in patients treated with direct oral anticoagulants. J Clin Med, 2020, 9(9): 2984. https://doi.org/10.3390/jcm9092984 PMID: 32942757 PMCID: PMC7563837
[53] Kietaibl S, Ferrandis R, Godier A, Llau J, Lobo C, Macfarlane AJ, Schlimp CJ, Vandermeulen E, Volk T, von Heymann C, Wolmarans M, Afshari A. Regional anaesthesia in patients on antithrombotic drugs: Joint ESAIC/ESRA guidelines. Eur J Anaesthesiol, 2022, 39(2):100–132. https://doi.org/10.1097/EJA.0000000000001600 PMID: 34980845
[54] Costa F, Alves OL, Anania CD, Zileli M, Fornari M. Decompressive surgery for lumbar spinal stenosis: WFNS Spine Committee Recommendations. World Neurosurg X, 2020, 7:100076. https://doi.org/10.1016/j.wnsx.2020.100076 PMID: 32613189 PMCID: PMC7322794
[55] Thavarajasingam SG, Vemulapalli KV, Vishnu K S, Ponniah HS, Vogel AS, Vardanyan R, Neuhoff J, Kramer A, Shiban E, Ringel F, Demetriades AK, Davies BM. Conservative *versus* early surgical treatment in the management of pyogenic spondylodiscitis: a systematic review and meta-analysis. Sci Rep, 2023, 13(1):15647. https://doi.org/10.1038/s41598-023-41381-1 PMID: 37730826 PMCID: PMC10511402

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