Clinical Reasoning:
A 61-year-old woman with neurogenic shock following percutaneous vertebroplasty

SECTION 1
A 61-year-old woman with a stable traumatic anterior L4 vertebral wedge fracture without spinal canal compromise was referred because of an intense and refractory pain at the level of fracture in spite of maximal medical therapy. MRI scans showed anterior wedging of L4 vertebral body involving the superior endplate with intact posterior wall (figure 1A). Percutaneous vertebroplasty (PV) was indicated for her high surgical risk. Under general anesthesia, right L4 transpedicular PV was performed under X-ray fluoroscopy using polymethylmethacrylate (PMMA; volume injected 3 cm³; SpinePlex®; Kalamazoo, MI). No critical leaks or lesions of the posterior cortex or the lateral recess were identifiable in postprocedure fluoroscopy.

Two hours after PV, the patient presented an intense burning pain in both legs, Lhermitte sign, and tactile hypersensitivity associated with low blood pressure (50/30 mm Hg), respiratory rate (8 breaths/minute), and body temperature (rectal temperature: 35.0°C), together with hypoxemia (SaO₂: 75%, in room air) and sinus tachycardia (heart rate 141/minute). The initial symptoms were followed by sustained (35–45 seconds) and almost continuous muscle spasms in bulbar, pharyngolaryngeal, intercostal, paravertebral, and leg muscles, spontaneous and in response to minimal stimuli, stiffness of the body, lockjaw, frothing of the mouth, opisthotonus, bilateral Babinski sign, and generalized hyperreflexia. The patient was fully conscious during these episodes. During severe spasms, there was respiratory arrest. The patient was immediately referred to the neurointensive care unit (NICU). She was intubated and mechanically ventilated.

Questions for consideration:
1. What is your evaluation to this point?
2. What are the appropriate testing and treatment?
Figure 1 Preinterventional, postinterventional, and postoperative neuroradiologic findings

(A) Preinterventional T2- (double chevron) and T1- (single chevron) weighted MRI show a chronic anterior wedging of L4 vertebral body involving the superior endplate. Axial MRI (not shown) did not reveal a posterior wall fracture. (B) Postvertebroplasty axial CT scans show cement extravasation into the prevertebral soft tissue (red arrow) and posteriorly into the spinal canal, filling epidural and subarachnoid spaces (yellow marker). (C) Postoperative MRI scans in axial and sagittal view (D) show a complete removal of intraspinal polymethylmethacrylate.
SECTION 2
This patient has a clinical picture of shock, respiratory failure, long tract signs, and sustained and almost continuous widespread muscle spasms. An immediate NICU admission is essential for strict monitoring and clinical stabilization. Therapy should be directed to hemodynamic, respiratory support, and control of muscle spasms.

Shock is characterized by inadequate organ perfusion and tissue oxygenation. It is often the final pathway of multiple disorders. She did not have signs of pump failure or extracardiac obstruction. No evidence of active bleeding or systemic infection were present, so the most likely diagnosis was neurogenic shock (NS). NS can occur following spinal cord injury, as a result of sympathetic denervation leading to reduced sympathetic outflow and subsequent reduction in cardiac output and systemic vascular resistance. It occurs more commonly in injuries above T6, but can also occur following thoracic and lumbar injuries. The primary treatment for NS is fluid resuscitation and vasopressors. Hemodynamic resuscitation was based on isotonic fluids and norepinephrine (0.7 µg/kg/min). Methylprednisolone (30 mg/kg) for minimizing the secondary effects of an acute spinal cord injury and regular IV insulin infusion for concomitant treatment of diabetic ketoacidosis were also given.

The development of sudden breathlessness was characterized by a severe hypoxemic respiratory failure (PaO₂/FIO₂ ratio = 71) with normal arterial carbon dioxide tension (PₐCO₂ = 43 mm Hg). This form of respiratory failure is frequently associated with pulmonary edema in the context of a cardiac failure or in the presence of an acute respiratory distress syndrome (ARDS). Physical examination and normal central venous pressure (CVP = 6 cmH₂O) ruled out the presence of cardiac failure, while bilateral, diffuse, and heterogeneous pattern of interstitial-alveolar infiltrates on chest X-ray together with refractory hypoxemia and rigid lungs (PaO₂/FIO₂ ratio; 71; static compliance: 19 mL/cm) suggested the presence of ARDS. In patients with acute spinal cord injury, ARDS may develop due to neurogenic pulmonary edema (NPE). NPE is a relatively rare form of pulmonary edema developing after a neurologic insult and caused by an increase in pulmonary interstitial and alveolar fluid. Respiratory functions were stabilized using protective ventilation (plateau pressure <35 cmH₂O, tidal volume 5 mL/kg, PEEP 15 cmH₂O, and recruitment maneuvers).

The patient was conscious and had intense pain. Patient jerks showed a motor pattern characterized by tonic extension of the body and limbs with hyperreactivity to stimuli. These aspects are uncommon in spinal myoclonus. Segmental spinal myoclonus is usually rhythmic and relatively unaffected by sensory input, with movements limited to contiguous segments of the cord. In propriospinal myoclonus, movements are typically slow, bilateral, synchronous jerks of flexion muscles of trunk and lower limbs. The involuntary movement patterns described in this patient were more consistent with the propriospinal form of myoclonus, reflecting the high level of spinal cord excitability.

Myoclonus was controlled with diazepam bolus (10 mg IV) followed by 10 mg/h infusion. Fentanyl was used for analgesia. EEG was normal (only an increase of fast, β-rhythms), suggesting the noncortical origin of myoclonus. Initial laboratory findings showed a white blood cell count increase (17,550/mm³) without shift to the left, elevations of glycemia (3.43 g/dL), creatinine (2.9 mg/dL), serum lactate dehydrogenase (834 IU/mL), and creatine phosphokinase (686 IU/mL), associated with myoglobinuria (>1 g/L) and metabolic acidosis (pH = 7.22, base excess = −16). Sustained muscle contraction may result in rhabdomyolysis, myoglobinuria, and lactic acidosis. The differential diagnoses include extrapyramidal side effects from concomitant medication use, opioid withdrawal, electrolyte abnormalities, neuroleptic malignant syndrome, and malignant hyperthermia. All these causes could be easily excluded.

Question for consideration:
1. What testing would you further pursue?
After cardiorespiratory stabilization, a lumbar spine CT scan was performed (figure 1B) showing a massive cement leakage into the spinal canal with spread into subarachnoid space with upper limit in L2 (figure 1B). To evaluate the extension of PMMA spread, CT scans were extended to thoracic and cervical spine and to the brain. There was no evidence of macroscopic cement leakage.

An extensive emergency laminectomy was performed from L1 to L5 for removing PMMA from the spinal canal and subarachnoid space. Intraoperative CSF sample showed moderate increase in cell counts (55 leukocytes/mm³; 50% neutrophils) and proteins (65 mg/dL), while glucose, LDH, and lactic acid were within normal range. Gram stain was negative and CSF culture revealed no growth. Liquor data together with the absence of typical clinical features of an acute meningitis permitted to discharge the diagnosis of infectious meningitis and made less plausible the hypothesis of chemical meningitis.

After PMMA removal, the patient became hemodynamically stable, showing reduction of frequency of tonic attacks, which disappeared at the fifth postoperative day. There was also a progressive respiratory improvement, and the patient was extubated at the seventh postoperative day. At this stage, neurologic examination showed only a flaccid areflexic paraparesis with preserved sphincter control and tactile and pain sensibility. One-month MRI follow-up is depicted in figure 1C. The patient started an intensive neurorehabilitation program and after 2 years she had a complete recovery.

**DISCUSSION**

PV is a technique developed in the late 1980s, consisting of injection of PMMA into vertebral collapse for the treatment of hemangiomas and for pain relief and mechanical strengthening of the vertebral body due to osteolysis by primary or metastatic tumors. Now it is extensively used for stabilization of osteoporotic fractures. PV is an efficient treatment but is not free of complications. They occur in 38% to 87% of cases, frequently without serious adverse effects. Cement leakage into prevertebral soft tissue, epidural space, foraminal ring, intervertebral disc, and venous and arterial beds represents the main source of complications. Less frequently, life-threatening complications were reported, such as highlighting pulmonary arterial embolism, ARDS, stroke, spinal cord compression syndromes, and death during or immediately after the procedure (table e-1 on the Neurology® Web site at www.neurology.org). Neurologic complications are mainly secondary to cement leakage into spinal canal and less frequently into intervertebral foramen producing a compressive syndrome.

Multiple mechanisms are potentially involved in PMMA-induced injury (figure e-1). Potentially, PMMA causes direct damage in different ways. The exothermic (110°C) polymerization reaction of methylmethacrylate (MMA) can cause thermal injury. PMMA also causes an intense local inflammatory reaction with generation of cytokines, oxygen free radicals, and excitatory aminoacids that contribute to chemical cellular injury. PMMA can also act as space-occupying lesion in the spinal canal. The PMMA effects in the spinal canal and in the subarachnoid space have been little studied and reported. To our knowledge, a PMMA-induced syndrome characterized by neurogenic shock, hyperesthesia, and myoclonic jerks of the skeletal musculature that occur both spontaneously and in response to sensory stimuli, accompanied by severe hypoxemia, hypothermia, lactic acidosis, and rhabdomyolysis, was not previously reported.

We hypothesized a direct PMMA toxicity due to leakage into subarachnoid space, not previously described. The etiology of this syndrome remains unclear, although the onset of symptoms and its relief was temporally associated with PMMA exposure. In several aspects, this syndrome resembles strychnine poisoning. Strychnine causes myoclonic jerks, opsichtonons, and ARDS, via competitive antagonism of the inhibitory neurotransmitter glycine on the postsynaptic spinal cord motor neuron and on alveolar macrophages, neutrophils, and lymphocytes. Similarly, paroxysmal tonic contractions with preserved consciousness to external stimuli are the major symptoms of strychnine poisoning. The release of MMA monomer into bloodstream is a potential cause of adverse general reaction, and several MMA esters show a strychnine-like activity. MMA monomers entered in the subarachnoid space may penetrate into the spinal cord, more so in the posterolateral cord than in the anterior parts of the cord. The effect of the MMA monomers on inhibitory neurons could have led to loss of inhibitory function in the spinal cord determining an impairment of the glycine/GABA-mediated inhibitory influence of Renshaw cells on motor neurons. However, the lack to detect serum and CSF MMA concentration limited our ability to draw more definite conclusions about a causal relationship between PMMA exposure and the described neuromuscular syndrome.

We report a novel rare syndrome associated with PMMA into subarachnoid space resuming a strychnine-like exposure syndrome. Its frequency may increase secondary to the widespread use of...
PV and kyphoplasty for osteoporotic compression fractures.

AUTHOR CONTRIBUTIONS
Dr. Daniel Agustín Godoy: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Rubén Manzi: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Carlos Vega Ramírez: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Erica Alvarez: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Bladimir Gonzales Ore: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Mario Di Napoli: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

ACKNOWLEDGMENT
The authors thank the nursing staff and Jorge Reyes for technical assistance in obtaining high-quality images.

DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Clinical Reasoning:: A 61-year-old woman with neurogenic shock following percutaneous vertebroplasty
Daniel Agustín Godoy, Rubén Manzi, Carlos Vega Ramírez, et al.
Neurology 2012;79:e126-e130
DOI 10.1212/WNL.0b013e31826e2595

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