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CLINICAL PROBLEM-SOLVING

The Daily Grind

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.

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CME



A 56-year-old woman was admitted to the hospital for gait instability. Eight weeks before presentation, she had noticed a gradual onset of ascending symmetric sensations of painful “pins and needles” that had begun in her feet. Two weeks before presentation, she began to have short-term memory impairment, difficulty concentrating, irritability, anorexia, and palpitations, along with paresthesias in her hands that were similar to those that had begun in her feet. She was unable to feel her feet on the ground when she walked, which led to frequent stumbling, and she braced herself against walls for stability. She reported no headaches, weakness, or weight loss.

Subacute gait instability may result from impairment of cognition; compromised motor, sensory, or coordination pathways; or osteoarticular dysfunction. Palpitations could signal intermittent arrhythmias. The prominent paresthesias and impaired sensation suggest a rapidly progressive polyneuropathy. The involvement of all four limbs also introduces the possibility of cervical myelopathy. Impaired concentration, forgetfulness, and irritability suggest encephalopathy. A metabolic disorder (e.g., vitamin B₁₂ deficiency), toxin (e.g., alcohol), or infection (e.g., syphilis) could lead to neuropathy and encephalopathy.

Her medical history included hypertension, hypothyroidism, depression, and anxiety. Hypothyroidism had been present for more than a decade and had been treated with a stable dose of levothyroxine. Thirty years before presentation, she had been in a vehicle collision that resulted in splenectomy and the development of post-traumatic arthritis of the left hip. Ten years after the accident (20 years before the current presentation), she underwent a left total hip arthroplasty. Her medications were amlodipine, levothyroxine, and fluoxetine. Four weeks before presentation, her primary care physician increased the levothyroxine dose in response to a newly elevated thyrotropin level of 8.8 μ IU per milliliter (normal range, 0.3 to 4.2); the free thyroxine level was 1.5 ng per deciliter (normal range, 0.9 to 1.8). She had consumed approximately three glasses of wine daily for the past two decades and had smoked one pack of cigarettes per day for the past 30 years.

Alcohol use can explain both polyneuropathy and cognitive impairment associated with direct toxic effects or nutritional deficiency. Recurrent falls related to alcohol use could also lead to subdural hematomas that impair cognition or cause behavior changes. Smoking puts the patient at risk for small-cell lung cancer, which could lead to encephalopathy and polyneuropathy through a paraneoplastic mechanism.

One year before presentation, she had an atraumatic dislocation of her left hip prosthesis, which was treated with closed reduction. During the subsequent year, persis-

tent pain in her left hip developed despite physical therapy. Given worsening hip instability and pain, gait instability, and radiographic findings that were suggestive of failure of the acetabular liner (Fig. 1A), she underwent revision hip arthroplasty at another hospital 12 weeks before the current presentation. The details of the surgery were unknown at the time of the current presentation.

Prosthetic hip replacements usually function properly for 20 years or longer. An atraumatic dislocation of a prosthesis suggests a structural failure caused by substantial wear or fracture of the acetabular liner or femoral head, impingement (abnormal contact between prosthetic components or surrounding bone), or infection.

The revision hip arthroplasty performed 12 weeks earlier could have caused direct injury to the sciatic or femoral nerve. However, such injuries are typically unilateral and would not explain the symmetric symptoms in her legs and feet or her cognitive impairment.

The patient was afebrile. The blood pressure was 128/90 mm Hg, the heart rate 105 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 98% while she was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 24. She was oriented to person, place, and time, but she had some impairment in memory (e.g., she was unable to remember what she had eaten for dinner the night before). Aside from tachycardia, her cardiac examination was normal, as were her lung, skin, and abdominal examinations. Her strength was normal in all four limbs. Sensation to light touch was reduced in all four limbs, with distal sensory loss in the hands and feet. She had decreased proprioception and vibratory sensation at the feet and ankles. Patellar deep-tendon reflexes were normal; ankle reflexes were not assessed. She had a wide-based gait and had difficulty walking with a tandem gait. The Romberg test was positive.

The impaired sensation that had started in her legs and hands is characteristic of length-dependent sensory polyneuropathy. Her impaired proprioception and vibratory sensation point to large-fiber sensory neuropathy, leading to sensory ataxia manifested by a wide-based gait and a positive Romberg test. Causes of subacute or chronic sen-

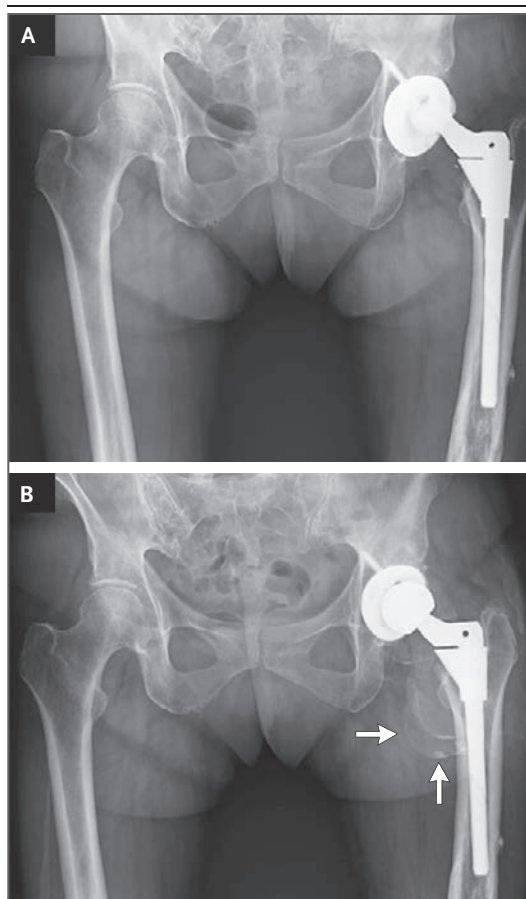


Figure 1. Anteroposterior Radiographs of the Pelvis.

A radiograph of the pelvis obtained 12 weeks before presentation (Panel A) shows that the prosthetic femoral head is positioned eccentrically within the acetabular shell, a finding that indicates degradation of the acetabular liner with resultant contact between the femoral head and the acetabular shell. This finding led to revision hip arthroplasty, with exchange to a cobalt–chromium femoral head and a polyethylene liner. A radiograph of the pelvis obtained 12 weeks after implantation of the cobalt–chromium femoral head (Panel B) shows amorphous, cloudlike periarticular opacities that are indicative of a large seroma, along with dispersed radiopaque deposits that are consistent with metallosis.

sory neuropathy include vitamin B₁₂ and copper deficiency, chronic inflammatory demyelinating polyneuropathy, Sjögren's syndrome, and paraneoplastic neuropathy. Preserved patellar reflexes could suggest a central process such as myelopathy; alternatively, a peripheral, length-dependent toxic or metabolic neuropathy may initially spare the patellar reflex arc, with involvement emerging later.

The white-cell count was 12,700 per microliter (of which 81% were neutrophils, 10% were lymphocytes, 7% were monocytes, 1% were eosinophils, and 1% were basophils); the white-cell count was 11,500 per microliter 7 weeks before presentation. The hemoglobin level was 18.8 g per deciliter with a mean corpuscular volume of 86 fL; previous hemoglobin measurements included a level of 12.5 g per deciliter 1 year before presentation, 17.8 g per deciliter 8 weeks before presentation, and 19.0 g per deciliter 1 week before presentation. The platelet count was 209,000 per microliter. The ferritin level was 355 ng per milliliter (normal range, 30 to 336).

The potassium level was 2.4 mmol per liter (normal range, 3.5 to 5.1), the magnesium level 1.6 mg per deciliter (0.7 mmol per liter; normal range, 1.7 to 2.2 mg per deciliter [0.7 to 0.9 mmol per liter]), and the glucose level 250 mg per deciliter (14 millimoles per liter). The glycated hemoglobin level was 7.5%, and the vitamin B₁₂ level 1100 pg per milliliter (812 pmol per liter; normal range, 232 to 1245 pg per milliliter [171 to 919 pmol per liter]). Both the potassium level and the magnesium level normalized after repletion. The levels of bilirubin, alkaline phosphatase, albumin, and C-reactive protein were normal, as were the international normalized ratio and the erythrocyte sedimentation rate. An electrocardiogram showed sinus tachycardia. Chest radiography and computed tomography of the head without the administration of contrast material showed no abnormalities. An echocardiogram showed normal biventricular systolic and diastolic function with no valvular or wall-motion abnormalities.

The results of serum protein electrophoresis and a serum free light-chain assay were normal. Testing for antinuclear antibodies and antibodies against Sjögren's syndrome-related antigen A and antigen B was negative. A rapid plasma reagin test was negative, as were serologic tests for human immunodeficiency virus, *Borrelia burgdorferi*, hepatitis C virus, and Epstein-Barr virus. Serum levels of thiamine and copper were not measured.

The most common cause of an elevated hemoglobin level is hemoconcentration due to hypovolemia. However, the repeatedly elevated hemoglobin levels over an 8-week period point to a true increase in red-cell mass — either primary erythrocytosis (e.g., polycythemia vera) or secondary erythrocytosis (e.g., hypoxia). Polycythemia vera

is associated with thrombocytosis and basophilia, both of which are absent in this patient; although the presence of mild leukocytosis is compatible with polycythemia vera, it is nonspecific. The oxygen saturation is normal, and she does not have sleep apnea or obstructive or interstitial lung disease. In rare cases, erythropoietin-secreting tumors such as renal-cell carcinoma can induce erythrocytosis. The patient's mild diabetes would not account for the rapid development of polyneuropathy and marked cognitive impairment. Hypokalemia and hypomagnesemia may arise from malnutrition, gastrointestinal losses, or renal tubule dysfunction (e.g., from chronic alcohol use).

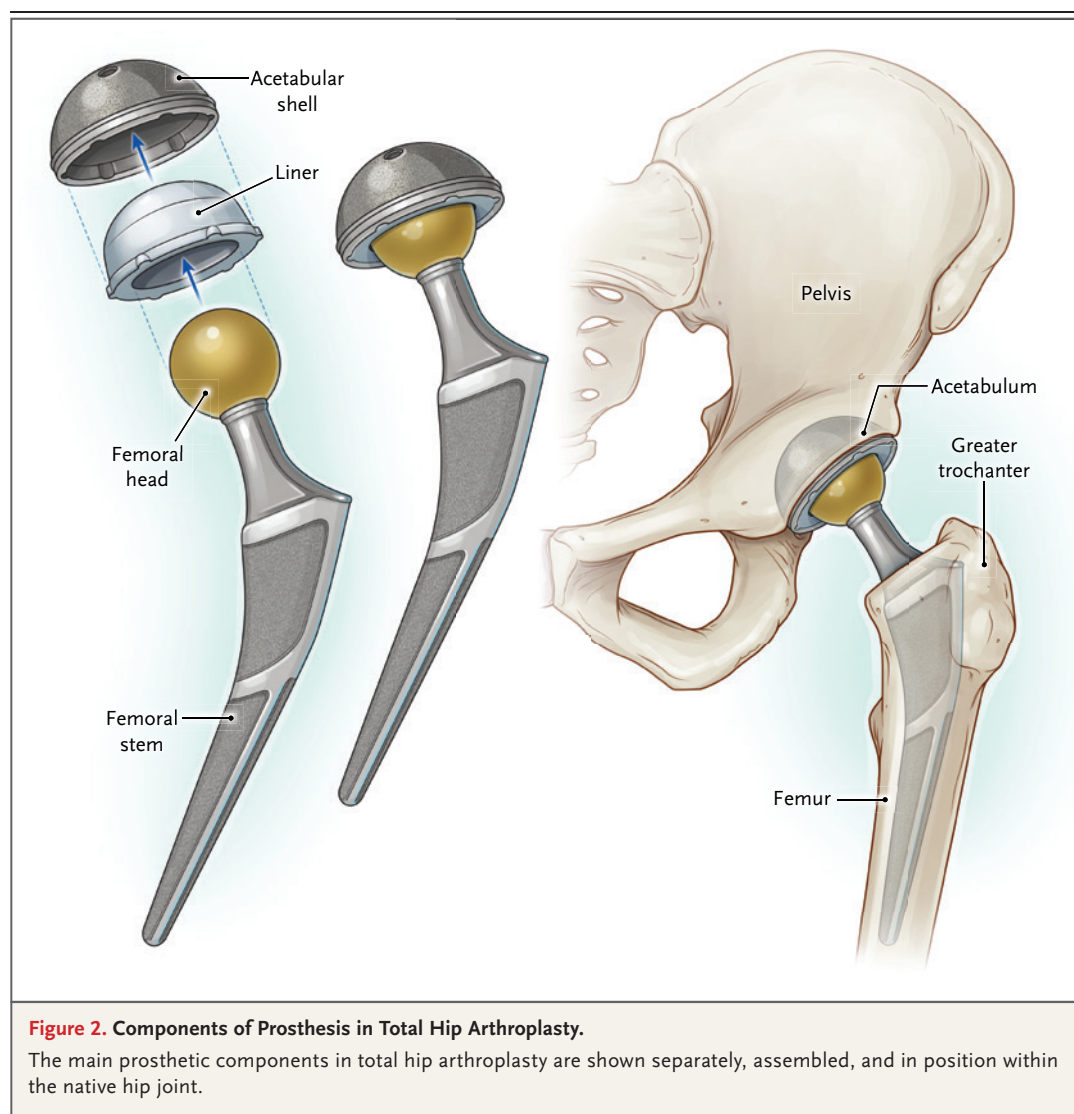
A radiograph showed that the hip prosthesis was in proper alignment, with no fracture or dislocation; however, radiopaque deposits were noted within the periarticular soft tissue (Fig. 1B). The records from her hip revision surgery 12 weeks earlier were obtained.

The surgical report identified the components of the original prosthesis that had been implanted 20 years earlier: a titanium femoral stem and a titanium acetabular shell with a ceramic liner and a ceramic femoral head (Fig. 2). The report noted that the ceramic femoral head had eroded through the ceramic liner and was articulating directly with the titanium acetabular shell.

The report also detailed the revision surgery that took place 12 weeks before presentation in which extensive débridement of the surrounding soft tissue was performed to remove the widely distributed particles from the destroyed ceramic liner. The ceramic liner was replaced with a polyethylene liner, and the ceramic femoral head was replaced with a metallic femoral head composed of a cobalt-chromium alloy. The titanium acetabular shell and titanium femoral stem were retained.

The recently implanted cobalt femoral head provides a plausible explanation for rapidly progressive peripheral and central neurologic injury. Cobalt toxicity manifests primarily as neurologic, cardiac, or thyroid dysfunction (or a combination of these) and in rare cases, as polycythemia. The patient's severe sensory neuropathy and cognitive impairment are characteristic of systemic toxic effects from cobalt.

An atypical aspect of this presentation of cobalt toxicity is the accelerated tempo, with symp-



toms developing over a period of weeks rather than months after the implantation of the cobalt–chromium femoral head. Although the surgeon removed the visible ceramic fragments, it is likely that residual microscopic ceramic particles remained lodged in the soft tissues and synovium. The continuous friction of those retained microparticles against the new femoral head probably led to accelerated mechanical wear of the cobalt–chromium surface, resulting in the release of cobalt into the local tissues and the circulatory system.

On hospital day 3, the patient underwent a second revision left hip arthroplasty with extensive débridement of the soft tissues, which had been in-

filtrated by cobalt–chromium (Fig. 3). The previous acetabular polyethylene liner was replaced with a new polyethylene liner. The cobalt–chromium femoral head was replaced with a ceramic femoral head.

The same day, chelation therapy with *N*-acetylcysteine and calcium EDTA was initiated. On hospital day 6, the serum cobalt and chromium levels that had been measured preoperatively became available. The cobalt level before surgery was 592 ng per milliliter (normal value, <10), and the chromium level before surgery was 62.4 ng per milliliter (normal value, <0.2).

After surgery, the hemoglobin level had decreased to 14.4 mg per deciliter and remained at that level throughout the hospitalization. Intraop-



Figure 3. Intraoperative Findings of Metallosis in the Left Hip.

During the second revision surgery, a gray fluid collection is present. The gluteus maximus, gluteus medius, and vastus lateralis show diffuse silver-gray discoloration consistent with cobalt-related metallosis. The involved tissue is noncontractile to stimulation and easily debrided, findings that are indicative of metallosis-associated soft-tissue necrosis.

erative blood loss was estimated to be 400 ml. An erythropoietin level was not obtained, and Janus kinase 2 mutation analysis was not performed.

The decrease in the patient's hemoglobin level probably reflects a combination of operative blood loss and hemodilution from intravenous fluids. However, the previous persistently elevated hemoglobin levels above 14.0 g per deciliter — as compared with her baseline level of 12.5 g per deciliter 1 year before presentation — suggest cobalt-induced polycythemia.

Additional chelation therapy with oral succimer (2,3-dimercaptosuccinic acid, at a dose of 650 mg every 8 hours for 2 weeks) and *N*-acetylcysteine (at a dose of 1800 mg twice daily) was prescribed by a medical toxicologist. Metformin was also prescribed; it was discontinued 3 months after dis-

charge because the patient's glycated hemoglobin level had decreased to 5.8%. Six months after discharge, her encephalopathy and ataxic gait had resolved, and the glycated hemoglobin level was 5.5%. The thyrotropin level was 1.12 μ IU per milliliter, and her levothyroxine dose was reduced to her previous dose of 150 μ g daily. The serum cobalt level was less than 10 ng per milliliter.

However, the patient continued to have paresthesias and dysesthesias, which were partially ameliorated with the use of gabapentin. A second 2-week course of oral succimer was prescribed, and *N*-acetylcysteine therapy was continued. Two weeks after discharge, tinnitus developed and persisted. Seven months after discharge, audiometry showed high-frequency sensorineural hearing loss in the left ear, with normal hearing in the right ear.

The patient's tinnitus and high-frequency sensorineural hearing loss point to cobalt-mediated injury of the cochlear hair cells or the auditory nerve. The changing and persistent nature of her otologic dysfunction despite undetectable blood levels of cobalt may reflect maladaptive changes in the auditory pathway or reequilibration of cobalt from extravascular tissue reservoirs, resulting in reexposure.

Eight months after discharge, examination by a neurologist showed normal strength, distal hyperalgesia, reduced pinprick sensation in the feet (with greater sensation above the knees) and hands (with greater sensation above the wrists), absence of vibration at the great toes, and absence of patellar and Achilles reflexes in both legs with preserved reflexes in the arms. Nerve-conduction testing, which was limited by pain, suggested sensory neuropathy. One year after discharge, the patient reported less neuropathic pain, improved gait, and less frequent tinnitus; the cobalt level remained undetectable.

Many features of this case point to peripheral-nerve injury, including the pattern of sensory deficits on the neurologist's examination, the otologic injury, and nerve-conduction testing. The slow, incomplete, and nonlinear recovery is characteristic of toxic peripheral-nerve injury. The encephalopathy was clear evidence of central nervous system involvement; cerebellar and myelopathic contributions to the ataxia cannot be fully ruled

out in the absence of magnetic resonance imaging of the head or spine.

COMMENTARY

This patient presented with gait instability and cognitive and distal sensory abnormalities. Although a local complication of her recent hip arthroplasty was considered to be a possible cause of her gait difficulties, the concomitant cognitive and sensory dysfunction and the subsequent recognition of new-onset polycythemia and endocrinopathy suggested a systemic disorder. Ultimately, cobalt toxicity from the prosthesis was recognized to be the cause of her multisystem illness.

A modern hip prosthesis is composed of four components: the femoral stem, the femoral head, the acetabular liner, and the acetabular shell. More than 90% of total hip arthroplasties are still intact after 30 years.¹ Common causes of hip arthroplasty failure are aseptic loosening, infection in the prosthetic joint, periprosthetic fracture, or wearing of the liner. In this patient, wearing of the liner prompted the first hip revision with new components because of instability and dislocation. At the time of the initial revision, the ceramic femoral head was replaced with a metallic (cobalt–chromium alloy) femoral head. Despite débridement of the macroscopic ceramic particles from the eroded ceramic liner, residual microscopic particles persisted in the joint and soft tissues.

Cobalt–chromium alloy is used in orthopedic implants because of its hardness, corrosion resistance, and favorable wear properties.^{2,3} Although the use of cobalt–chromium in hip arthroplasty has declined substantially over the past 15 years owing to improvements in ceramics and polyethylene and heightened awareness of metal-related complications, cobalt–chromium components remain in use in selected contexts (such as revision hip arthroplasty and fracture-related hip arthroplasty).

Cobalt toxicity results from mechanical stress on a cobalt component; the resulting metal debris causes a local inflammatory reaction (metallosis), and cobalt enters the bloodstream. In this patient's case, residual ceramic debris formed a "third body," which refers to the interposition of abrasive particles between the two primary bearing surfaces (the cobalt–chromium femoral head

and the polyethylene liner).³ This mechanism leads to accelerated metal release as compared with the gradual wear that occurs in metal-on-metal articulations.

Cobalt accumulation in organs triggers disruption of cellular pathways, oxidative damage, and cytotoxicity.⁴ Clinical manifestations include sensory neuropathy,⁵ cognitive impairment,⁶ auditory changes,⁷ dilated cardiomyopathy,⁸ arrhythmias, hypothyroidism,⁹ and hyperglycemia.¹⁰ Cobalt-mediated stabilization of hypoxia-inducible factor, a transcription factor that promotes erythropoietin production, accounts for polycythemia.^{11,12} In this patient's case, the unexplained rise in the hemoglobin level (ultimately reaching 19.0 g per deciliter) was an early unrecognized manifestation of cobalt toxicity. Changes in glucose and thyroxine levels were also early clues but less specific, given the frequency of such abnormalities in clinical practice and their relatively modest deviations.

Chromium is often released concurrently from cobalt–chromium alloy (as in this patient, who had a markedly elevated chromium level), but when this causes harm, it is typically through local bone destruction.¹² Implant-derived chromium is predominantly trivalent; this form of chromium has limited cellular uptake as compared with hexavalent chromium, the form responsible for environmental and occupational chromium toxicity. Thus, multiorgan toxic effects associated with implants are generally ascribed to cobalt rather than to chromium.⁹

Early consultation with a medical toxicologist is advised for diagnosis and management of cobalt toxicity. The cornerstone of management is removal of the cobalt source and soft-tissue débridement.¹³ Elevated serum levels of cobalt or organ toxic effects are often adjunctively treated with systemic chelation with *N*-acetylcysteine, calcium EDTA, or succimer.^{13,14} In a systematic review of case reports and case series of cobalt toxicity involving prosthetic hips, adjunctive measures were used in 27% of the patients, but clinical improvement was primarily associated with hardware removal rather than chelation.¹³

Cognitive and neuropathic symptoms may abate after source control, but recovery is often incomplete.¹³ This patient's persistent tinnitus reflects irreversible damage to cochlear structures (most likely mediated by oxidative stress–induced apoptotic cascades) that can persist even after a re-

duction in exposure.¹⁵ In the current case, the daily grind of the ceramic microparticles against a cobalt femoral head transformed a mechanical problem into a systemic toxic illness.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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