CASE REPORT

Acute peripheral polyneuropathy with multiorgan failure: a diagnostic dilemma

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SUMMARY

We describe the case of a young man who presented with abdominal pain, vomiting and acute symmetric peripheral polyneuropathy. He was noted to have high anion gap metabolic acidosis with high lactate levels and persistently high arterial and venous pO₂ values. The cerebrospinal fluid was acellular with a high protein and the nerve conduction study was consistent with axonal sensorimotor neuropathy. His clinical condition deteriorated rapidly despite full supportive care and he subsequently died of multiorgan failure. An extensive workup for various infectious, autoimmune and other possible aetiologies was carried out to identify the underlying cause for his fulminant illness. All diagnostic workup was non-conclusive except for a significantly elevated serum aluminium level. We have discussed the possibility of aluminium phosphide poisoning in view of the clinical presentation.

BACKGROUND

Aluminium phosphide (AlP) toxicity is a relatively uncommon cause of poisoning in our region. It usually presents as a severe multiorgan failure that is often fatal due to the absence of an effective antidote.

However, the concomitant presence of acute peripheral polyneuropathy with multiorgan failure is an unusual combination of findings that posed a diagnostic dilemma in this case. We have discussed the work up of this case and the differential diagnosis of such a presentation.

CASE PRESENTATION

A 24-year-old Indian man with no significant medical history presented to the emergency department with a 2-day history of loss of appetite, abdominal pain and recurrent vomiting. He also reported progressive weakness in upper and lower extremities due to which he was finding it difficult to ambulate. He denied sensory and sphincter involvement or any other symptom suggestive of cranial nerve or autonomic dysfunction. There were no other systemic symptoms.

He was a non-smoker and denied drug and alcohol abuse. He denied any intentional drug or toxin ingestion. He was employed as a domestic worker. There was no history of any occupational exposure to toxins. There was no recent history of travel.

His vital signs at presentation were stable and he was afebrile. He appeared pale and jaundiced, but there were no other features suggestive of chronic liver disease. Abdomen examination revealed a

tender hepatomegaly with mild ascites. Chest examination showed bilateral basal crepitations. Neurological examination revealed an alert, oriented and communicating young man with intact cognitive functions. Pupils were reacting normally. He had symmetric flaccid, areflexic quadriparesis with a strength of 4/5 in upper limbs and 2/5 in the lower limbs. The planter reflexes were down-going bilaterally. Cranial nerve and sensory examination was normal. There was no sign of respiratory compromise.

INVESTIGATIONS

Initial laboratory investigations revealed: white cell count $22 \times 10^3/\mu\text{L}$, haemoglobin 8.9 g/dL (normocytic) and platelet $600 \times 10^3/\mu\text{L}$. His random glucose level was 125 mg/dL. Blood smear showed normocytic anaemia with neutrophilic leucocytosis and a left shift. Renal function was normal at admission. Arterial blood gas (ABG) showed a pH 7.14, pCO₂ 38 mm Hg, pO₂ 90 mm Hg, HCO₃ 13 mEq/L, lactate 80 mmol/L (range 4–14 mmol/L) and anion gap of 18 mEq/L after correcting for mildly low albumin of 3.3 g/dL. Chest and abdominal X-ray were unremarkable. Derangements were noted in his liver function test: total bilirubin 8.8 mg/dL (direct 6.6 mg/dL), alanine aminotransferase 49 U/L, alkaline phosphatase 49 U/L, gamma-glutamyl transferase 261 U/L, albumin 3.3 g/dL, globulin 2.9 g/dL. Coagulation profile showed mildly prolonged prothrombin time with an international normalized ratio of 1.6. A baseline ECG showed sinus tachycardia. Paracetamol and salicylate drug levels in the blood were undetectable.

He was initially admitted with the presumptive diagnosis of acute hepatitis to rule out sepsis. He was started on intravenous crystalloids, empiric antibiotics and full supportive care. Meanwhile a full septic workup was requested. Results revealed the following: procalcitonin was 1.75 ng/mL, C reactive protein 28 mg/L and erythrocyte sedimentation rate 4 mm/1 h. Blood, urine, sputum and cerebrospinal fluid (CSF) cultures were all negative. Urine analysis was normal. All viral hepatitis serology including hepatitis A and E were negative. Syphilis, HIV, Mycoplasma, Legionella, Leptospira, Coxsackie, Cytomegalovirus and Epstein-Barr virus serologies were negative. Blood smear was negative for malaria parasite. Monotest and T-spot tests were also negative.

Ultrasound of the abdomen showed moderate hepatomegaly with mild splenomegaly and ascites. There was no evidence of biliary tract obstruction

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or portal vein thrombosis. Transthoracic echo was reported to be normal.

Since the septic workup was unremarkable, other possible aetiologies such as an autoimmune process, intoxication or paraneoplastic aetiology were considered. There was no significant family history of autoimmune illness. Autoimmune markers including atrial natriuretic factor, rheumatoid factor, anticardiolipin, phosphatidyl serine, antimitochondrial, antismooth muscle, liver kidney microsomal, antiglomerular basement membrane, anti-neutrophil cytoplasmic antibody and extractable nuclear antigens antibody profile were all negative. Thyroid function test was normal. CT scan of the chest, abdomen and pelvis was performed which only revealed basal atelectasis and mild pleural effusion. There was no evidence of any infective or malignant pathology on the imaging studies. Tumour markers were also negative.

One significant finding was the presence of persistently high arterial and venous pO_2 values with very high peripheral lactate levels and severe metabolic acidosis. The ABG readings were as follows: pH 7.14, pO_2 370 mm Hg, pCO_2 38.5 mm Hg, HCO_3^- 13 mEq/L and SpO_2 100%. Whereas the venous blood gas readings consistently showed the following trend: pH 7.14, pO_2 234 mm Hg, pCO_2 42 mm Hg, HCO_3^- 13.5 mEq/L and SpO_2 99.6%. This indicated peripheral shunting and suggested cellular poisoning, which raised the possibility of intoxication. This possibility was considered in view of severe multiorgan dysfunction with negative septic, autoimmune and malignancy workup. Although screening heavy metal levels is not part of initial routine diagnostic workup, it was requested for this patient.

The neurology team was consulted from the time of initial presentation in view of the muscle weakness. The possibility of Guillain-Barré syndrome (GBS) was raised and a lumbar puncture was done. The CSF was acellular with a high protein of 273 mg/dL, lactate of 4 mmol/L and normal glucose level. Nerve conduction study showed findings consistent with axonal sensorimotor polyneuropathy marked by low-amplitude sensory and motor action potentials with relatively preserved conduction velocities.

TREATMENT

In view of acute symmetric polyneuropathy, the neurology team recommended starting plasmapheresis with a total of five cycles. Unfortunately the patient could not complete the five cycles of plasmapheresis as he developed haemodynamic instability. Meanwhile he also developed acute kidney injury due to which intravenous immunoglobulins (IVIG) could not be considered. He was subsequently given a 3-day course of pulse methylprednisolone.

The patient's condition continued to deteriorate and he remained febrile despite broad spectrum antibiotic coverage. Septic markers and repeated cultures were consistently negative. However, in view of his deteriorating clinical condition he was also started on empiric antifungals.

His worsening clinical status required mechanical ventilation for respiratory failure as well as vasopressor and inotropes for haemodynamic instability. His laboratory parameters showed further deterioration, including worsening hepatic and renal function as well as disseminated intravascular coagulation. Although renal replacement therapy was being considered in view of refractory metabolic acidosis, anuria and fluid overload, it could not be initiated due to haemodynamic instability.

OUTCOME AND FOLLOW-UP

Unfortunately the patient's condition worsened and he went into deep coma with a Glasgow coma scale of 3/15. He finally succumbed to his illness after a rapid and fulminant course of illness. After his demise the blood levels for metals became available. Lead, nickel and arsenic were within normal range. However, the aluminium level was elevated at 86 $\mu\text{g/L}$ (normal range: 0–9 $\mu\text{g/L}$). In retrospect the patient's X-ray films were reviewed but did not show radiological signs of osteopenia, which is indicative of chronic aluminium toxicity. His friends and relatives were contacted once again; they reconfirmed that he was not using any aluminium-containing antacids or other 'herbal' medications. There were no other reported cases of sudden unexpected death in their vicinity. There was no previous occupational exposure to aluminium.

In view of the sudden onset of fulminant multiorgan failure with concomitant polyneuropathy, the intoxication was more suggestive of an acute rather than chronic exposure. Since aluminium intoxication alone per se does not cause such a rapid and fatal course of illness, other concomitant intoxication that can occur concomitantly with aluminium were considered. The most likely agent that could explain the fulminant nature of the disease was ALP poisoning.

DISCUSSION

Aluminium toxicity is a relatively uncommon clinical entity that is classically reported in a select category of patients: those with peptic ulcer disease who consume large amounts of aluminium salts as antacids; those with chronic kidney disease who consume aluminium salts as phosphate binders and in whom renal clearance of aluminium is reduced; those on haemodialysis; and those who are maintained on long-term total parenteral nutrition. It has also been reported in subjects with a history of long-term occupational exposure to aluminium in smelting plants.^{1–3} Such patients become prone to haematological, skeletal and neurotoxic effects of aluminium.⁴ The neurotoxic effects of aluminium are mainly directed towards the central nervous system and manifests in the form of encephalopathy. It usually starts as a progressive decline in cognitive functions and then gradually progresses to cause speech disturbances, motor incoordination, myoclonus, seizures and frank dementia.⁵ Unlike arsenic, thallium and lead, acute or chronic aluminium toxicity is not commonly associated with peripheral neuropathy.^{6–9} The toxicological profile of aluminium released by the US government shows that severe, fulminant multiorgan involvement is not known to occur following intermediate or chronic oral exposure to aluminium in humans.¹⁰ Therefore we conclude that although the aluminium levels were significantly elevated in our patient, the rapidly progressing multiorgan failure could not be explained by aluminium metal toxicity alone.

On the other hand, ALPs are highly toxic substances that are commercially used as potent insecticides and rodenticides for the storage of grain in developing countries. Exposure may be in the form of accidental or suicidal ingestion. In fact, phosphide salts are some of the frequently encountered pesticide agents used for suicidal purposes, particularly in India and Iran. It has been associated with a high mortality rate due to unavailability of an effective antidote.^{11–13} Its commercial use is restricted in the UAE, however it is still available from unlicensed pest control companies. There were a few reported cases in the media that highlighted fatalities after its illegal use as an insecticide in residential areas. The lethal dose of ALP is

0.5 g. Those who survived had either taken a much smaller dose or taken expired tablets where the phosphine gas had evaporated due to exposure to air.¹⁴

Metal phosphide releases phosphine gas once it is in contact with acid content of the stomach. Phosphine exerts its toxic effect at the cellular level by inducing morphological changes in the mitochondria and blocking cytochrome-c activity. It thereby inhibits the process of oxidative phosphorylation and cellular respiration.¹⁵ It also triggers the generation of reactive oxygen species, which further propagates the process of cellular injury.^{16 17}

In contrast to aluminium metal toxicity, acute poisoning with AIP is well known to cause multiorgan failure.¹⁴ The manifestation depends on the route of administration of the toxin. In cases of oral administration of the toxin, it initially manifests as non-specific gastrointestinal symptoms and then progresses to acute hepatitis, renal failure, metabolic disturbances, coagulation disturbances and cardiac failure.¹⁸ A characteristic feature is the garlic odour from the breath of the victims. As our patient presented with mainly gastrointestinal manifestations which progressed to severe systemic involvement and as he had high aluminium levels in the blood, we believe that he had accidental or intentional oral poisoning with AIP.

Known neurological complications following ingestion of AIP include headache, dizziness, altered mental status, convulsion, acute hypoxic encephalopathy and coma.¹⁸ Since the clinical presentation in our patient mimicked GBS, he was initially treated with plasmapheresis. To the best of our knowledge there are no previously reported cases of acute peripheral neuropathy due to AIP poisoning or even due to acute aluminium poisoning. Among the metals, arsenic poisoning is known to manifest as a severe, progressing polyneuropathy which can appear clinically and electrodiagnostically similar to GBS; such cases have been described to progress to ventilatory failure.^{19 20} So whether the acute peripheral neuropathy was attributable to the AIP poisoning or aluminium metal toxicity, or whether it was an incidental case of GBS in an unfortunate patient with AIP poisoning is still debatable.

One of the important clinical clues that helped in reaching the provisional diagnosis was the presence of high anion gap metabolic acidosis with very high lactate levels and high arterial and venous pO₂ values. This combination of findings was highly suggestive of failure of respiration at a cellular level. Severe metabolic acidosis with very high lactate levels are commonly seen in AIP toxicity. In an observational study of 40 patients with AIP poisoning, Jaiswal *et al*²¹ found the average pH to be 7.201±0.143 and a base excess ranging from -21 to -11. This is probably related to inhibition of cellular respiration at the mitochondrial level and inadequate tissue perfusion. Another explanation is the occurrence of methemoglobinaemia due to AIP poisoning.²²

A positive history of AIP ingestion is the basis of diagnosis in most cases. There is no role for routine measurement of phosphine levels in blood or urine as it is rapidly oxidised to phosphite and hypophosphite.²³ The most feasible test for diagnosis of AIP toxicity is by using silver nitrate-impregnated paper on gastric content or on breath to detect the presence of phosphine gas.²⁴ However, the most specific diagnostic test is gas chromatography on samples obtained for autopsy studies.²⁵ Elevated blood and tissue aluminium levels have been described in several case reports of AIP toxicity, and therefore this can be indirect laboratory evidence of the toxin in cases where the clinical suspicion for AIP poisoning is raised.²⁶ Anger *et al*²⁷ have described a fatal case of oral AIP poisoning where the victim was discovered 10 days after death and where the aluminium

concentration was shown to be very high in the blood: 1537.5 µg/L. Gary *et al*²⁶ also reported a fatal case of oral AIP poisoning where the blood aluminium levels were 713 µg/L.

Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II scoring systems have been demonstrated to be good predictors of outcome in AIP poisoning.^{28 29} An observational study by Singh *et al*³⁰ showed that non-survivors have more severe hypotension and metabolic acidosis whereas survivors were noted to have more severe vomiting. The most common cause of death in AIP toxicity is cardiogenic shock.³¹ Most fatalities that occur within the first 24 h after ingestion are due to arrhythmia and those that occur after 24 h are due to refractory shock, acidosis and Acute Respiratory Distress Syndrome.³² This is the course of complications that was seen in our patient.

Management in cases of AIP toxicity is mainly supportive. Gastric lavage with potassium permanganate or a mixture of coconut oil and sodium bicarbonate solution can be performed; however, there is no consensus agreement on these recommendations.³³ There is insufficient data about the efficacy of activated charcoal in settings of acute AIP poisoning. Decontamination should be followed by early, vigorous resuscitation with fluid, vasopressors and ventilatory support. The treating personnel must take personal protection measures to reduce the risk of potential exposure to phosphine gas during contact with the patient. Intravenous sodium bicarbonate can be considered for patients with metabolic acidosis.²¹ Patients with severe acidosis, volume overload or renal failure may require haemodialysis. However, the role of haemodialysis in removing phosphine from the circulation is questionable.³⁴ Since there is no specific antidote for AIP intoxication, most patients die despite intensive supportive care due to multiorgan failure.¹⁶

AIP poisoning is a challenging diagnosis to make as it mimics a wide range of clinical conditions that are seen in critically ill patients who are admitted in the intensive care unit. In the absence of a clear history of toxin ingestion its diagnosis requires a high index of clinical suspicion. Although our patient initially denied ingesting any toxin, the possibility of accidental or even intentional ingestion could not be ruled out. We could not demonstrate the presence of phosphine gas in our patient as the possibility of AIP poisoning was only raised in retrospect, after his demise. In summary, the fulminant nature of the illness, the presence of high anion gap metabolic acidosis with high venous pO₂ values and the elevated aluminium levels point towards the most likely diagnosis of fatal intoxication with AIP.

Learning points

- ▶ The possibility of intoxication should be considered in critically ill patients with progressive, refractory and unexplained multiorgan failure.
- ▶ Persistently high partial pressure of oxygen in venous blood can be a clue to cellular poisoning.
- ▶ A high index of suspicion followed by early diagnosis and aggressive early supportive care can be helpful in AIP poisoning cases. No effective antidotes are available.

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