CASE REPORT

Severe reversible myocardial injury associated with aluminium phosphide toxicity: A case report and review of literature

Wael Elabbassi [a,*], Mohammed Andaleeb Chowdhury [b], Arif Al Nooryani Fachtartz [a]

[a] Department of Cardiology, Al Qassimi Hospital, Sharjah; [b] Department of Internal Medicine, University of Toledo, OH
[a] United Arab Emirates, [b] USA

Aluminium phosphide is commonly used as an insecticide and can be toxic to humans at the cellular level by interfering with mitochondrial energy metabolism. We report on three cases of severe aluminium phosphide cardiotoxicity, resulting in severe decrease in both ventricular heart functions. The first case succumbed to intractable ventricular arrhythmias complicated by multi-organ failure before she died; while the other two cases required invasive hemodynamic support and eventually improved over the course of 10–14 days. We describe our experience and the challenges faced while managing one of them.

Keywords: Cardiomyopathy, Extra corporal membrane oxygenation (ECMO), Intra-aortic balloon pump, Aluminium phosphide toxicity

Established facts

Established fact 1: Aluminium phosphide toxicity causes cardiac toxicity.

Established fact 2: No known antidote for this type of poisoning at present.

Novel insights

Novel addition 1: Aluminium phosphide causes reversible cardiac toxicity whose effects may last 10–14 days. According to our local experience, optimal aggressive hemodynamic support throughout the injury period results in better outcomes.

Novel addition 2: To our knowledge, this is one of the first reported cases of aluminium phosphide poisoning treated using a combination of intra-aortic balloon pump and extra corporeal membrane oxygenation to treat severe prolonged cardiogenic shock.

Novel addition 3: Drugs which work at the mitochondrial level to improve the metabolism of cardiac muscle cells may be a useful adjunct to invasive hemodynamic support in such severe cases of poisoning.

Disclosure: Authors have nothing to disclose with regard to commercial support.
Received 4 November 2013; accepted 30 November 2013.
Available online 7 December 2013

* Corresponding author. Address: P.O. Box 3500, Sharjah, United Arab Emirates. Tel.: +971 506153522; fax: +971 65387200.
E-mail address: welabbassi@yahoo.com (W. Elabbassi).

Peer review under responsibility of King Saud University.
URL: www.ksu.edu.sa
http://dx.doi.org/10.1016/j.jsha.2013.11.006

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

Production and hosting by Elsevier

Case report

A 45-year-old woman, accompanied by her seven-year-old son and 11-year-old daughter, presented to the emergency department with vague symptoms of fatigue, nausea and recurrent vomiting. They were initially treated with intravenous normal saline, anti-emetics and discharged home after several hours. The next day, they presented with severe deterioration in clinical status as evidenced by hypotension, tachypnea and tachycardia (See Fig. 1).

The 11-year-old daughter followed a steeply declining clinical course. Within 12 h she was intubated, developed intractable ventricular tachycardia twice, requiring prolonged CPR and multiple DC shocks, followed by persistent hypotension and anuria despite multiple inotropes. She succumbed to her fate and died within 36 h.

The 6-year-old son had a bedside echo showing left ventricular ejection fraction (LVEF) of 35% and was started on milrinone infusion 0.25/kg/min. He was later moved to another facility for further treatment which included extra corporeal membrane oxygenation (ECMO) (See Fig. 2).

Our index patient had been initially started on triple inotropes (Dobutamine 20 μg/kg/min, Dopamine 20 μg/kg/min, Noradrenaline 8 μg/h), which did not deter her hemodynamic deterioration. Her initial bedside echocardiogram showed severe biventricular systolic dysfunction, and LVEF of 25–30%. No valvular abnormality, no pericardial effusion. On the second day, she required intubation, and an intra-aortic balloon pump (IABP) was inserted. Six hours later, she continued to be anuric with high oxygen requirement and low blood pressure, and she was placed on ECMO via right femoral vein and artery access, while her IABP was kept via left femoral artery access. Cardiac output was set at 3.7 l/min. Unfractionated heparin was initiated by bolus 1000 units followed by 800 units/h, with target ACT of 150–180. She was started on 8 L/min oxygen. The patient also required CRRT during the initial two days due to acute kidney injury and anuria (See Fig. 3).

Medication wise, the patient was started early on high dose L-carnitine 1 g three times a day for 10 days along with broad spectrum antibiotics. Initial hypo-magnesemia was treated intravenously by supplemental magnesium sulphate (2 gm) daily for four days. She was also started on Candesartan 2 mg bid, Spironolactone 12.5 mg daily, and Carvedilol 3.125 mg bid (See Fig. 4).

Over the next day, the patient was weaned off inotropes. Daily bedside echo via sub-costal window showed initial deterioration of overall cardiac function up to day 3; in the form of severe global myocardial hypokinesia/akinesia. LVEF had reached a nadir of 10%; right ventricular dysfunction was evidently moderately severe. Slow improvement ensued over the next 10 days with LVEF rising up to 45–50%. Initial improvement had commenced in the lateral and inferior left ventricular walls, while last walls to improve were the septal and anterior walls. Initial echo pictures had also shown a mild increase of wall thickness involving myocardial mid and distal segments (up until the apex). As heart function improved, this regressed. A repeat echo performed 3 weeks after index event confirmed the almost complete resolution of systolic dysfunction in all wall segments except distal apex. There was resolution of all the myocardial increased thickness except at the distal lateral wall segment where it persisted.

ECG at presentation showed normal sinus rhythm, normal PR interval and partial left bundle branch block with QRS duration of 94 ms. Over

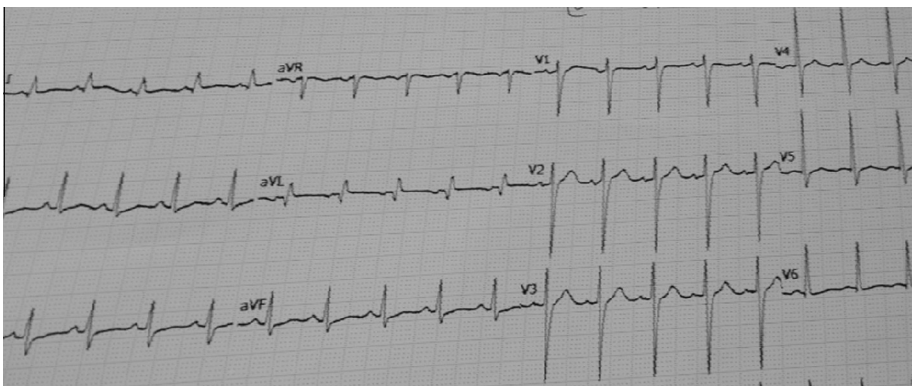

Figure 1a. Initial ECG showing minimal QRS prolongation and non-specific ST and T wave changes.

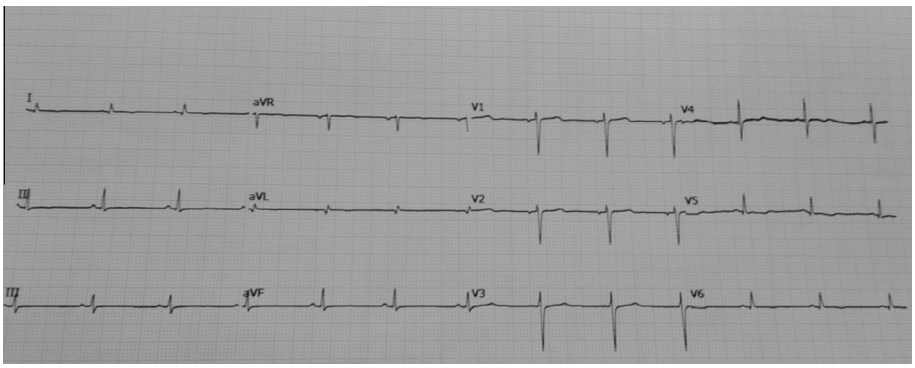

Figure 1b. Latest ECG showing shortening of QRS duration and resolution of ST/T wave changes.

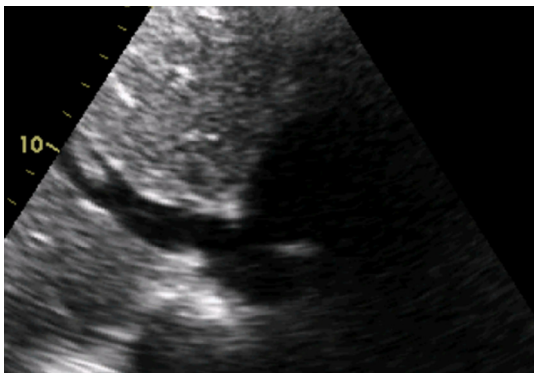

Figure 2a. Initial dilated IVC with thrombus.

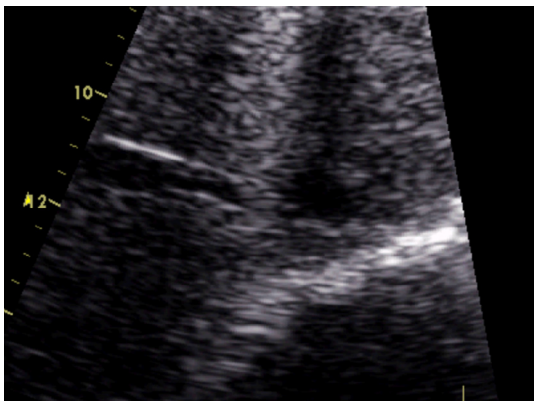

Figure 2b. Final view via echo showing collapsing IVC and resolution of thrombus.

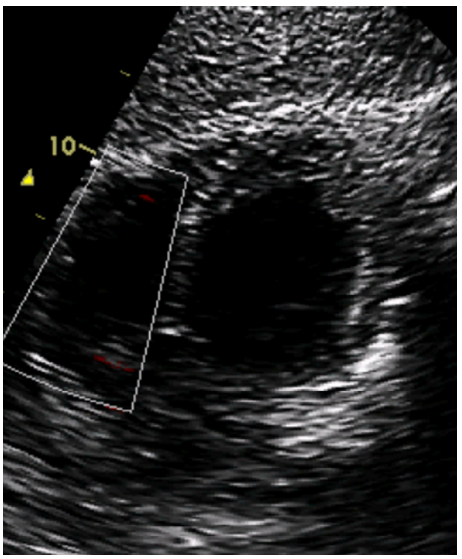

Figure 3a. Initial 4 chamber view showing dilated LV with poor systolic function.

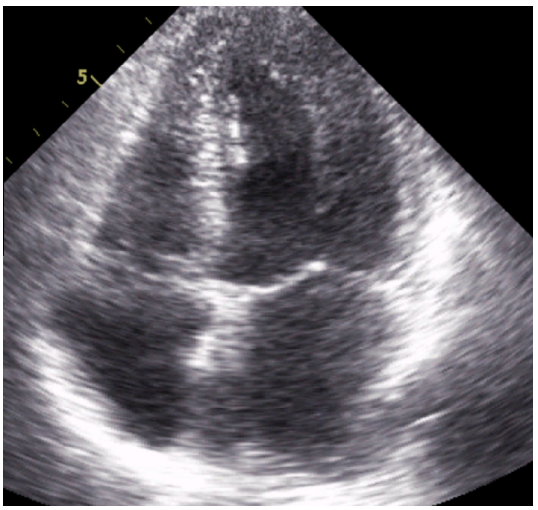

Figure 3b. Resolution of lateral and inferior WMA and improved LV systolic function.

the coming days ECG would become narrower while a pattern of T wave inversions evolved in antero-lateral leads. Ten days later, ECG showed complete resolution of these changes.

After day 10, the patient was weaned off IABP and the next day off ECMO with accesses closed surgically. Bedside echo then showed a small pedunculated thrombus in the IVC, 2–3 cm from

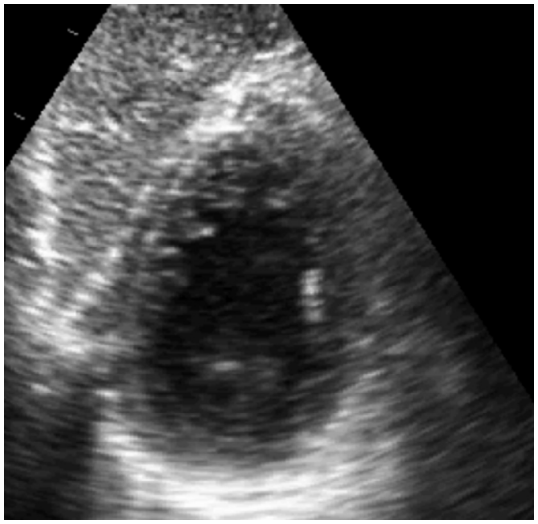

Figure 4a. Initial short axis view showing WMA in inferior, lateral walls.

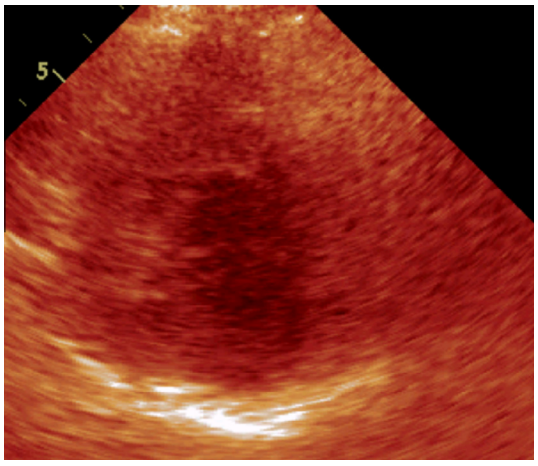

Figure 4b. Final short axis view showing smaller LV cavity with resolution of WMA.

its entrance into the right atrium. Patient had initially developed transient slurring of speech and increased tremors which improved over 2 days. A CT of the brain showed no evidence of CVA and this was attributed to side effects of poly pharmacy (especially haloperidol). Patient was finally discharged home on warfarin, target INR 2.0. Three weeks later, a repeat echo showed resolution of the IVC thrombus with shrinking of IVC, and warfarin was then discontinued.

A police report had noted traces of aluminium phosphide at the patient's flat. The source of aluminium phosphide was from an insecticide used 3 days earlier. They were told to leave the flat and close all windows and ventilator ducts, which the mother and children did, but only after several hours of inhaling the pungent odor.

Discussion

Aluminium phosphide (AlP) is an insecticide, rodenticide and fungicide, commonly used in the Indian subcontinent as well as in other developing countries. Since the 1970s there have been increasing reports of AlP poisoning with a mortality rate of 70% [1]. Boogle et al. reported that the majority of poisoning cases were accidental [2].

The toxic effects of the AlP are due to deadly phosphine gas, which, when liberated, reacts with water or hydrochloric acid in the stomach [3]. Phosphine gas (PH3) is the active pesticide component of AlP, which is rapidly absorbed by inhalation, ingestion, and skin or mucosal contact [3]. PH3 works at the mitochondrial level where it can rapidly perturb mitochondrial conformation and inhibit oxidative respiration by up to 70%, severely decreasing mitochondrial membrane potential [4]. PH3 mainly inhibits cytochrome C oxidase (Complex IV) and decreases Complex I and Complex II activity, resulting in decreased ATP formation [5]. This results in the slowing down of the electron flow with resultant electron leakage, initiating reactive oxygen species production (ROS). PH3 further inhibits the antioxidant enzymes, catalase and peroxidase, decreasing the scavenging of ROS [6].

Clinically, cardiac manifestations among cases of poisoning are due to PH3 induced myocardial damage. In fact, acute cardiovascular collapse is the most common mode of presentation seen in 60% to 100% of cases [10]. Autopsy results show congestion of heart, separation and fragmentation of myocardial fibers, nonspecific vacuolation of myocytes, focal necrosis as well as neutrophilic and eosinophilic infiltration [7]. The focal myocardial necrosis and changes in membrane action potentials result in non-specific ST-T wave changes in the EKG [8].

In our patient, the EKG showed changes initially as incomplete LBBB, followed by narrowing of QRS complex and developing repolarization changes in the antero-lateral leads, which normalized in 10 days. Singh et al. [9] reported that EKG changes reverts to normal pattern within 10–14 days in survivors.

Echocardiogram showed a drastic reduction in systolic function with global severe hypokinesia. Similar cases have been reported with significant decrease in ejection fraction [2]. Bhasin et al. demonstrated a similar pattern of global hypokinesia of the LV walls in 80% of their cases [11].

Echocardiographic findings correlated with hemodynamic stability and our patient showed remarkable gradual improvement in left

ventricular ejection fraction by the 10th day. Gupta et al. had reported normalization of ECHO findings in AlP survivors by the 5th day [12].

Laboratory parameters had shown initial hypomagnesemia and were aggressively treated. Magnesium ions help in scavenging free radicals and acts as an anti-arrhythmic agent. Previous reports suggest it may be beneficial in treating AlP poisoning cases, [13] while others found it confers no difference on survival [14].

Siwach et al. [15] noted that ventricular tachycardia occurs in 40% of AlP-poisoned patient cases, ventricular fibrillation in 23.3%, supraventricular tachycardia in 46.7%, and atrial flutter/fibrillation in 20%. Our index cases did not suffer such complications possibly related to early aggressive intervention with correction of electrolyte imbalance. The daughter notably suffered refractory arrhythmias and eventually expired due to multi-organ failure. She also had hypomagnesemia and had commenced treatment for that.

The cardiac function of both the mother and son improved within 10–14 days. Akkaoui et al. [16] reported two cases of aluminium phosphide poisoning with reversible myocardial injury, which improved after 7–10 days.

L-carnitine is an essential co-factor in fatty acid metabolism which is the primary source of energy for cardiac muscles, and where it shuttles long-chain fatty acids and activated acetate across the inner mitochondrial membrane [17]. A decrease in fatty acid oxidation after myocardial ischemia leads to accumulation of long-chain acyl-CoA esters, which inhibits adenine nucleotide translocation, with a net result that lowers the energy charge of the cell, adversely affecting muscle contraction and electrical conduction [18].

Liedtke et al. [19] demonstrated that use of L-carnitine in ischemic hearts preserves mechanical function under conditions of excess free fatty acid (FFA), by modifying the toxic effects of FFA intermediates. CEDIM trial [20] reported that treatment with L-carnitine in ischemic hearts resulted in a significant reduction of left ventricular dilatation, with significant reduction in both end-diastolic and end-systolic volumes in the levocarnitine-treated group. No modification of left ejection fraction was observed, while the incidence of death, congestive heart failure, and ischemic events were fewer.

Aluminium phosphide toxicity interferes with the electron transport chain and gives rise to myocardial necrosis similar to what occurs during ischemia. Such an event leads to the accumulation of long chain acyl-CoA metabolites. A decrease of the impact of these additional metabolites on the cardiac metabolism promotes better outcomes. The use of L-carnitine in aluminium phosphide poisoning has not previously been reported to the best of our knowledge. Whether its use influenced the positive outcome in our case is anecdotal and hypothesis-generating at best, and remains to be tested in a randomized trial.

Conclusion

Aluminium phosphide poisoning can result in severe cardiac toxicity. This may be reversible provided the patient can be sustained during the ''insult period''. At present, no specific antidote for this poisoning is known, and treatment strategy is supportive until the injury induced by the active compound (phosphine) subsides. Patients with severe intoxication benefit from aggressive hemodynamic support, as in our case. Our use of L-carnitine for this patient with encouraging result needs further validation by others, as it may be a useful adjunct to IABP and ECMO alongside other conventional treatments for heart failure. This remains to be verified.

Conflict of interest

None.

Disclosure

None.

References

[1] Chugh SN, Dushyant, Ram S, Arora B, Malhotra KC. Incidence and outcome of aluminium phosphide poisoning in a hospital study. Indian J Med Res 1991;94:232–5.
[2] Bogle RG, Theron P, Brooks P, Dargan PI, Redhead J. Aluminium phosphide poisoning. Emerg Med J 2006;23(1):e3.
[3] Sudakin DL. Occupational exposure to aluminium phosphide and phosphine gas? A suspected case report and review of the literature. Hum Exp Toxicol 2005;24(1):27–33.
[4] Valmas N, Zuryn S, Ebert PR. Mitochondrial uncouplers act synergistically with the fumigant phosphine to disrupt mitochondrial membrane potential and cause cell death. Toxicology 2008;252(1–3):33–9.
[5] Dua R, Gill KD. Effect of aluminium phosphide exposure on kinetic properties of cytochrome oxidase and mitochondrial energymetabolism in rat brain. Biochim Biophys Acta 2004;1674(1):4–11.
[6] Anand R, Binukumar BK, Gill KD. ROS-induced tissue damage propagates with organ dysfunction-Aluminium phosphide poisoning: an unsolved riddle. doi 10.1002/jat.1692.

[7] Arora B, Punia RS, Kalra R, Chugh SN, Arora DR. Histopathological changes in aluminium phosphide poisoning. J Indian Med Assoc 1995;93(10):380–1.
[8] Chugh SN, Chugh K, Ram S, Malhotra KC. Electrocardiographic abnormalities in aluminium phosphide poisoning with special reference to its incidence, pathogenesis, mortality and histopathology. J Indian Med Assoc 1991;89(2):32–5.
[9] Singh S, Dilawari JB, Vashist R, Malhotra HS, Sharma BK. Aluminium phosphide ingestion. Br Med J (Clin Res Ed) 1985;290(6475):1110–1.
[10] Tripathi SK, Gautam CS, Sharma PL. Clinical pharmacology of aluminium phosphide poisoning. Ind J Pharmacol 1992;24:134–7.
[11] Bhasin P, Mital HS, Mitra A. An echocardiographic study in aluminium phosphide poisoning (abstract). J Assoc Phys India 1991;39:851.
[12] Gupta MS, Malik A, Sharma VK. Cardiovascular manifestations in aluminium phosphide poisoning with special reference to echocardiographic changes. J Assoc Phys India 1995;43(11). 773–4, 779–80.
[13] Chugh SN, Kumar P, Aggrawal HK, Sharma A, Mahajan SK, Malhotra KC. Efficacy of magnesium sulphate in aluminium phosphide poisoning – comparison of two different dose schedules. J Assoc Phys India 1994;42(5):373–5.
[14] Siwach SB, Singh P, Ahlawat S, Dua A, Sharma D. Serum and tissue magnesium content in patients of acute aluminium phosphide poisoning and critical evaluation of high dose magnesium sulphate therapy in reducing mortality. J Assoc Phys India 1994;42(2):107–10.
[15] Siwach SB, Singh H, Jagdish, Katyal VK, Bhardwaj G. Cardiac arrhythmias in aluminium phosphide poisoning studied by on continuous holter and cardioscopic monitoring. J Assoc Phys India 1998;46(7):598–601.
[16] Akkaoui M, Achour S, Abidi K, Himdi B, Madani A, Zeggwagh AA, et al.. Reversible myocardial injury associated with aluminium phosphide poisoning. Clin Toxicol (Phila) 2007;45(6):728–31.
[17] De Vivo DC, Tein I. Primary and secondary disorders of carnitine metabolism. Int Pediatr 1990;5:134–41.
[18] Shug AL, Shrago E, Bittar N, Folts JD, Koke JR. Acyl-CoA inhibition of adenine nucleotide translocation in ischemic myocardium. Am J Physiol 1975;228(3):689–92.
[19] Liedtke AJ, Nellis SH, Whitesell LF. Effects of carnitine isomers on fatty acid metabolism in ischemic swine hearts. Circ Res 1981;48(6 Pt. 1):859–66.
[20] Iliceto S, Scrutinio D, Bruzzi P, D'Ambrosio G, Boni L, Di Biase M, et al.. Effects of L-carnitine administration on left ventricular remodelling after acute anterior myocardial infarction: the L-Carnitine Ecocardiografia Digitalizzata Infarto Miocardico (CEDIM trial). J Am Coll Cardiol 1995;26(2):380–7.