CASE REPORT

Aluminium phosphide-induced leukopenia

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SUMMARY

Acute intoxication from the pesticide aluminium phosphide is a relatively rare, life-threatening condition in which cardiovascular decompensation is the most feared problem. We report the case of a patient exposed to aluminium phosphide-liberated phosphine gas. It resulted in the development of a gastroenteritis-like syndrome accompanied by severe reduction in white blood cell numbers as an early and prominent manifestation. By affecting important physiological processes such as mitochondrial function and reactive oxygen species homeostasis, phosphine could cause severe toxicity. After presenting the characteristics of certain leucocyte subpopulations we provide the current molecular understanding of the observed leukopenia which in part seems paradoxical.

BACKGROUND

Aluminium phosphide (AP) is a highly potent insecticide and rodenticide, widely used in commercial agriculture, especially in grain storage facilities. Interaction with water vapour generates phosphine, which is the actual drastic compound. There are two routes to intoxication, either from ingestion or from inhalation of AP-liberated phosphine gas. On the basis of existing scientific data, mitochondrial dysfunction considered to play the central role in the pathogenesis of this clinical condition.¹ Shortly after exposure, gastrointestinal manifestations including epigastric pain, vomit and diarrhoea are commonly observed. Over time, in severe cases, patients develop cardiac arrhythmias and shock, which is often refractory to therapy. There may be delirium or coma, pulmonary oedema, metabolic acidosis, methemoglobinemia, adrenal insufficiency, hepatic failure and acute kidney injury. Phosphine toxicity is associated with a high risk of death. Despite proposed strategies to avert the lethality of this compound, treatment remains largely symptomatic.²⁻⁴

According to published literature, phosphine inhalation could lead to leukopenia.⁵ We discuss the case of a patient with aluminium phosphide-induced leukopenia after involuntary intoxication and provide an insight into the mechanisms triggering this toxic effect on white blood cells.

CASE PRESENTATION

A previously healthy 49-year-old man presented to the emergency department of our hospital with vomiting, diarrhoea, general malaise and chest tightness of the acute onset. Careful history revealed that he dispersed 15 aluminium phosphide

tablets in his house in order to fight rodents. Being unaware of the dangers, he and his whole family exposed overnight to highly deadly phosphine gas. On physical examination no significant alterations were found except from mild epigastric tenderness. Instead, severe leukopenia (1400/ μ L) was revealed from the laboratory evaluation. In particular, the patient developed significant decreases in neutrophil and lymphocyte counts, while monocytes remained unaffected (neutrophils 350/ μ L, lymphocytes 760/ μ L, monocytes 280/ μ L, eosinophils 0/ μ L, basophils 10/ μ L). A peripheral blood smear performed to confirm the results. On ECG, bradycardia and right branch block were observed. Cardiac enzymes and echocardiogram were normal. Additionally a slight increase in serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels was observed, compatible to the well-known AP hepatotoxicity. His clinical condition was improved rapidly and 24 h later the leucocyte count returned to safe levels (white cell count (WCC) 3900/ μ L, neutrophils 1780/ μ L, lymphocytes 1420/ μ L, monocytes 580/ μ L, eosinophils 100/ μ L, basophils 20/ μ L). Lacking specific antidote, treatment was supportive. Additionally another family member experienced mild symptoms with WCC 3000/ μ L. Unfortunately his 4-year-old child passed away few days later in the paediatric intensive care unit due to severe toxic myocarditis.

DISCUSSION

Data from *Caenorhabditis elegans* and rat mitochondria indicate that phosphine compromises mitochondrial function as the cells power plant. This effect is attributed mainly to respiratory chain complex IV inhibition (cytochrome *c* oxidase). As a result, mitochondrial inner membrane potential ($C_{\psi m}$) collapses.⁶⁻⁷ It is well known that $C_{\psi m}$ drives ATP synthesis and its breakdown is regarded as a proapoptotic factor.⁸ Another consequence of this defective respiratory chain is excessive reactive oxygen species (ROS) generation. Interestingly phosphine decreases ROS scavengers glutathione peroxidase and catalase levels, disrupting the balance between oxidative and antioxidative factors even further. Therefore, it is unsurprising that phosphine induces lipid peroxidation.⁹ At last, we have to underscore that phosphine is a nucleophile reducing agent, able to interact with metalloproteins and reduce disulfide bonds.¹⁰ Taken together, these deleterious effects promote cellular death.

On theoretical grounds, there are some peculiarities in neutrophil physiology that makes the observed neutropenia hard to conceive. Previous

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published studies have shown that neutrophils only after incubation with high concentration of the potent complex IV inhibitor potassium cyanide (KCN) displayed 30% reduction in ATP levels. Importantly, in neutrophils cytochrome *c* oxidase levels are hardly detectable. Eosinophils and neutrophils rely on glycolysis for energy production.^{10 11} Additionally, neutrophils are short-lived cells preprogrammed to undergo cellular death and there is a recognised role for ROS in regulating this process.¹² The above mentioned ROS deregulation may offer a potential explanation for the observed neutrophil vulnerability in our patient. On the contrary peripheral blood mononuclear cells (PBMCs, lymphocytes and monocytes) exposed to the same KCN concentration showed a 90% reduction in ATP levels. Thus after phosphine exposure, PBMCs probably experience a severe bioenergetic crisis. Additionally, respiratory chain poisons induce apoptosis in human lymphoblast precursors *in vitro*.¹³

The observed leukopenia does not seem to be related to the low-WCC that occur in critical illness, because of our patient's other clinical and laboratory parameters. Interestingly, a study involving 39 patients, reported WCC ranging between 4800 and 18 300/ μ L and high WCC counts was considered as a poor prognostic factor.¹⁴ Concerning therapeutic implications, in our patient the observed leucopenia was transient and whether granulocyte growth factor administration is indicated, is an open question. In the initial phase, significant is patient decontamination by transferring to clean air, removing his clothes with precautions to keep staff from breathing phosphine. In cases of aluminium phosphide ingestion gastric lavage with potassium permanganate, H₂ receptor antagonists and bicarbonate solution lowers phosphine absorption (HCL increases phosphine liberation from aluminium phosphide) and even an approach with orogastric tubes to remove phosphine was described. N-acetylcysteine and vitamin C have been used to minimise oxidative stress. Additionally magnesium supplementation, methylene blue administration in cases of methemoglobinemia, trimetazidine, pralidoxime, digoxin, corticosteroids in cases of adrenal dysfunction is proposed. At last, management of those patients requires cardiorespiratory monitoring.^{1 2 4 5 15 16}

In summary, aluminium phosphide intoxication remains a difficult clinical problem accompanied with a high mortality rate. Consistent with existing evidence, severe leucopenia is an infrequent complication after aluminium phosphide intoxication. At last, understanding the molecular targets of phosphine in WCCs and identifying the related pathological disturbances may have important implications for disease management and leucocyte biology in general.

Learning points

- ▶ Aluminium phosphide intoxication is a difficult clinical problem.
- ▶ Severe leukopenia is an infrequent complication, maybe transient.
- ▶ Understanding the molecular targets of phosphine in white blood cells is challenging.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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