

Underdiagnosed Paraquat Induced Pneumothorax and Pneumomediastinum, The “Daisley Barton Syndrome”: A Clinical Feature Of Paraquat-Induced Acute Lung Injury

Case Report

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Abstract

The incidence of paraquat ingestion for self-harm, occurs at an alarming rate in Trinidad and Tobago W.I and is virtually synonymous with acute multi-organ failure and death in most settings. Yet recognition of pneumothorax and pneumomediastinum as clinical signs of acute paraquat lung injury remains a challenge amongst medical practitioners. We present a case of paraquat poisoning with these clinical features, which were recognized two days after presentation. The pathophysiological mechanisms for this clinical entity are presented in an effort to alert physicians of this feature as a part of acute paraquat lung injury and to stimulate research in effective therapy.

Keywords: Paraquat Poisoning; Pneumothorax and Pneumomediastinum; Acute Lung Injury.

Abbreviations: ROS: Reactive Oxygen Species.

Introduction

The purpose of this manuscript is to highlight the proposed mechanism of paraquat induced acute lung injury, namely pneumothorax and pneumomediastinum. This entity, as a consequence of paraquat ingestion, was first published by Daisley and Barton in 1990 [1], hitherto called the Daisley Barton syndrome. Since then, recognition of this entity has been underdiagnosed and undervalued.

Our case presents the Daisley Barton syndrome as part of paraquat induced acute lung injury which developed in a matter of 2 - 3 days post ingestion.

Case Report

The patient was a 23-year-old male who presented to the district

health facility with vomiting, diarrhea and severe chest and abdominal pain after alcohol binge drinking the night prior. He was assessed as having acute alcoholic gastritis with possible acute pancreatitis and was referred to the General Hospital for further management. Initial blood investigations were normal except for a mildly elevated serum amylase, although his renal function declined progressively during his hospital stay (Table 1).

His chest x-ray on admission showed a mild increase in respiratory infiltrates. He developed respiratory distress within the first 24 hours of admission, and was noted to have subcutaneous emphysema involving his neck and upper trunk and a left pneumothorax. A left thoracostomy was performed and 'he was' also mechanically ventilated.

The general surgeons attributed the finding of pneumothorax and pneumomediastinum and the copious amount of frank blood emanating from the nostrils and oropharynx to Boerhaave's syn-

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Table 1. Showing Normal Renal Function Profile On Admission, Mildly Elevated Amylase And Worsening Respiratory Acidosis And Renal Function Until His Demise.

Parameters	Admission	HDU (Day 1)	ICU (Day 2)	Death (Day 3)	Reference Range.
WCC	-	15.65	13.3	11.76	4 – 10.3 x 10 ³ /UL
Na+	137	128	132	133	135 - 145 mmol/L
K+	4.9	4.4	6.4	7.6	3.5 - 5.1 mmol/L
Cl-	97	89	89	94	97 - 110 mmol/L
Creatinine	1.1	5.4	8.2	9.2	0.7 - 1.2 mg/dl
Urea	-	41	62	-	4 - 24 mg/dL
Amylase	500	866	781	609	28 - 100 U/L
AST	27	48	95	46	5 - 40 IU/L
ALT	14	23	53	35	5 - 40 IU/L
Total protein	8.4	-	-	5.2	6.5 - 8.5 g/dL
pH		7.293	7.164	7.045	7.35 - 7.45
pCo2		31.8	52.1	84.1	35 - 45 mmHg
pO2		79	92.6	47.7	80 - 100 mmHg
SO2		94.3	94.6	62.1	95 - 100 %
HCO3-		15.6	18.9	23.3	24 - 26 mEq/L

drome. Respiratory acidosis ensued (Table 1), and Spo₂ saturation remained low despite high settings on the ventilator. The patient died on the third day. It was shortly before he died that his relative alluded to the fact that an empty bottle of paraquat was found at his home.

Post Mortem Findings

There were erosions to the lower lip and tongue, and significant erosive hemorrhagic gastritis and esophagitis, more so at the gastro esophageal junction. The trachea, bronchi and lower airways were severely hyperemic which was indicative of aspiration pneumonitis. The lungs were rubbery in consistency, markedly overweight, 1000 gms each, and were congested and edematous. There was a left pneumothorax and pneumomediastinum with air churned in the pericardial sac and the mediastinal fat (Figure 1).

There was also right heart failure with chronic passive venous congestion of the liver and congestive splenomegaly. The brain was edematous and overweight. The kidneys were edematous as seen in acute renal failure. The pancreas was grossly unremarkable.

Histopathology

Many histologic sections of the lungs were examined. There were many areas that showed atelectasis and emphysematous changes. The alveolar spaces contained polymorphs, lymphocytes and many macrophages, occasional giant cells, edema and frank blood. There were ballooning of some macrophages with blue collagen like material. These latter macrophages were found within alveolar spaces and alveolar walls (Figure 2).

The alveolar walls showed marked widening with round cells, giant cells and deposits of procollagen. There was alveolar capillary congestion and multiple pulmonary micro-thrombi in small vessels.

The cor-pulmonale was secondary to the pathological repair of the alveoli, producing early pulmonary fibrosis and micro thrombi.

The pancreas did not show acute inflammatory changes nor was there saponification of the omentum and surrounding fatty tissue.

There was evidence of esophagitis demonstrated with denuded mucosa, congested mucosal blood vessels and round cells infiltrates that extended into the submucosal space. There was vascular congestion within the muscle layers. Serial sectioning of the esophagus was done and no inflammatory/bloody sinus tracts breaching the serosa to confirm a ruptured esophagus was observed.

Discussion

Paraquat (1,1-dimethyl-4, 4-bipyridylum dichloride) is a herbicide, which belongs to the bipyridil quaternary ammonium herbicide. Gramoxone is its most common trade name. Absorption by plant leaves inhibits photosynthesis and leads to death of the leaves and ultimately the plant. This is a complex process, which involves cyclic reduction-oxidation reactions, which produces reactive oxygen species (ROS), hydrogen peroxide, and hydroxyl radicals. This hydroxyl radical is extremely reactive and readily destroys unsaturated lipids including membrane fatty acids and chlorophyll.

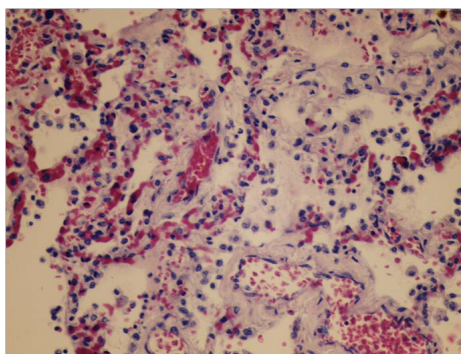
The hydroxyl radical produces lipid radicals, which react with oxygen to form lipid hydroperoxides; such lipid hydroperoxides (also called Reactive oxygen species) destroy the integrity of cell membranes allowing cytoplasm to leak into intercellular spaces, which leads to rapid leaf wilting and desiccation [2].

Paraquat is very toxic to humans and animals. The LD₅₀ for humans is around 30mg/kg. In Trinidad, it is often used in self-harm/suicide¹. It is poorly absorbed in the stomach. Fuller's earth

Figure 1. Showing Air Bubbles Below The Sternum Indicating A Pneumomediastinum On Post Mortem Examination.



Figure 2. Showing Alveolar Spaces Infiltrated By Inflammatory Cells, Collagen Deposition And Thickening Of Alveolar Walls Observed On Day 3 On The Demise Of The Patient. H&E.



or activated charcoal can detoxify unabsorbed paraquat in the stomach and should be administered to all patients as a first line of therapy who presents to hospital with a history of paraquat ingestion.

Once paraquat is absorbed, its entry into the blood stream has deleterious effects on all organs.

Hyperamylasemia originating from mild acute pancreatitis has been used as an early predictor of mortality in patients with acute pancreatitis [3]. There was no evidence of pancreatitis in this patient in discussion and his moderately elevated amylase would have had contribution from salivary glands stimulation following alcohol and paraquat consumption and poor renal clearance following his acute renal failure [4, 5].

Both the ingestion of alcohol and paraquat produce esophagitis and gastritis. There was no evidence of esophageal rupture in the patient in discussion thereby negating the phenomenon of Boerhaave's syndrome. The histological findings of the esophagus are suggestive of Mallory-Weiss syndrome without perforation of the esophagus which would account for the upper gastro intestinal tract hemorrhage in this patients as a result of his binge drinking and or paraquat ingestion [6].

The deleterious effect of paraquat is seen more so in the lung

where its concentration is much higher than those in plasma and other organs. This selective accumulation of paraquat in the lung occurs through the polyamine uptake system, and provides an explanation for its selective toxicity to the lung [7].

The pathogenesis of paraquat induced pulmonary toxicity producing Acute Lung Injury is often categorized into an early and late phase, although both phases occur simultaneously (See figure above). The first toxicological effects to the lung correspond to a destructive phase in which type I and type II pneumocytes are destroyed by ROS. Damage of type I epithelial cells causes their rupture, which prevents gas exchange and thereby exposing the basement membrane of the alveolar wall. Type II cells are also destroyed thereby limiting the production of surfactant and the transfer of water and ions and epithelial regeneration [2].

Decrease in surfactant causes increase in surface tension within alveoli, which draws fluid from capillaries to produce edema. It is also postulated that endothelial cells are damaged by reactive oxygen species, causing capillary permeability by resultant edema, and hemorrhage. In the pathogenesis of the paraquat induced acute lung injury, chemokines are released [8, 9], thereby generating an inflammatory response causing an influx of inflammatory cells. These are composed mainly of neutrophils, monocytes and lymphocytes and also endothelial cells and myofibroblasts, which promotes pathological repair with collagen production and depo-

sition within the alveolar wall and alveolar spaces [10, 11].

This production and deposition of collagen in acute paraquat toxicity occurred in the lung as early as day 3 in the patient in discussion (Figure 2).

It is the increase in surface tension within alveoli brought about by the destruction of type II cells which cause secondary atelectasis, rupture and emphysematous changes, thereby allowing alveoli gas to escape, causing pneumothorax and or the escaped gas to dissect along vascular sheaths and connective tissue planes to the mediastinum to cause pneumomediastinum. Peripheral or sub-pleural, pulmonary alveoli rupture would rapidly facilitate pneumothorax and pneumomediastinum. This pathophysiological mechanism of pneumothorax and pneumomediastinum was first described by Macklin [12] in his experimental animal model and has been observed in many clinical settings where there is acute lung injury [13-15].

Yet another mechanism for increase alveolar pressures and the adverse effects of paraquat pulmonary toxicity is the early development of secondary pulmonary hypertension. The initiation of pathological repair at the alveolar level, with widening of the interstitium with inflammatory cells, and early deposits of collagen, together with alveoli capillary congestion and destruction, and microthrombi formation (Figure 2) cause secondary pulmonary hypertension and cor-pulmonale [16]. This inadvertently leads to increase alveolar pressures and the vicious cycle of pneumothorax and pneumomediastinum. This phenomenon of pneumothorax and pneumomediastinum hitherto called the Daisley Barton syndrome [17] together with other pathological features of acute lung injury discussed above leads ultimately to the acute respiratory distress and failure, which was experienced by the patient in the discussion and led to his ultimate death.

Conclusion

Pneumothorax and pneumomediastinum are clinical signs of paraquat induced acute lung injury and its proposed pathophysiology is revised above. Daisley and Barton first described this clinical observation in 1990 [1]. These clinical signs are not uncommon and have a high index of early mortality, and must be looked for in all cases of paraquat poisoning [17, 18].

In regions like Trinidad and Tobago where there is a high incidence of paraquat assisted suicide [19], paraquat poisoning should be included in the differential diagnosis in patients presenting with acute respiratory distress and or evidence of **the Daisley Barton syndrome (Daisley Barton 1990 [19] namely pneumothorax and pneumomediastinum in acute paraquat toxicity.**

More research needs to be done on therapy to combat paraquat toxicity based on the proposed pathophysiology of acute lung injury [20-22].

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