POLONIUM-210 POISONING; A FIRST-HAND ACCOUNT

AMIT C. NATHWANI[1,2,3,4]; JAMES F. DOWN[5];JOHN GOLDSTONE[5];JAMES YASSIN[5]; PAUL I. DARGAN[6]; ANDREAS VIRCHIS[2]; NICK GENT[8]; DAVID LLOYD[8]; AND JOHN D. HARRISON[8].

[1]Department of Haematology, UCL Cancer Institute, U.K.; [2]Department of Haematology, [3]Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free London NHS Foundation Trust Hospital, U.K.; [4]National Health Services Blood and Transplant, U.K;[5]Intensive Care Unit, University College London Hospitals NHS Foundation Trust, U.K; [6]Clinical Toxicology, Guy's & St Thomas' NHS Foundation Trust, London, U.K; [7]Faculty of Life Sciences and Medicine, King's College London, U.K., and [8]Public Health England, U.K.

Corresponding Author:

Amit C. Nathwani,
Department of Haematology,
UCL Cancer Institute,
London,
WC1E 6BT,
U.K.
Phone: (+44) 207679 6225
Fax: (+44) 207679 6222
e-mail: a.nathwani@ucl.ac.uk

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Summary

Background

Polonium-210 (^{210}Po) gained widespread notoriety after the poisoning and subsequent death of Mr Alexander Litvinenko in London in 2006. Exposure to polonium-210 resulted initially in a clinical course that was indistinguishable from infection or exposure to chemical toxins, such as thallium.

Methods

A 43-year-old man presented to his local hospital with acute abdominal pain, diarrhoea and vomiting and was hospitalised because of dehydration and persistent gastrointestinal symptoms. He was initially diagnosed with gastroenteritis, and treated with antibiotics. *Clostridium difficile* toxin was subsequently detected in his stools, which is when he first raised the possibility of being poisoned and revealed his true identity, having been admitted under an alias. Within 6 days the patient had developed thrombocytopenia and neutropenia, initially thought to be drug-induced. By two weeks, in addition to bone marrow failure, there was evidence of alopecia and mucositis. Thallium poisoning was suspected and investigated but ultimately dismissed as blood levels were below toxic concentrations. The patient continued to deteriorate and within three weeks had developed multiple organ failure requiring ventilation, haemofiltration and cardiac support, associated with a drop in consciousness. On the 23rd day after he first fell ill, he suffered a pulseless electrical activity cardio-respiratory arrest from which he could not be resuscitated and was pronounced dead.

Findings

Urine analysis using gamma ray spectrometry showed a characteristic 803 keV photon emission, raising the possibility of ^{210}Po poisoning on day 22. Results of confirmatory analysis that became available after his death established the presence of ^{210}Po at concentrations about 10^9 times higher than normal background levels. Post-mortem tissue analyses showed autolysis and retention of ^{210}Po at lethal doses in multiple organs. Based on the measured levels and tissue distribution of ^{210}Po, it was estimated that the patient had ingested a dose of polonium chloride

salt, equivalent to 1,000 gigabecquerels (GBq), delivering very high and fatal radiation doses over a period of a few days.

Interpretation

Early symptoms of ^{210}Po poisoning were indistinguishable from those of a wide range of chemical toxins. Hence, the diagnosis can be delayed and even missed without a high level of suspicion. Although body surface scanning with a standard Geiger counter was unable to detect the radiation emitted by ^{210}Po, an atypical clinical course prompted active consideration of poisoning with radioactive material, with the diagnosis being ultimately made with gamma-ray spectroscopy of a urine sample.

Introduction

Alexander Litvinenko (born 4 December 1962) was an officer of the Russian secret service who, in 2000, was granted asylum in the United Kingdom and began working as a consultant for the British intelligence services. On 1 November 2006, Mr Litvinenko fell ill and was hospitalised. His illness was later attributed to poisoning with polonium-210 (^{210}Po), as significant amounts of this highly toxic radionuclide were found in his body by the Health Protection Agency (now Public Health England). An inquest into Mr Litvinenko's death was opened in November 2006 but was suspended pending conclusion of an inquiry established in July 2014. A public hearing commenced at the Royal Courts of Justice in London in January 2015 and included review of the patient's medical records, clinical course, spectroscopy results, and statements by experts. The hearing concluded on 31 July 2015 and the final report into the death of Mr Litvinenko is expected to be delivered to the British Home Secretary by the end of 2015.

Following the public hearing we the primary clinicians and toxicology experts involved in the care of Mr Litvinenko in 2006 are now free of any restrictions to describe the clinical aspects of this highly unusual case. In this report, we provide a first-hand account of the events leading to the

diagnosis of ^{210}Po poisoning as well as detailed toxico-kinetics of this, the first documented case of lethal poisoning with polonium.

Presentation

On 3 November 2006, a 43-year-old man named Edwin Carter presented to the Accident and Emergency department of Barnet General Hospital (now part of Royal Free Hospital, London) complaining of abdominal pain, vomiting and diarrhoea, which had started on 1 November 2006 (designated as day 1 in the following chronology). On examination, he was appeared dehydrated. He was afebrile and had a normal pulse and blood pressure. Abdominal examination revealed epigastric tenderness. Given the profuse nature of his diarrhoea, a provisional diagnosis of gastroenteritis, possibly of infective origin, was made. He was admitted for further investigation and commenced on intravenous fluids and oral ciprofloxacin 500mg 12 hourly. Investigations revealed serum urea and conjugated bilirubin levels were mildly elevated at 12.1mmol/L and 49µmol/L, respectively, and creatinine high at 101µmol/L, suggesting dehydration. Haemoglobin was 201g/L (reference 120-180g/L) associated with a leucocytosis (WBC, 22x10^9/L, reference 4.0-11.0 x10^9/L) and neutrophilia (19.8x10^9/L, reference 2.0-7.5 x10^9/L; Table 1).

Clinical course

On day 7, *Clostridium difficile* (*C. difficile*) toxin was identified in the stools by the microbiology department at Barnet General Hospital. The possibility that this may have been secondary to ciprofloxacin was raised. When the diagnosis was discussed with the patient he revealed his true identity (he had been admitted under an alias) and raised the possibility of being poisoned. He disclosed that his real name was Alexander Litvinenko and that he had defected from the Russian Security Service. Mr Litvinenko explained that on the day he became ill, he had met with former KGB agents and feared that he had been poisoned (Figure 1A and Table 1).The patient and his wife asked medical staff whether poisoning by infection with *C. difficile* might have occurred as they had a friend who had been killed in this way. Mr Litvinenko was commenced on

oral metronidazole (400mg three times daily) but gastrointestinal symptoms persisted. The working diagnosis was of *C. difficile* diarrhoea associated with a possible underlying viral gastroenteritis. By day 9, Mr Litvinenko had become neutropenic with a neutrophil count $1.1x10^9$/L (Table 1). His platelet count had also dropped from normal levels to $63x10^9$/L. The cause for the cytopenia was unknown but thought to be due to a viral gastroenteritis or as a result of ciprofloxacin toxicity.

On day 11, his neutrophil count was < $0.5x10^9$/L and he had spiked a fever. He was commenced empirically on intravenous piperacillin/tazobactam (4.5g, 6 hourly) in order to avoid progression to a sepsis syndrome. He was also given a single dose of pegylated G-CSF (Neulasta, 6mg) to stimulate recovery of the neutrophil count. By day 13, alopecia was evident together with mucositis, this together with progressive cytopenia gave the appearance of someone who had been exposed to toxin, chemotherapy or radiation. Reverse barrier nursing was instituted and on toxicological advice from the Clinical Toxicology Unit at Guy's & St Thomas' NHS Foundation Trust, London, UK, samples were sent to for a heavy metal screen. A screen of the patient with a standard Geiger counter revealed only background values. Bone marrow trephine sample taken on day 15 was acellular (Figure 1B). He was therefore transferred to the Haematology Unit at University College London for specialist support and treatment of bone marrow failure. Samples were sent for human leukocyte antigen typing in case a bone marrow transplant was needed. On day 17 results of the heavy metal screen revealed a marginally elevated urine thallium concentration at 30nmol/L (normal <10nmol/L) but this was below the toxic concentration (800-1000nmol/L). The patient had told staff that the Russians' used radioactive thallium as a poison. It was not felt likely that thallium poisoning was the cause of the patient's deterioration, particularly as there was no evidence of a peripheral neuropathy, which is a cardinal feature of thallium poisoning. However, in the absence of other clear aetiology, treatment with oral Prussian blue (Ferric ferrocyanide; 4g, 8 hourly) was commenced because of the mildly raised urine thallium level together with gastrointestinal symptoms and alopecia, two clinical features that are typically associated with thallium poisoning.

On day 18, he was jaundiced with normal alanine transaminase levels. Diarrhoea and abdominal pain were settling and his oral intake was improving although haematemesis was noted that evening. On day 19, the rapid assessment team was called because of concerns about heart rate irregularity: inverted T-waves were noted on the lateral leads of an electrocardiogram. Troponin-T levels were normal. He was, nevertheless, transferred to the intensive care unit for further monitoring. To mitigate against further abnormalities of heart rhythm, it was decided to maintain serum potassium at about 5.5mmol/L. He remained pyrexial, despite antibiotics. Because of raised inflammatory markers (C-reactive protein 100mg/ml, erythrocyte sedimentation ratio 130mm/hour) but no evidence of disseminated intravascular coagulation, he was commenced on systemic antifungal therapy with Ambisone. Repeat analyses of plasma and urine revealed a normal thallium concentration (<10nmol/L). By this stage the conjugated bilirubin level was high (230μmol/L). Over the subsequent two days (days 20-22) his renal function deteriorated rapidly (Table 1). An abdominal ultrasound scan demonstrated that the liver, spleen and kidneys were of normal size and appearance with no evidence of obstruction.

The possibility of chemotherapeutic agents causing mucositis and bone marrow failure was considered but dismissed as covert administration at the doses required to cause rapid multi-organ failure would have been difficult. A search for a radiotoxin was pursued along several lines, which in its simplest form entailed the exposure of the patient's blood smear on a glass slide to an X-ray film on day 22. This speculative study revealed a surprising result in that the X-ray film exposed to parts of the blood smear not covered by a glass coverslip developed opacity (Figure 1C), consistent with the presence of a radioactive substance in the blood. Later that day, gamma ray spectrometry measurements on a urine sample showed a characteristic 803 keV photon emission, raising the possibility of polonium-210 (^{210}Po) poisoning. Further urine and blood samples were sent for confirmatory spectrometric analysis. However, the patient's condition deteriorated rapidly that day with the onset of a florid macular skin rash, abdominal distension, progressive metabolic acidosis and oliguria. He became hypothermic (35.5^{o}C) and

progressed to cardiogenic shock with an associated acute drop in consciousness. This was followed rapidly by a pulseless electrical activity (PEA) cardio-respiratory arrest. He was successfully resuscitated but was dependent on escalating doses of adrenaline. A further PEA cardiac arrest occurred 2 hours later. Echocardiography showed poorly contracting ventricles with no evidence of tamponade or valvular pathology. Oesophageal Doppler demonstrated a stroke volume of 40ml (normal = 70ml) despite high doses of adrenaline (2.0µg/kg/min). For the next 16 hours the patient remained unstable and required inotropes, continuous veno-venous hemofiltration and full mechanical ventilation. On day 23 Mr Litvinenko suffered a third PEA cardiac arrest and was pronounced dead. Results of the day 22 urine sample became available shortly after the patient's death and revealed the presence of 825 becquerel (Bq)/mL of ^{210}Po, consistent with polonium poisoning.

Post-mortem results

A limited post-mortem examination was conducted by a consultant forensic pathologist on day 31 in the presence of a radiation protection officer. Precautions to avoid radiation exposure included the wearing of two protective suits, two pairs of gloves taped at the wrists and large battery-operated plastic hoods into which filtered air was piped. Key gross macroscopic findings were the presence of blood-tinged fibrinous pericarditis, a pleural effusion associated with bilateral congestion of lungs, gross ascites and generalised tissue autolysis of most organs although the brain looked normal. Because of the hazardous nature of the tissue samples microscopy of the internal organs was not carried out and further analyses were limited to studies of the biodistribution of ^{210}Po using gamma-ray spectrometry. The results were used to estimate total organ levels of ^{210}Po at the time of death. As shown in Table 2, ^{210}Po was retained in all organs and tissues, with the highest levels in the liver (30MBq/g) and kidney (49MBq/g), consistent with published data on the biodistribution of ^{210}Po.[1-3] The lower concentration of ^{210}Po in lung tissue (3.5MBq/g) was consistent with intake largely by ingestion. Assuming ingestion of ^{210}Po on day 1 with 10% being absorbed into the systemic circulation, the measured levels of ^{210}Po in liver, kidneys and urine were used to estimate intake as 4,400 MBq (4.4 GBq)[2,3]

Estimates were made of the cumulative radiation doses to the body organs of a reference 70 kg adult male over 22 days following the ingestion of 4.4 GBq of ^{210}Po (Table 3). Radiation doses causing lethal damage to body organs are generally quantified in terms of the lethal dose of acute gamma radiation estimated to kill 50% of people so exposed (LD_{50}values), with corresponding LD_0 – LD_{100} ranges. Doses required to cause prodromal symptoms of vomiting and diarrhoea are expressed as effective doses (Note: LD and effective dose [ED] are toxicological terms and ED should not to be confused with the radiation protection quantity of effective dose). When estimating values for ^{210}Po, it was necessary to take account of the reduced effectiveness of protracted irradiation and the greater damage caused per Gy by alpha particles compared to gamma rays (i.e. relative biological effectiveness for alpha particles is >1). Taking account of dose protraction and assuming a relative biological effectiveness of 2, it was estimated that the ED_0 and ED_{50} values for vomiting and diarrhoea are about 0.6–0.8Gy and 7Gy respectively.[3] Our estimated dose rate to all regions of the gut of about 0.2Gy per day for the first few days after intake (Table 3) does not, therefore, appear to be sufficient to cause the prodromal symptoms that the patient presented. However, it is possible that gut doses may have been underestimated by the model assumptions, especially as animal data suggest that a proportion of ingested ^{210}Po is retained in the gastric and intestinal mucosa.[3] Alternatively, these symptoms were due to or compounded by infection with *C. difficile* or cumulative radiation dose delivered by the radiotoxin in the gut lumen as well as that absorbed into the blood stream. In contrast, the estimated dose to the red bone marrow was about 6Gy after one week, rising to 17Gy after 22 days. The estimated radiation doses to the liver and kidneys were also very high; respectively about 5 and 9Gy per day over the first few days and reaching 92 and 140Gy after 22 days.

Discussion

Polonium-210 is a naturally occurring radioactive element that was discovered in 1898 by Marie Curie. It has no stable isotopes and decays by emitting a large quantity of alpha particles, which

cause excitation in the nucleus and emission of gamma rays with a maximum energy of 803 keV. It has a half-life of 138 days and high specific activity, so that a very small mass corresponds to a high level of radioactivity. Humans are constantly exposed to ^{210}Po, which is found at low concentrations in the environment as part of the uranium decay chain. However, annual intake from natural sources is about 10^9 times less than the intake estimated in our subject at around 4 GBq.

Polonium is used in various industrial applications and as a power supply in small satellites but its manufacture requires sophisticated equipment. It is, therefore, not widely available. However, it is an effective poison for several reasons. It forms water soluble, colourless salts that are readily absorbed across biological membranes, becoming widely distributed in body organs and tissues where the alpha particles deliver a large amount of energy to surrounding cells resulting in cell death and organ damage. Early symptoms of ^{210}Po poisoning are indistinguishable from those of a wide range of chemical toxins. Therefore, the diagnosis can be delayed and even missed without a high level of suspicion. Furthermore, ^{210}Po can be transported easily and safely without detection because its high-energy alpha particles have a short range and can be blocked by a relatively thin barrier including the skin, while the associated gamma ray emissions are very low yield. Hence, the use of a Geiger counter in this case was unable to detect the radiation emitted by ^{210}Po. Alpha-particle spectroscopy represents the best way to test for radiotoxins such as ^{210}Po which emit alpha particles. These instruments are not readily available in the majority of hospitals.

Reports on human subjects are limited; a Russian accident case involving inhalation of an aerosol of ^{210}Po at an approximate dose of 530 MBq ^{210}Po resulted in death in 13 days.[3,4] The time-course of rapid clinical deterioration observed in our patient, resulting in death within 23 days, is, however, consistent with animal data for a number of mammalian species.[3] Aside from the gastro-intestinal tract, the bone marrow was among the first organ systems to be damaged. From an initial neutrophilia, a feature of acute radiation injury,[5] the neutrophil count declined

rapidly over a two week period. The LD_{50} for the bone marrow was estimated to be about 3Gy, with an LD_0 – LD_{100} range of 1-4Gy. Our calculations indicate that the LD_{100} value for the red bone marrow was exceeded after 5 days (Table 3), causing irreversible damage to the hematopoietic stem cell and stromal compartments.[3] At significantly lower doses of ^{210}Po, transplanted progenitor cells may provide transient support but animal data indicate that death in such a setting may occur at later times, predominantly as a consequence of radiation damage to the kidneys.[6] Similarly, the estimated LD_{50} value for acute kidney damage was 6Gy, with a corresponding value for liver failure of 8Gy. Our estimates of the cumulative dose delivered to the kidney and liver were 44 and 28Gy respectively at day 5. Hence, the wide distribution of ^{210}Po likely resulted in the delivery of lethal radiation doses to a number of organs at an early stage after intake.

A number of chelating agents have been assessed in animal models of ^{210}Po poisoning to reduce organ retention and enhance excretion.[7,8] Unithiol (sodium 2,3-dimercaptopropane-1-sulphonate) has been used in children accidentally exposed to ^{210}Po in the former Soviet Union[9] and has recently been given to two individuals thought to have been exposed at around the same time as Mr Litvinenko: both survived but had received considerably lower doses of ^{210}Po than our patient. Animal data suggest that chelation may decrease ^{210}Po retention in the blood, spleen and bone, although this may be associated with increased retention in the kidneys and the brain. Typically the amounts used in animal studies are generally higher than recommended for administration to humans.

Conclusion

This case has raised our awareness of the possibility that radioactive materials may be used as poisons with catastrophic effect. Importantly, early symptoms of ^{210}Po poisoning were indistinguishable from those of a wide range of chemical toxins, including thallium, thus causing a delay in diagnosis. Additionally, body surface scanning with a standard Geiger counter was unable to detect the alpha radiation emitted by ^{210}Po. Nevertheless, an atypical clinical course

including mucositis, alopecia and bone marrow failure prompted active consideration of poisoning with radioactive material, with the diagnosis being ultimately made with gamma-ray spectroscopy of a urine sample. An earlier diagnosis in our patient would not have enabled him to survive as the high level of ^{210}Po absorbed and distributed to body organs within hours of intake would have resulted in rapid cell death and multiple organ failure. Preparedness for such cases in the future would require a high level of clinical suspicion and investment in sensitive detection instrumentation by hospitals. However, such cases would remain untreatable without research into effective antidotes that reduce levels and biodistribution of ^{210}Po, and limit the extent of organ damage. Nevertheless, early diagnosis of poisoning with radiotoxin is important for environmental safety and to protect hospital staff from the hazards of radiation.

Acknowledgements

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Authorship Contributions

Amit C Nathwani, Nick Gent, David Lloyd and John Harrison collated all the data and prepared the first draft

Amit C Nathwani, provided the UCLH clinical data for the patient

James Down, John Goldstone and James Yassin provided the data relating to the ITU management of the patient.

Paul Dargan provided the toxicology input

Nick Gent, David Lloyd and John Harrison provided the ^{210}Po biodistribution data

Andreas Virchis provided data from the initial management of the patient in Barnet

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Table 1. Progression of the patient's haematological parameters and hepatic and renal biochemistry after suspected poisoning, day 1

	Haematological Parameters					Liver and Renal Biochemistry			
Day	Hb (g/L)	WBC ($x10^9$/L)	Neutrophils ($x10^9$/L)	Lymphocytes ($x10^9$/L)	Platelets ($x10^9$/L)	Bilirubin (µmol/L)	ALT (IU/L)	Urea (mmol/L)	Creatinine (µmol/L)
3	201	21.7	19.8	1.0	178	49	16	12.1	101
4		--	--	--	--				
5	149	17.2	16.1	0.6	105			7.9	76
6		--	--	--	--				
7	130	7.1	6.8	0.1	92			4.4	79
8		--	--	--	--				
9	129	1.3	1.1	0.0	63	66	50	4.6	76
10		--	--	--	--				
11	136	0.3	0.3	0.0	35	60	92	4.4	90
12	147	0.2	0.1	0.0	21	69	107		
13	145	0.1	0.0	0.0	9	76	102		
14	113	0.0	0.0	0.0	2*			10	102
15		0.0	0.0	0.0	17				
16		0.0	0.0	0.0	21				
17		0.0	0.0	0.0	13				
18	91	0.1	0.0	0.0	10	153	40	9.2	132
19	84	0.01	0.0	0.0	7	181	34	9.8	133
20	91	0.01	0.0	0.0	15	228	39	11.8	190
21	82	0.05	0.0	0.0	18	242	48	16.6	218
22	90	0.01	0.0	0.0	8	254	54	23.9	286^+
23	108	0.02	0.0	0.0	15	158	112	24	353^+
Normal	120-180	4 - 11	2.0 – 7.5	1.0 – 4.0	150 - 400	3-20	5 – 50	3.5-6.5	60-120

WBC = white blood cells. ALT = Alanine Transaminase $^+$ Enzymatic creatinine
*Platelet and plasma transfusions started.

Table 2. Measurements of polonium-210 in post-mortem samples, blood and urine, estimates of organ content and excretion and model predictions of organ content and excretion

Sample	Activity, Bq per g of tissue	Total estimated activity in organ/ tissue, MBq[a]	Model prediction of total activity in organ/tissue, MBq[b]
Muscle (psoas)	1100	72[c]	71[c]
Brain	5500	8	-
Lung	3500	1.8	-
Spleen	9900	1.5	4.5
Kidney	49000	15	17
Bile	13000	3 – 14 per day	4[d]
Liver	30000	54	66
Heart	2500	2[e]	-
Skin	1800	6	35
Blood: day 20	3300	19	25
Blood: day 23	1500	8	23
Urine: day 22	825 per ml	1.3	1.0

[a]Scaled from measurements using data for organ masses, and blood, urine and bile volumes.(10)
[b]An estimate of intake by ingestion of 4.4 GBq ^{210}Po on day 1, assuming 10% absorption to blood, was made based on the most reliable measurements (urine, liver and kidneys) using a model for the behavior of polonium-210 in the body(2)and the model was then used to calculate the tabulated values.
[c]Assuming that the concentration of polonium-210 in muscle is representative of "Other" tissues in the model.(2)
[d]Based on the assumption that biliary excretion accounts for all fecal excretion.
[e]Including blood content.

Table 3. Cumulative doses to organs / tissues of a reference adult male after ingestion of 4.4 GBq of polonium-210, assuming 10% absorption to blood.

Time after intake(days)	Cumulative dose(Gy)						
	R.B.M.	Gut	Liver	Kidneys	Spleen	Skin	Testes
1	0.8	0.2	5.0	8.1	2.9	0.6	0.8
2	1.8	0.4	11	18	6.4	1.3	1.9
3	2.7	0.6	17	27	9.9	2.0	2.9
4	3.6	0.8	22	36	13	2.8	4.1
5	4.5	1.1	28	44	16	3.6	5.2
10	8.7	2.0	51	80	31	7.9	12
15	12	2.8	70	110	44	13	19
20	16	3.5	86	130	55	18	26
22	17	3.7	92	140	59	20	29

1 Bq = 1 dissociation per second (releasing one alpha particle per second, with associated low yield [10^{-5}] gamma rays).RBM = Red bone marrow. 1 Gy = 1 joule per kg.

Figure 1A: Schematic of clinical milestones following exposure to ^{210}Po on day 1

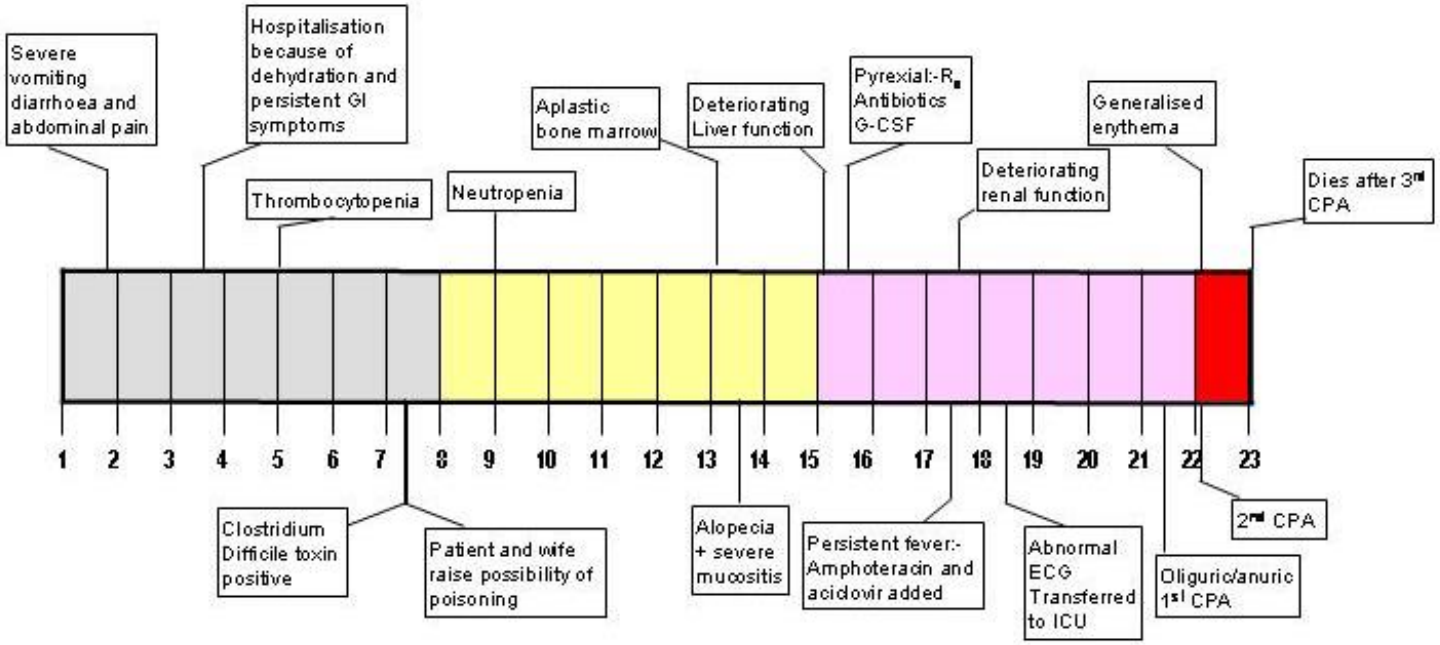

Figure 1B: H&E stained bone marrow trephine showing cartilage and adipocytes with very few haematopoietic precursors

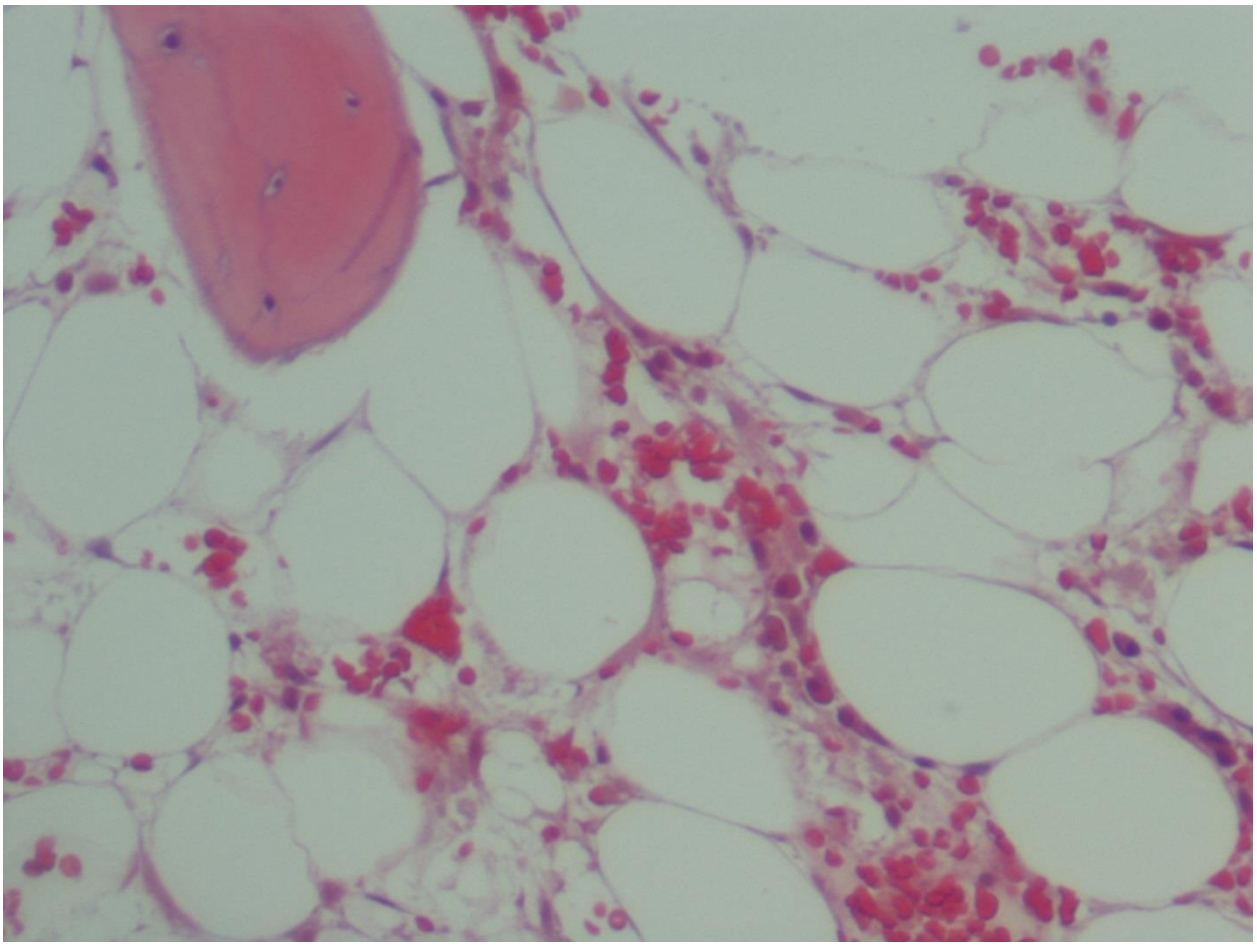

Figure 1C: X-ray film (Right image) exposed to the patient's blood smear (Left Image) showing opacification (red arrow) in the exposed area of the smear but not in the adjacent area that was covered by a glass coverslip (Blue arrow)